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AN EXAMINATION OF THE CROSS-OVER EFFECTS OF FATIGUE WITH AND
WITHOUT MIRROR VISUAL FEEDBACK

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DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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This work is dedicated to the memory of three great men that passed during my doctoral studies: my mentor – Dr. Travis Beck, my father-in-law – John Hering, and my step-father – Bobby Lange.

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Abstract

      Skeletal muscle fatigue is a multifactorial process that leads to decrements in the force generating capacity of the neuromuscular system. During a maximal unilateral and bilateral contraction, complex interactions occur along the length of the neuromuscular system. These interlimb limb interactions occur with and without the presence of fatigue, however, it is unknown whether illusionary mirror visual feedback moderates the effects. The primary purpose of this study was to examine the influence of unilateral fatigue, with and without illusionary mirror visual feedback, on the maximal force of the fatigued and non-fatigued limb during unilateral and bilateral contraction. A secondary purpose was to examine the bilateral index and whether sex moderated the responses. Thirty healthy right-hand dominant participants (n = 15 males; 15 females) completed this study. After a familiarization session, the participants completed four experimental visits (no-mirror, mirror, non-dominant, and control) in a pseudo-randomized order. The fatigue protocol required the participants to perform nine, 20 second maximal unilateral handgrip contractions. This protocol was performed with (mirror) and without (no-mirror) illusionary mirror visual feedback with the dominant hand. The fatigue protocol was also performed with the non-dominant (non-dominant) hand without mirror visual feedback. Maximal strength and electromyographic (EMG) amplitude of the flexor carpi radialis and extensor carpi radialis were collected for both hands during unilateral and bilateral contractions before and after the fatigue protocol. The relative change (%Δ) in maximal strength and EMG amplitude was compared between visit, contraction, and sex. The bilateral index was also compared between hands and sex. The main findings show that: 1) bilateral force loss was significantly (p

< 0.05) greater than unilateral force loss during the no-mirror and non-dominant visit, but not during the mirror visit ($p > 0.05$), 2) there were no significant ($p > 0.05$) changes in maximal force for the contralateral, non-fatigued hand during maximal unilateral contractions, yet there was for the bilateral contraction following the non-dominant visit ($p < 0.05$), 3) there was a significant ($p < 0.05$) increase in EMG amplitude for the non-fatigued flexor carpi radialis during the mirror visit, 4) there was a significant ($p < 0.05$) bilateral deficit and it was greater for the dominant hand compared to the non-dominant hand ($p < 0.05$), and 5) sex did not have a significant influence on any of the comparisons ($p > 0.05$). Together, these findings present several novel observations related to neuromuscular fatigue and cross-limb interactions.

CHAPTER 1: INTRODUCTION

1.1. Introduction

In 1894, Edward Scripture provided an unknown framework for the properties of bilateral limb interactions. In his pioneering study, it was observed that unilateral strength and skill training not only improved the strength and skill for that limb, but the improvements were also transferred to the untrained limb through "indirect practice" (Scripture et al., 1894). These adaptations were termed 'cross-education' and have since been incorporated into clinical rehabilitation settings (Andrushko et al., 2018; Magnus et al., 2013). A principal hypothesis put forth by Scripture et al., (1894) has only recently been given critical attention and is summarized by the following excerpt (Scripture et al., 1894).

"Thus, training of one portion of the body trains at the same time the symmetrical part and also neighboring parts… the training seems to be of a psychical rather than a physical order and to lie principally in the steadiness of attention."

These observations demonstrate the astounding foresight that Edward Scripture had regarding the mechanisms responsible for cross-education. For instance, it is now well accepted that neural (i.e., psychical) mechanisms are primarily responsible for cross-education, and the influence of attentional focus has recently been the subject of investigation in a variety of training paradigms (Buccino, 2014; Howatson et al., 2013; Ramachandran and Altschuler, 2009; Schoenfeld et al., 2018; Zult et al., 2014, 2016). Moreover, there is evidence that fatigue may also be transferred between limbs, though

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there is considerable variability in the magnitude of transfer and the muscles susceptible to these effects (Halperin et al., 2014; 2015; Sidhu et al., 2015; Todd et al., 2003; Zijdewind et al., 1998). This interlimb transfer has been referred to as the 'cross-over' of fatigue and has been quantified as the reduction of maximal force or performance of the contralateral muscle pair (Halperin et al., 2015). The use of interlimb models are particularly useful for investigating the compensatory adaptations of the neuromuscular system.

A recent hypothesis has been presented that suggests that the magnitude of cross-education may be augmented with the use of mirror visual feedback (Howatson et al., 2013). The basis for this hypothesis is grounded in two separate, yet similar discoveries from the mid-1990's: mirror neurons (Di Pellegrino et al., 1992) and mirror box therapy (Ramachandran and Rogers-Ramachandran, 1996). In short, with a mirror along the midsagittal plane, the mirror image of one limb is superimposed over the opposite limb, providing the illusion that the contralateral limb is active (Ramachandran and Altschuler, 2009). This type of illusionary mirror visual feedback has been shown to produce unique patterns of brain activation compared to control conditions and is hypothesized to activate mirror neurons (Howatson et al., 2013; Molenberghs et al., 2012; Ramachandran and Altschuler, 2009; Zult et al., 2014). Mirror neurons are distributed across brain regions involved with sensory integration, motor planning, and movement execution, thus forming the 'mirror neuron system' (Rizzolatti and Craighero, 2004). Importantly, the hypothesis put forth by Howatson et al., (2013) suggests that the mirror neuron system overlaps with cortical areas that are also involved with cross-education. The evidence provided from clinical populations with

asymmetric limb disorders clearly demonstrates the utility of mirror visual feedback interventions (Altschuler et al., 2009; Dohle et al., 2009; Ramachandran and Altschuler, 2009).

The mirror training hypothesis is supported by one study that has examined the possibility that mirror visual feedback augments the magnitude of cross-education (Zult et al., 2016). Moreover, it was observed that the level of cross-education was ~27% greater in the mirror training group compared to the group that did not receive mirror visual feedback during training (Zult et al., 2016). Interestingly, the cross-over effects of fatigue with mirror visual feedback are poorly defined (Tsutsumi et al., 2011). It may be reasoned that central factors moderating interlimb interactions can be examined with the use of mirror visual feedback and fatigue. The importance of examining interlimb interactions is directly related to its application for asymmetric orthopedic and neurological conditions.

1.2. Purpose.

To examine the cross-limb effects of unilateral hand grip fatigue with and without mirror visual feedback.

1.3. Research questions.

1. Does unilateral limb fatigue reduce contralateral limb strength and muscle activation?

2. Does illusionary mirror visual feedback moderate the cross-over effects?

   a. Does illusionary mirror visual feedback influence the fatigue response for the fatigued hand?

3. Are there differences between unilateral and bilateral force losses for the fatigued and non-fatigued hands?

4. Does limb dominance affect the fatigue responses?

5. Does sex moderate the fatigue responses?

6. Is there a difference between maximal bilateral and unilateral force values?

   a. Are there sex differences?

   b. Are there differences between limbs?

1.4. Hypotheses.

1. Unilateral limb fatigue will significantly reduce contralateral limb strength and muscle activation.

2. Mirror visual feedback will produce greater reductions in contralateral limb strength during unilateral and bilateral contractions compared to the other fatigue visits.

   a. Mirror visual feedback will result in greater reductions of strength for the fatigued hand.

3. Bilateral force loss will be greater than unilateral force loss.

4. Mirror visual feedback will produce greater reductions in force for the working muscle during unilateral and bilateral contractions compared to the no-mirror condition.

5. Males will experience greater fatigue-based force loss than females.

6. Maximal bilateral force will be less than maximal unilateral force.

   a. Females will have a greater bilateral deficit than males

b. The dominant hand will have a greater bilateral deficit than the non-dominant hand.

1.5. Significance.

The results of this study will provide mechanistic insight into two important areas of exercise physiology, central fatigue and cross-education. Moreover, by examining the cross-over effects of unilateral fatigue on the contralateral limb with and without the use of mirror visual feedback, the relative influence of higher-order visual processing on the magnitudes of fatigue accrued for both limbs may be considered. In theory, if mirror visual feedback moderates the level of interlimb fatigue transfer, it may be reasoned that visual input influences the development of central fatigue, and it would support the use of visual feedback when designing cross-education interventions.

1.6. Assumptions.

The assumptions within this study are important to consider. It is assumed that all participants will answer the health history questionnaire accurately, will give a maximal voluntary effort during each contraction, and the mirror visual feedback will provide a genuine illusionary effect.

1.7. Delimitations.

This study will recruit healthy participants aged 18 – 35 years with various training backgrounds. The interpretations of these results will be specific to the wrist flexors.

1.8. Limitations.

The major limitations of this study relate to the lack of cortical measurements. This limits our assessment to areas downstream of the adaptive cortical sites. In addition, the participants will not reflect a truly random sample.

1.9. Abbreviations.

Electromyography – EMG

Isometric maximal voluntary contraction – MVC

Mirror visual feedback - MVF

1.10. Operational Definitions.

EMG – an electrical signal non-invasively detected from the surface of the skin
which reflects the excitation delivered to the muscle from the central
nervous system.

MVC – the MVC value is designated as the highest force produced in a defined
time window during a maximal voluntary effort.

Fatigue – the progressive reduction in the ability of a muscle to generate force.

Cross-over – the transfer of fatigue from one limb to the homologous muscle.

Mirror visual feedback – illusionary mirror visual feedback is provided by
placing a mirror in the midsagittal plane, with the mirror reflection of
one limb superimposed over the contralateral, hidden limb.

CHAPTER 2: REVIEW OF LITERATURE

This chapter is divided into three subsections that are organized in a chronological study-by-study format. A summary is provided at the end of each section. This review primarily focuses on data from the upper limbs.

2.1. Maximal Voluntary Contractions and the EMG response.

This subsection provides novel findings related to the physiological adaptations that take place during sustained maximal voluntary contractions with an emphasis on the EMG response.

Bigland-Ritchie et al., 1982.

This study was critical for its observation that neuromuscular transmission is maintained during sustained maximal voluntary contractions. The participants (n = 4) performed sustained, 60-second MVCs of the dominant adductor pollicis and first dorsal interosseous muscles while surface and intramuscular EMG signals were detected and compound muscle action potentials delivered in 10-second intervals. The authors reported that during the sustained MVCs, there were inter-individual differences in the rate of decline in force, as force after the fatigue protocol fell between 30 – 50% of the maximum value. Nevertheless, the authors found no evidence of neuromuscular junction impairment as neither the amplitude nor the area of the compound muscle action potential was changed during the fatigue protocol.

Bigland-Ritchie et al., 1983a.

This study was important for documenting the firing rate changes for a large population of motor units during sustained maximal voluntary contractions. The participants (n = 5) performed sustained 40 - 120-second MVCs of the adductor pollicis

while intramuscular EMG was recorded. The authors reported that there was inter-individual variability in the range of maximal firing rates (10 – 50 Hz). It was reported that all detected motor units showed ~50% decline (i.e., 27 to 15 Hz) in firing rate after 60 seconds. The authors reported that there was some evidence that motor units with the highest initial firings exhibited firing rate changes most rapidly. An important consideration made from this paper was that the decline in motor unit firing rate was not responsible for force loss, but the modulation of which was the primary mechanism retained for force control.

Bigland-Ritchie et al., 1983b.

This study was important for documenting the contractile and EMG changes that occur during sustained maximal voluntary contractions. The study required the participants (n = 8, 4 females) to perform sustained 60-second MVCs of the adductor pollicis muscle. Moreover, surface and intramuscular EMG, contractile speed and rate of relaxation, and compound muscle action potentials were recorded at specified intervals during the fatigue protocol. The authors observed that during the sustained MVC, 1) participants were able to fully activate the adductor pollicis, 2) EMG fell to approximately ~50 - 70% of its maximum, 3) there was no reduction in the size of the compound muscle action potential, 4) contractile twitch duration was prolonged ~50%, and 5) contractile relaxation rate increased ~70%. The authors concluded that the slowing of contraction speed would necessitate a lower motor unit firing rate to maintain force output, and the continuous depression in EMG may reflect the progressive reduction in motor unit firing rates. Lastly, the authors highlighted the similarities between the rates of change between contractile speed and EMG.

Importantly, the authors suggest that the fall in maximal force output is not determined by the decline in EMG.

Bigland-Ritchie et al., 1986a.

This study provided novel evidence for the linkage between motor unit firing rates and afferent sensory input. The participants (n = 7) performed a series of 20 second sustained MVCs of the elbow flexors with or without local blood flow occlusion while EMG was collected. Brief MVCs were performed before and after the fatiguing MVCs and motor unit firing rates were determined. The main findings of this study showed that after a sustained MVC with normal blood supply, MVC values and average motor unit firing rates return to baseline levels within 3 minutes. However, when the muscle was held ischemic after the sustained MVC, strength and motor unit firing rates remained depressed. In fact, the authors observed similar levels of strength and motor unit firing rates after the sustained MVC compared with the end of the 3-minute ischemic rest. This study was critical for documenting the influence that local sensory receptors (i.e., Group III/IV) have on motor unit firing properties.

Macefield et al., 1991.

This study was important for documenting muscle spindle adaptations along with changes in EMG during sustained isometric contractions. In a variety of experiments (n = 8), the authors recorded the discharge properties of muscle spindle afferents from the peroneal nerve during submaximal isometric contractions of the dorsiflexors. The novel findings from this study showed that for the majority of the detected muscle spindles, their firing rates progressively declined during the sustained contraction, falling to approximately half after 1 minute. Though not the primary aim of

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the investigation, the authors noted that Golgi tendon organs exhibited similar adaptations. The progressive increase in EMG amplitude during the sustained contraction together with the decline in muscle spindle discharge led the authors to conclude that muscle spindle disfacilitation results in a reduction of fusimotor drive to the alpha motor neuron.

Gandevia et al., 1996.

This study was important for providing evidence of central fatigue during prolonged MVCs of the elbow flexors. The participants (n = 8, 2 females) performed a 3-minute sustained MVC of the right elbow flexors while receiving motor point and transcranial magnetic stimulation in 10 – 15-second intervals. Local blood flow occlusion was used in half of the participants during the sustained MVC. The authors reported that at the end of the sustained MVC, 1) voluntary force fell to 25.9 ± 8.6% of initial MVC, 2) motor point stimulation of the resting muscle produced 29.5 ± 5.1% of the force produced at baseline, 3) additional elbow flexor force generated through cortical stimulation increased from 1 ± 1.1% at baseline to 9.8 ± 8.3%, 4) voluntary activation fell to 90% compared to over 99% at baseline, 5) central fatigue occurred in all participants, 6) MVC force nor voluntary activation recovered with local ischemia, despite recovered EMG responses through transcranial magnetic stimulation. Collectively, these findings demonstrated that during prolonged MVCs, there is a progressive reduction in the magnitude of neural drive from the motor cortex. This was evidenced by the additional force produced from TMS despite maximal voluntary effort. The authors summarize their findings to indicate that cortical sites that drive the motor cortex likely have a fundamental role in the development of central fatigue.

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Taylor et al., 2000.

This study examined the time-course of central fatigue development during sustained, intermittent MVCs of the elbow flexors. The total duration was 3 minutes of maximal activity partitioned into different MVC durations and duty cycles. Specifically, 5, 10, 15, and 30-second MVCs were performed with duty cycles ranging from 50 – 86%. The authors examined voluntary activation, corticospinal excitability (MEP), and intracortical inhibition (cSP). It was reported that central fatigue developed in all of the fatiguing protocols. The magnitude of change in voluntary activation and corticospinal excitability did not differ between protocols, yet there were unique responses for intracortical inhibition. Moreover, the individual responses for these variables demonstrated different patterns of recovery, with dissociated time intervals between protocols. The recovery was quickest for intracortical inhibition (~5 seconds), then corticospinal excitability (~10 seconds), and finally voluntary activation (~1 minute). The unique temporal aspects for the markers of central fatigue led the authors to suggest that the supraspinal fatigue demonstrated with intermittent MVCs was primarily due to factors upstream of the motor cortex.

Hunter et al., 2006.

This study was important for examining the central factors that may contribute to the sex-related differences in fatiguability. The participants (n = 17, 8 females) performed six, 22-second MVCs of the elbow flexors interspersed by 10 seconds of recovery. Measurements of voluntary activation, corticospinal excitability (MEP), intracortical inhibition (cSP), and evoked twitch responses were performed before and after the fatiguing protocol. The results showed that the males exhibited greater muscle

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fatigue compared to females. Specifically, males demonstrated greater reductions in MVC values ($65 \pm 3\%$ versus $52 \pm 9\%$) and force twitch responses ($59 \pm 12\%$ versus $27 \pm 19\%$) compared to females, respectively. However, the reductions in voluntary activation and increases in corticospinal excitability and intracortical inhibition were not different between males and females. The authors concluded that peripheral, but not supraspinal fatigue is greater for males compared to females. The authors suggested that these responses may be a result of gender-related differences in total muscle mass, muscle fiber type, and different contributions of glycolytic metabolism between the sexes.

2.1.1. Summary.

The use of maximal voluntary contractions are particularly well-suited for the study of fatigue for a variety of reasons: 1) the task is maximal and therefore the entire motor pathway is tested, 2) force loss occurs rapidly with central and peripheral factors involved, and 3) all of the motor units should be maximally active and undergoing similar fatigue-based changes (Taylor and Gandevia, 2008). It has been suggested that fatigue should be recognized as a process (Basmajian and De Luca, 1985), to which central and peripheral mechanisms contribute (Bigland-Ritchie et al., 1986b). Simply put, central factors relate to the inability of the nervous system to drive the motor neurons maximally (Gandevia, 2001), whereas peripheral factors are related to the biochemical changes that occur within the intramuscular environment (Kent-Braun et al., 2012). Surface EMG is likely the most common method used to assess the neural changes that occur during sustained voluntary contractions. Below is a summary of the common physiological adaptations that have been reported.

Although task-dependency is a governing principle of fatigue, consistent reports regarding some of the changes that occur with sustained maximal contractions can be seen. For instance, observations of a ~50% fall in force after ~1 minute of maximal activity is typical for small and large muscles of the upper limb (Bigland-Ritchie et al., 1984). Similarly, motor unit firing rates are reduced by comparable magnitudes for these muscles (Bigland-Ritchie et al., 1983; 1984; 1986a; 1986b; Gandevia et al., 1990; Fuglevand and Keen, 2003). This reduction in motor unit activity is a major contributor to the decline in EMG amplitude and occurs irrespective of muscle, gender, or age (Taylor et al., 2016). The depression in EMG amplitude is a result of fatigue-based impairments that occur at every site along the motor pathway. In turn, the diminished EMG response may be credited to several factors: 1) motor unit activity is reduced due to the motor neurons becoming less responsive to synaptic input, 2) descending drive from supraspinal centers is suboptimal, 3) there is a decline in muscle spindle facilitation to the motor neuron, 4) motor neurons receive increased levels of inhibition from group III and IV afferents, and 5) muscle fiber conduction velocity is reduced due to the deleterious intracellular environment (Bigland-Ritchie et al., 1986a; Butler et al., 2003a, 2003b; Brody et al., 1991; Broman et al., 1985; Gandevia et al., 1996; Macefield et al., 1991). All of these factors may uniquely contribute to the decline in motor unit output, yet it is not possible to parse out the relative influence of motor unit decruitment and firing rate depression on the lowered EMG response.

Although the amplitude of the EMG signal reflects motor unit activity, the frequency content of the EMG signal is primarily dominated by the muscle fiber's conduction velocity (Broman et al., 1985; De Luca, 1985). Accordingly, the buildup of

metabolic byproducts (i.e., H^+ and K^+) within the intramuscular environment reduces both muscle fiber conduction velocity and the frequency content of the EMG signal (Bigland-Ritchie et al., 1981; Brody et al., 1991; Broman et al., 1985). However, conduction velocity and EMG frequency do not change in parallel (Brody et al., 1991; Broman et al., 1985; Merletti et al., 1990; Beck et al., 2017), indicating that factors other than muscle fiber conduction velocity influence the frequency response. Although motor unit firing rate has little influence on the frequency spectrum, the prolonged duration of the motor unit action potential strongly associates with the compression of EMG frequency (McManus et al., 2015). Therefore, the consistent declines in both EMG amplitude and the EMG frequency content that are observed during a sustained MVC reflect both central and peripheral aspects of muscle fatigue (Bigland-Ritchie et al., 1981; 1986a; 1986b; De Luca, 1985). It is important to note that the interpretation of the EMG response requires careful design considerations as a variety of physiological and non-physiological factors can modulate the signal. The most faithful interpretations that can be made from the EMG signal are performed within-subject and relate to the level of muscle activation, muscle activation kinetics, and the relative level of muscle activation (Vigotsky et al., 2018).

It has been hypothesized (Marsden et al., 1983) that the slowing of the motor units firing rates is a compensatory mechanism to match the fatigue-induced elongation of its twitch mechanics (i.e., the muscle wisdom hypothesis). The basis for this hypothesis comes from the observations (Bigland-Ritchie et al., 1983) that motor unit firing rate and contractile speed were reduced in a similar time-dependent manner. Theoretically, this would delay fatigue by shifting the force-frequency relationship

towards lower frequencies (Bigland-Ritchie, 1984). Instead, more recent data (Fuglevand and Keen, 2003) has shown that force loss is accentuated through reduced motor unit firing rates, yet better preserved with high (physiological) rates of activation. These observations (Fuglevand and Keen, 2003) together with the consistent reports of reduced voluntary activation demonstrate a failure of the nervous system to drive the motor neurons maximally (Bigland-Ritchie et al., 1982; Gandevia et al., 1996).

However, the delineation of neural versus peripheral elements of fatigue is confounded by occlusion studies that clearly show a sensory-mediated reduction of central motor drive when a muscle is rendered ischemic following fatigue. For instance, maximal force, motor unit firing rates, EMG amplitude, and voluntary activation remain depressed during ischemic-rest, despite the recovery of corticospinal excitability (Bigland-Ritchie et al., 1983; Marsden et al., 1983; Bigland-Ritchie et al., 1986a; Woods et al., 1987; Gandevia et al., 1996; Taylor et al., 1996; Taylor et al., 2000; Butler et al., 2003b). Thus, it is possible that group III and IV afferents elicit a sensory-mediated reduction of voluntary activation through a reduction of central motor drive (Amann et al., 2011; Amann et al., 2013; Taylor and Gandevia, 2008; Taylor et al., 2016). These findings, and others (Blain et al., 2016; Hureau et al., 2014), bolster the recently proposed 'sensory tolerance limit hypothesis', a hypothetical construct that incorporates the magnitude of afferent feedback with the corresponding level of central motor drive (Hureau et al., 2018). Interestingly, the model highlights observations of individually specific levels of intramuscular perturbation at the end of maximal isometric and whole-body exercise (Amann et al., 2011; Blain et al., 2016; Burnley et al., 2010). Although enhanced feedback from Group III and IV muscle afferents

diminishes central motor drive, it is integral for the maintenance of adequate cardiorespiratory responses to exercise (Amann et al., 2011; Hureau et al., 2016; Taylor et al., 2016), thus demonstrating the highly integrated nature of the central and peripheral elements involved with muscle fatigue.

Studies that have employed sustained MVCs together with EMG and stimulation methods have demonstrated that both central and peripheral impairments contribute to force loss. The combined evidence shows that in conjunction with reduced contractile performance due to intramuscular perturbation, motor unit firing rates decline to suboptimal levels as central fatigue develops. The diminished motor unit activity that accompanies maximal contractions suggests two possibilities, fatigue-based alterations are expressed either by changes in the intrinsic excitability of the motor neuron or its responsiveness to excitatory synaptic input (Taylor et al., 2016).

2.2. Acute and Chronic Bilateral Limb Interactions.

This subsection provides novel data regarding acute and chronic interlimb effects mediated through unilateral fatigue and training. The focus is placed on unilateral and bilateral limb strength as opposed to interlimb coordination.

Howard and Enoka, 1991.

This study documented multiple features of interlimb interactions. The authors investigated: 1) the bilateral index of homologous and heterologous muscle groups, 2) the associated EMG response from these contractions, 3) the effects of unilateral limb stimulation on the maximal voluntary force of the contralateral limb, and whether the magnitude of this response was related to the inter-individual bilateral deficit. An important aspect of this study was that the groups (n = 6) consisted of untrained individuals, trained weightlifters, and trained cyclists. The participants performed unilateral and bilateral MVCs of the elbow flexors and knee extensors, and simultaneous MVCs of the left elbow flexors and right knee extensors. The main findings showed: 1) a bilateral deficit for the knee extensors of the untrained (-9.5 ± 6.8%) and cyclist (-6.6 ± 7.1%) groups, whereas the weightlifters (+6.2 ± 4.7%) experienced a facilitation, 2) there were no differences between groups for the bilateral index for the arm-leg task and the values were not significantly different from zero, there was a great deal of inter-individual variability (-16 to +26%) within and between groups, 3) the corresponding EMG responses were not significantly different between groups, however the weightlifting group showed a trend for facilitation (+13.7 ± 12.0) during bilateral knee extension, 4) all participants experienced significant unilateral facilitation of the left knee extensors when the right leg was stimulated, interestingly the

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magnitude was different for those with a bilateral deficit (+6.2 ± 3.6%) and a bilateral

facilitation (16.2 ± 7.4%). The findings from this study showed that a range of inter-

individuality in regard to bilateral force production and the bilateral EMG response did

not match those of force. The entirely novel finding presented in this study showed

unilateral limb stimulation resulted in a facilitation of force for the homologous

contralateral limb. The authors hypothesized that muscle stimulation facilitated the

contralateral limb force through a sensory-mediated augmentation of the descending

drive within the spinal cord. The observations presented in this study were important for

showing that the neural elements of interlimb interactions vary between individuals and

afferent feedback manipulates these interactions.

Carr et al., 1994.

The purpose of this study was to examine surface EMG for right and left

homologous muscle pairs that are normally co-activated (i.e., masseter, rectus

abdominis, diaphragm) versus those which may activate independently (i.e., first dorsal

interosseous, biceps brachii, deltoid) to assess whether these different muscle types

possess a common innervation. The authors used cross-correlation analysis of the EMG

response from the simultaneous activation of right and left muscle pairs during a weak

isometric contraction to determine the presence of a common innervation for the

respective muscle pair. In addition, the authors used TMS to probe the descending

pathways of the homologous muscle pairs. The cross-correlation analysis revealed that

central peaks of short duration (11 – 13ms) were observed for the right and left muscle

pairs of the masseter, rectus abdominis, and diaphragm. These findings were not

observed in the upper limb muscles. Interestingly, when unilateral TMS was applied

over the left motor cortex, bilateral short latency EMG responses were observed for the right and left muscle pairs for the masseter, rectus abdominis, and diaphragm. Yet, for the upper limb muscles, only contralateral short latency EMG responses were observed. The authors reported that the size of these responses was greater for the distal muscles (i.e., the FDI) and suggest that differences in the strength of the corticomotoneuronal pathway may explain this observation. The authors summarize their findings to indicate that right and left axial homologous muscle pairs share a common innervation, likely through the corticospinal pathway, and thus exhibit a common drive from the CNS when activated. The EMG and TMS findings for the upper limb muscles showed no evidence for shared bilateral projections to homologous motoneuron pools.

Herbert and Gandevia, 1996.

This study was the first to examine the bilateral deficit phenomenon for small hand muscles. The authors examined the level of voluntary activation for the adductor pollicis muscle (n = 11, 6 female, 10 right hand dominant) during maximal bilateral contractions of both thumbs, and when participants performed maximal elbow flexions of the contralateral arm. The authors assessed voluntary activation through nerve and cortical stimulation. The authors observed that the participants could fully active their thumb adductor in only ~22% of trials, with a median value of 90.3% (range: 81.2 – 100%). In agreement with previous reports, there was no effect of bilateral heterologous contractions of the maximal level of force and voluntary activation. However, during maximal bilateral thumb adduction, there was a significant, though small decline in maximal force and voluntary activation (~2%). The authors questioned whether this decline has meaningful physiological and practical importance. An important aspect of

this study relates to the controlled postural stability during the force assessments of the thumb adductors, given the sole innervation to the adductor pollicis which is not shared by its antagonists, the negligible influence of synergists, and the lack of postural compensations, the results provide a robust level of interpretation regarding the bilateral deficit for small muscles of the hand.

Jakobi and Cafarelli, 1998.

This investigation sought to characterize the three possible mechanisms that could explain the bilateral force deficit phenomenon in the leg extensors. The authors specifically examined agonist EMG activity, antagonist EMG activity, and average motor unit firing rates during submaximal contractions. They also compared the rate of force development and muscle activation, as well as the response from the interpolated twitch technique. The findings of this study provided no support for the bilateral deficit, as there was no significant difference in maximal force, EMG amplitude of the vastus lateralis nor the biceps femoris, the rate of force development or muscle activation, or the average motor unit firing rates during submaximal contractions between unilateral and bilateral leg extensions. The authors discussed that for there to be a genuine bilateral deficit, the neuromuscular system must exhibit an alteration in either descending drive (i.e., decreased agonist motor unit recruitment and/or firing rate) or antagonist muscle coactivity, and the results of this investigation did not provide any evidence for this. The authors discussed how many studies that had observed a bilateral deficit prior to this investigation examined muscles of the upper extremity. The observation that on average the participants of this study could maximally activate ~90% of the quadriceps during unilateral and bilateral leg extension supports the notion

that muscles which exhibit lower ceilings for motor unit recruitment may be more susceptible to a bilateral deficit.

Zijdewind et al., 1998.

These authors examined the cross-over effects of fatigue for the first dorsal interosseous muscles during sustained submaximal isometric contractions (30% MVC) to task failure. The participants (n = 7, 4 females, 1 ambidextrous) performed a sustained contraction to failure of the right index finger then immediately performed the same task with the left finger. After thirty minutes of recovery, the participants performed the same task again for the left finger. Intermittent MVCs with twitch interpolation were performed every 30 seconds. The authors reported that the twitch interpolation superimposed during MVCs elicited a twitch more often during the first fatigue protocol for the left finger compared to the right (78 ± 15% versus 58 ± 28%; paired t-test, $p < 0.05$). There were no other meaningful differences between the conditions. The authors suggested that the limited cross-over effects observed with their intervention may be related to insufficient intensity or duration.

Hortobágyi et al., 1999.

This study demonstrated greater magnitudes of cross-education with unilateral training when the trained limb received stimulation. The participants were divided into four groups (n = 8, all female): a voluntary training group, a stimulation group, a nonlocal stimulation group, and a control. The training protocol consisted of isokinetic eccentric contractions of the left knee extensors at 60°/s. Training duration was 6 weeks and required 4 sessions a week with progressive volume (i.e., 4 sets of 6-8 reps, 6 sets of 6 – 8 reps). Maximal grip strength for both hands was also tested. Maximal eccentric

and isometric strength were tested with and without local stimulation. The results showed that the stimulation group demonstrated that the greatest level of cross-education for eccentric (104%) and isometric (66%) strength with stimulation. However, the level of cross-education for isometric strength was similar (p > 0.05) for the voluntary (19%), stimulation (27%), and nonlocal stimulation (28%) groups without stimulation. Maximal EMG was not different between groups, yet when collapsed across groups there were 20 and 33% increases during isometric and eccentric testing. This study was important for demonstrating that 1) the magnitude of cross-education was augmented through the stimulation of the homologous muscle groups during training, 2) eccentric training produced large, training-specific interlimb strength transfer, 3) local muscle stimulation significantly increased knee extensor strength for both isometric and eccentric contractions, 4) no change in grip strength was observed for either arm. The authors suggested that these observations challenge the cross-activation hypothesis and instead they hypothesized a dominant role for adaptations at the spinal cord level.

Todd et al., 2003.

This study examined whether unilateral elbow flexor fatigue influenced contralateral elbow flexor strength, voluntary activation, and intracortical inhibition. The participants (n = 10, 3 females) performed two different sustained MVC protocols. Specifically, the first protocol required them to perform a sustained unilateral MVC for 1 minute and then immediately perform the task for the contralateral elbow flexors for a total of 2 minutes for each arm. The other protocol was the same except it was intermittent for one arm instead of alternating. Transcranial and peripheral nerve

stimulation was performed at specified intervals. Voluntary force declined by ~35-45%

during each sustained MVC, yet interestingly the two different protocols did not show

time-dependent differences in the relative amount of force loss. However, the

alternating protocol resulted in lower levels of voluntary activation (-4.1%) during the

second sustained MVC. The size of the MEP and cSP increased during each sustained

MVC but did not differ between protocols. Collectively, this study demonstrated that

unilateral elbow flexor fatigue imposes slight decrements in voluntary activation for the

contralateral arm.

Lagerquist et al., 2005.

This study examined the effects of five weeks of unilateral isometric strength

training of the dominant plantar flexors on MVC and H-reflex in both limbs. The

control (n = 6) and training group (n = 10) were tested for MVC of the plantar flexors

along with soleus H-reflex amplitude in both limbs before and after the training

intervention. The training intervention consisted of five sets of eight, six second MVC's

with 1-second rest between repetitions and 1-minute rest between sets. The authors

observed significant increases in MVC for both the trained (15.3%) and untrained

(17.9%) legs of the training group. H-reflex amplitudes on the ascending limb of the

recruitment curve were increased (25.4%, p = 0.04) in the trained leg but not the

untrained leg (24.4%, P = 0.30). The maximal H-reflex and M-wave were unchanged by

training. There were no changes for any of the variables in the control group. The

increased H-reflex for the trained leg indicates adaptations for the Ia spinal reflex

pathway, that may be a result of increased descending drive of motor neuron

excitability, altered presynaptic input, and/or postsynaptic facilitation and inhibition.

The differential responses between limbs show that spinal and supraspinal centers uniquely adapt to unilateral training. Specifically, these observations show that spinal reflex excitability did not account for the improvements in muscle strength for the untrained limb, suggesting that supraspinal sites were responsible for the improvement in strength. The authors concluded that the increased somatosensory input for the trained limb, paired with the descending drive, synergistically potentiated the Ia reflex pathway. The improvements in strength for the untrained limb despite the lack of somatosensory input reflects supraspinal adaptations, possibly reflecting Hebbian plasticity of paired neural inputs.

Škarabot et al., 2016.

The purpose of this investigation was to investigate transcallosal or corticospinal pathways during unilateral and bilateral contractions of the leg extensors. The specific aims were to determine if interhemispheric or intracortical inhibition contributed to the bilateral deficit phenomenon between a trained bilateral (n = 7 weightlifters), trained unilateral (n = 5 jumpers) and a control group (n = 8). The authors assessed the ipsilateral silent period and the cortical silent period with TMS to evaluate transcallosal and corticospinal pathways, respectively. The target muscle group was the vastus lateralis, and the supporting outcome variables were: voluntary activation, motor evoked potentials (MEP), EMG activity normalized to the maximum compound action potential (M_{Max}), and the duration of the silent periods. The contralateral and ipsilateral response of these variables were evaluated. The results of the study showed no interaction amongst groups. The three main findings indicated that (1) bilateral deficit was present for the whole sample (force: $-8.76 \pm 13.4\%$ $p<0.05$; EMG amplitude: -

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2.67± 14.2%, p>0.05), but not for individual groups, (2) there were no differences in the properties of the cortical and ipsilateral silent periods between bilateral and unilateral contractions, and (3) voluntary activation (~97% versus 92%) and the size of the MEP from contralateral and ipsilateral muscles were greater during bilateral compared to unilateral contractions. The TMS responses in this study indicate that neither transcallosal nor intracortical inhibition contributes to the bilateral deficit. Surprisingly, both contralateral and ipsilateral MEPs were greater during bilateral compared to unilateral contractions, indicating bilateral facilitation. It is important to note that the silent period evoked by TMS, whether interhemispheric or intracortical, is a measure of inhibition; whereas the size of MEP is indicative of excitation. The average ipsilateral MEP was ~24% greater during bilateral contractions. It is believed that excitatory axons cross the corpus callosum and modulate the ipsilateral silent period through action on contralateral inhibitory neurons in the contralateral motor cortex, and the authors hypothesized that during bilateral contractions of the lower limbs, the firing rate of the excitatory axons is reduced resulting in disinhibition of the contralateral projections in the motor cortex. The authors further discussed how the apparent bilateral facilitation, evidenced by the enhanced transcallosal (ipsilateral MEP) and corticospinal (contralateral MEP), may be influenced by corticoreticulospinal or corticopropriospinal projections. Finally, the authors discussed the fact that lower limb movements possess stronger spinal cord circuitry and are distributed over cortical, cerebellar, and subcortical brain regions. For this reason, it is not possible to exclude the existence of inhibition or facilitation at sub-cortical levels of the neural hierarchy for lower limbs. In conclusion, the unaltered silent periods, greater MEP values and voluntary activation

levels during bilateral contractions show that transcallosal and corticospinal inhibition is not related to the bilateral deficit, instead, the possibility of cortical facilitation during bilateral contractions are suggested.

Boyes et al., 2017.

The primary purpose of this study was to compare the effects of training frequency on the magnitude of cross-education. The rationale for this relates to the development of an at-home training intervention that may be used to restore limb muscle symmetry. Participants were randomly assigned to either a high-frequency (HF: n = 10) or low-frequency (LF: n = 9) training group that was matched for training volume. The training intervention was 4 weeks in duration and was performed at home. The mode of training was isometric handgrip contractions with a handgrip trainer with approximately 90-100% of their maximal isometric grip strength. The total number of contractions for both groups was 120 per week, where the LF group performed 5 sets of 8 repetitions on 3 separate occasions per week, and the HF group performed 2 sets of 6 repetitions on 10 separate occasions per week (i.e., twice per day for five consecutive days). Each repetition was performed for 3 seconds with 3 seconds rest, rest between sets was 1 minute. The authors assessed training compliance with a training log. All of the participants were right-hand dominant. The outcome variables were maximal isometric handgrip strength, forearm muscle thickness, maximal isometric wrist flexion, and EMG amplitude. The results showed that for the HF group, grip strength was increased by 6.1% and 8.4% for the right and left arm, respectively. And for the LF group, grip strength was increased by 9.7% and 9.8% for the right and left arm, respectively. The analysis for muscle thickness showed that when collapsed across

group, right limb muscle thickness was significantly increased for the HF (2.4%) and LF (3.4%) groups. There were no significant changes for the untrained limb. The authors observed no significant changes in wrist flexion strength or EMG amplitude. The results of this study showed that volume-matched training frequency did not influence the strength and hypertrophy gains for the trained limb. Moreover, the two groups showed similar task-specific cross-education of strength for the untrained limb following training.

Souron et al., 2017.

This study examined the effects of eight weeks of unilateral local vibration training (LVT) of the right tibialis anterior muscle on MVC, cortical voluntary activation, motor evoked potential (MEP), cortical silent period (CSP), and H-reflex for both legs. These tests were performed at baseline, after four and eight weeks of training, and two weeks after training cessation. The authors parsed the participants into a training (n = 22, 14 female) and control (n = 22, 10 female) group. The vibration training group received twenty-four, 1-hour sessions of local vibration of the right tibialis anterior muscle at 100 Hz. The results showed that MVC was increased after four (7.4, 6.2%) and eight (12.0, 10.1%) weeks of training for the trained and untrained legs, respectively. In addition, voluntary activation was significantly increased after four (4.4, 4.7%) and eight (4.9, 6.2%) weeks of training, and these variables remained elevated after the two weeks of training cessation. MEP, CSP, and H-reflex did not change as a result of training. Therefore, the increased MVC and voluntary activation for the trained and untrained limb despite no observable changes in corticospinal excitability (i.e., MEP), spinal excitability (i.e., H-reflex), and intracortical inhibition

(i.e., CSP), suggests that supraspinal sites are responsible for the increased strength and cortical voluntary activation values observed in the present study. The authors speculate that bilateral activation of the somatosensory and motor cortex elicited via the tonic vibration reflex may explain the cross-education of strength in the present experiment.

2.2.1. Summary.

There are numerous examples of the complexity in which bilateral limb interactions occur. From the lateralization of hemisphere dominance to the transfer of strength to the untrained limb with unilateral training, it is clear that multiple segments along the nervous system exhibit *simultaneous* inhibitory and excitatory processes. This summary will focus on the interlimb interactions that occur during maximal bilateral contractions, unilateral fatigue, and unilateral training.

Since it was first documented (Henry and Smith, 1961), the bilateral deficit phenomenon has received considerable attention but has been met with mixed results and continued debate. The bilateral deficit is defined as the reduction of maximal force during bilateral contractions of *homologous* muscles compared to the summed forces of both limbs during maximal unilateral contractions (Jakobi and Chilibeck, 2001). A reduced capacity of maximal force production would represent a limitation of the neuromuscular system, thus identifying the locus may attenuate its effects through training (Howard and Enoka, 1991). A recent review reported that ~70% of the investigations regarding the bilateral index have observed the bilateral deficit effect (Škarabot et al., 2016). Importantly, the magnitude varies depending on a variety of factors. For instance, the muscle groups involved, training status, posture, the mode of contraction, the speed of contraction, and upper versus lower limb musculature can

influence the consistency, direction, and magnitude of the bilateral deficit (Jakobi and Chilibeck, 2001; Škarabot et al., 2016)

The bilateral deficit has consistently been observed during isometric contractions for the muscles of the upper limb, on average showing a $-9 \pm 8\%$ deficit (Škarabot et al., 2016). There have been several mechanisms hypothesized to contribute to the bilateral deficit, psychological factors such as an increased sense of exertion and a division of attention, task demands relating to familiarity, limb dominance, postural stability, and biomechanics. Yet, it is most likely that neural mechanisms are involved (Jakobi and Chilibeck, 2001; Škarabot et al., 2016). The strongest support for a neural contribution to the bilateral deficit is demonstrated by the observations showing no deficit of maximal force, EMG, or voluntary activation during maximal contractions of heterologous muscles (Howard and Enoka, 1991; Herbert and Gandevia, 1996). In addition, increased antagonist activity (Koh et al., 1993; Jakobi and Cafarelli, 1998) or spinal reflex inhibition (Howard and Enoka, 1991; Cattagni et al., 2018) likely does not account for the bilateral deficit. For instance, it has been observed that unilateral muscle stimulation provides spinal reflex facilitation, as it increases the MVC of the contralateral homologous muscle (Howard and Enoka, 1991; Cattagni et al., 2018). Instead, it is likely that supraspinal mechanisms have a dominant role. Both inhibitory and excitatory cortical mechanisms have been hypothesized to contribute to the bilateral deficit. Specifically, increased interhemispheric and intracortical inhibition, along with decreased corticospinal excitability are plausible mechanisms, but it has recently been demonstrated (Škarabot et al., 2016) that neither of these factors was associated with the bilateral deficit during knee extension in trained athletes. In fact, the

electrophysiological data suggested evidence of bilateral facilitation, as corticospinal excitability and voluntary activation were greater during bilateral contractions (Škarabot et al., 2016). Although it is apparent that central motor drive is impaired during maximal bilateral contractions, the inhibitory influences are yet to be determined but may reside in areas upstream of the primary motor cortex.

The effects of local muscle fatigue on the performance of contralateral homologous and heterologous muscle groups have received considerable attention recently. This is likely due to the unique examination of central fatigue processes that are offered through this line of inquiry. Indeed, there have been reports of 'cross-over' and 'non-local' reductions in strength and performance for muscles not involved in the fatiguing task (Zijdewind et al., 1998; Todd et al., 2003; Rattey et al., 2006; Post et al., 2008; Kennedy et al., 2013; Sidhu et al., 2014). An important distinction must be made between the cross-over and non-local effects of fatigue. The cross-over of fatigue refers to the transfer of fatigue to the contralateral homologous muscle group, whereas the non-local effects of muscle fatigue refer to a reduction of performance for any contralateral, ipsilateral, inferior, or superior muscles (Halperin et al., 2015). Nevertheless, these two models provide similar insight regarding the mechanisms contributing to the central manifestations of fatigue.

There is a great deal of variability in the reported magnitude, and even the existence of the non-local and cross-over effects (Halperin et al., 2015). For example, a thorough review has recently shown that approximately half of the studies investigating the non-local effects of fatigue have observed impairments in either strength or performance of non-involved muscle groups. Importantly, the observations for the

upper limbs are particularly conflicting, as only ~32% of studies have documented non-local effects of fatigue for the upper limbs. Moreover, the magnitude of the cross-over effects on force loss are relatively small for the upper limbs (~2 – 8%) compared to the lower limbs (~8 – 13%) (Halperin et al., 2015; Martin and Rattey, 2007; Post et al., 2008; Rattey et al., 2006; Todd et al., 2003; Zijdewind et al., 1996). These discrepancies are not fully understood, though several factors have been suggested. Some of the anatomical and physiological factors that may account for the different magnitudes of cross-over effects between upper and lower limbs relate to the total muscle mass, the number of motor units, motor unit recruitment thresholds and ceilings, muscle fiber types, and the circuitry of postural versus dexterity-based muscles (Todd et al., 2003; Post et al., 2008; Halperin et al., 2015). Other factors related to the fatiguing intervention are also important to consider. Although the data is sparse, it appears that repeated high-intensity contractions produce greater cross-over effects compared to submaximal or sustained contractions (Aboodarda et al., 2015; Halperin et al., 2015; Ye et al., 2017). Lastly, it appears that sex moderates the magnitude of fatigue cross-over. It has been observed that females exhibit a lower level of transfer to the non-fatigued knee extensors compared to males (Martin and Rattey, 2007; Ye et al., 2017). Specifically, following repeated MVCs of the dominant knee extensors, the MVC value for the contralateral leg was reduced by ~10 and 13% for males and ~0 and 1% for females (Martin and Rattey, 2007; Ye et al., 2017). Moreover, these responses appear to be mediated by sex-related differences in the magnitude of central fatigue that is accrued with fatigue. The basis for this stems from observations (Martin and Rattey,

2007) that show greater deficits in voluntary activation for the contralateral, non-fatigued leg for the male (~9%) compared to the female (~3%) groups.

There are several mechanisms that may be responsible for the non-local and cross-over effects of fatigue that have been observed. A hypothesis that has been extensively considered relates to reduced central motor drive due to both physiological and psychological factors mediated by group III and IV afferents (Martin and Rattey et al., 2007; Amann et al., 2013; Halperin et al., 2015). The inhibitory actions of group III and IV afferents delivered to the central nervous system from the fatigued muscle increases the level of perceived exertion, and even more, there is evidence that the feedback delivered by these afferents augments the level of supraspinal fatigue for non-local muscles (Sidhu et al., 2015). More specifically, following exhaustive lower limb fatigue, elbow flexor MVC and voluntary activation were significantly reduced; however, when a local anesthetic was used to block afferent feedback from the lower limbs, elbow flexor MVC and voluntary activation remained unchanged (Sidhu et al., 2015). These findings (Sidhu et al., 2015) likely provide the strongest evidence for the involvement of group III and IV afferents in the development of central fatigue. Interestingly, unilateral elbow flexor fatigue produced no contralateral effects of force, EMG, or voluntary activation, yet increased corticospinal excitability (MEP) and decreased spinal motor neuron excitability (CMEP). Together, the evidence suggests that supraspinal adaptations occur with fatigue and modulate the strength and performance capacity of non-involved muscles, though this may be muscle dependent (Halperin et al., 2014; Halperin et al., 2015).

Another strong example of bilateral limb interaction is seen through chronic unilateral strength training. Following a unilateral strength training program, muscle strength and motor skill are transferred to the untrained, contralateral muscle pair. This effect is commonly referred to as cross-education. The mechanisms which underpin the improvement in maximal muscle strength and the transfer of motor skill to the untrained limb with unilateral training likely have a cortical origin (Farthing et al., 2009; Ruddy and Carson, 2013). Moreover, two uniquely different theoretical models have been put forth to explain how cortical adaptations mediate the cross-education of strength, they are not mutually exclusive, and both describe the complex interhemispheric interactions that may account for the observed adaptations of the ipsilateral (i.e., 'untrained') motor cortex. One theory, the 'cross-activation' hypothesis also referred to as the 'cross-facilitation' and 'spillover' hypotheses, reasons that the bilateral cortical activation that is generated with forceful unilateral contractions excites the contralateral homologous motor network, resulting in facilitation of the corticospinal projections. Evidence in support of the cross-activation hypothesis shows that after acute (Carroll et al., 2008; Lee et al., 2010) and chronic training (Lee et al., 2009; Hortobágyi et al., 2011), there are prolonged increases in the excitability of the contralateral homologous muscles. Another theory, the 'bilateral access' hypothesis posits that during unilateral training, a motor engram is formed and stored within sites that are accessible by the untrained motor cortex (Ruddy and Carson, 2013). The bilateral access model is particularly applicable for the acquisition of motor tasks requiring complex sequencing and coordination as opposed to maximal motor output (Taylor and Heilman, 1980). Though these models depict different processes of cross-education, they are more similar than

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they are different in that interhemispheric plasticity is the basis for the interlimb transfer.

The precise neuronal locus that is responsible for cross-education is not known. However, there is strong evidence that unilateral training produces rapid adaptations within the ipsilateral motor networks (Carroll et al., 2008; Lee et al., 2010; Stöckel et al., 2016). The complexity of which is evidenced by the contralateral improvements in strength observed with concentric, eccentric, and isometric strength training (Komi et al., 1978; Hortobágyi et al., 1997; Carroll et al., 2008; Coombs et al., 2016), unilateral muscle vibration (Souron et al., 2017) and stimulation (Hortobágyi et al., 1999), even imagined unilateral contractions have produced contralateral improvements in strength (i.e., motor imagery) (Yue and Cole, 1990). These findings show that multiple sites along the central nervous system, from motor planning to sensorimotor centers, adapt to yield contralateral improvements in strength. The various training interventions and magnitudes of transfer reported demonstrate the challenge for identifying one, unifying site of adaptation. Nevertheless, a recent systematic review (Manca et al., 2018) of the neural substrates that adapt to unilateral training has provided some direction. The authors (Manca et al., 2018) reported that there were generally no significant changes for EMG amplitude, M-wave, and H-reflex responses. Moreover, the changes in corticospinal excitability for the untrained hemisphere are controversial, with reports of increases (Griffin and Cafarelli, 2007; Carroll et al., 2008; Goodwill et al., 2012) and no change (Carroll et al., 2002) after training. Importantly, reductions in intracortical and interhemispheric inhibition from the trained to untrained motor cortices appear to be strong candidates for the neural mediation of cross-education. In theory, greater

corticospinal excitability and reduced interhemispheric and intracortical inhibition for the ipsilateral motor cortex may be interpreted as stronger synaptic facilitation for the intended motor program. This facilitation would shift the excitatory-inhibitory balance along the cortical, subcortical, and spinal tracts, providing greater neural drive to the motor neuron pools. Collectively, the available data support both the cross-activation and bilateral-access hypotheses as ipsilateral mediators of cross-education.

The influence of limb dominance on the transfer of fatigue, strength, and skill remains unresolved (Farthing et al., 2005; Farthing, 2009; Coombs et al., 2016, Halperin et al., 2014; Halperin et al., 2015; Ruddy, 2017). There is a hypothesis that greater strength and skill transfer occurs from dominant to non-dominant limbs (Farthing et al., 2005; Jensen et al., 2005; Farthing, 2009; Parlow et al., 1989) and has been credited to the greater proficiency of the dominant limb and stronger neural networks, thus allowing for a rapid training acquisition that is better transferred to the non-dominant limb. However, this hypothesis is undermined by the studies that have observed non-dominant to dominant limb transfer of fatigue (Halperin et al., 2014), strength (Coombs et al., 2016), and motor skill (Aiken et al., 2015; Hinder et al., 2013; Ruddy et al., 2016). Critically, it appears that task novelty, complexity, and the visual attention directed to the movement strongly moderate the observed interlimb effects (Aiken et al., 2015; Ruddy et al., 2016; Poole et al., 2018). Sensorimotor integration is greater for the upper versus lower limbs (Ruddy et al., 2016), thus the majority of studies regarding dominant and non-dominant strength and skill transfer have examined the upper limbs.

The neural complexities of bilateral limb interactions are obvious. This is easily seen during simple unilateral isometric contractions, as highly integrated excitatory-inhibitory processes occur along the length of the central nervous system. Though far from a complete understanding, there are several lines of evidence that have identified key sites and mechanisms related to these interactions. Namely, it appears that areas upstream of the motor cortex have a vastly larger role in interhemispheric communication than has been previously considered (Ruddy, 2017; Ruddy et al., 2017). For instance, the greater density of interhemispheric connections between the premotor and supplementary motor areas compared to the primary motor cortex suggests that these sites support a high volume of colossal traffic (Ruddy et al., 2016). Moreover, there is evidence that interhemispheric motor communication is much greater for the areas involved in movement preparation and planning (Ruddy et al., 2016; Ruddy et al., 2017), further supporting the mediating roles of visual input and attention on the interlimb transfer effects. Yet, several questions remain regarding interlimb interactions. Although bilateral fatigue (Vandervoort et al., 1984; 1987) has been used to examine the bilateral index, and unilateral fatigue has been used to examine the cross-over effects, there is a lack of understanding regarding the contralateral adaptations that occur following unilateral fatigue during a maximal bilateral contraction. In theory, this may further demonstrate compensatory interhemispheric adaptations. Moreover, the observations that females have a greater resistance to the cross-over effects of fatigue (Martin and Rattey, 2007; Ye et al., 2017), yet demonstrate similar magnitudes central fatigue (Hunter et al., 2006) and cross-education compared to males is challenging to

reconcile (Hendy et al., 2017; Manca et al., 2018). These discrepancies demonstrate the need for more data regarding the effects of bilateral limb interactions.

2.3.1. Mirror Visual Feedback, Action Observation, and Motor Imagery.

This subsection provides novel evidence related to the acute and chronic adaptations mediated through mirror visual feedback. It should be noted that mirror visual feedback, along with motor imagery, are forms of action observation. All three modalities are hypothesized to activate the mirror neuron system. Therefore, novel findings related to mirror visual feedback, action observation, and motor imagery are provided for completeness.

Gandevia et al., 1997.

This study examined the effects of motor imagery on motor neuron and muscle spindle activation and the H-reflex response. Specifically, the participants (n = 12) were instructed to imagine either relaxation or complex motor tasks of the wrist (i.e., alternating flexion and extension, handwriting tasks) and EMG and H-reflex, and microneurographic measurements were performed on the flexor carpi radialis or extensor carpi radialis. The findings from this study showed that mental rehearsal did not influence muscle spindle discharge. Notably, motor imagery did increase motor neuron activation, yet in some instances, it did activate muscle spindle discharge. Baseline EMG levels for both the flexor carpi radialis and extensor carpi radialis significantly increased during motor imagery for the majority of the participants. A novel finding of this study was that motor imagery augmented H-reflex amplitude (~10 – 15%) for both muscles. Together, these findings show that motor imagery not only activates motor neurons involved in the imagined movement but also augments the descending inputs to spinal reflex circuits.

Buccino et al., 2001.

      This study provided crucial evidence in support of the mirror neuron system in humans and its task-specific involvement. The authors had participants observe actions of the mouth, hand, and foot while fMRI measurements were taken. Control conditions consisted of viewing the same body part in a static position. The results of the study showed that action observation of different body parts activated different areas within the premotor cortex. The authors showed that during action observation, there was a bilateral activation of the ventral premotor and supplementary motor areas and the pars opercularis. Moreover, the authors reported that there was a defined shift in the activation of the premotor cortex from ventral to dorsal as the action observation shifted from the mouth, hand, and foot, respectively. This somatotopic organization is in line with the known motor arrangement of this region. Action observation also activated a part of the parietal cortex that surrounds the superior temporal sulcus. The authors summarize their findings to indicate that the cortical structures involved with the execution of the movement are also activated through the observation of that *specific* action.

Garry et al., 2005.

      This study provided substantial evidence for the cortical effects of illusionary mirror visual feedback. The authors had the participants (n = 8, 4 female) view their arms in different arrangements. Specifically, the participants were instructed to view their active arm, inactive arm, a marker between arms, and the mirror image of the active arm superimposed onto the inactive arm, both at rest and during simple finger movements. During these viewing conditions, the authors examined corticospinal excitability of the ipsilateral motor cortex. It was observed that ipsilateral motor cortex

excitability was greater during hand movement compared to rest. Yet, the largest

corticospinal excitability responses for the ipsilateral motor cortex were observed

during mirror viewing. In addition, there was no effect of hand dominance on the

responses. The authors suggested that greater intracortical facilitation or decreased

inhibition may account for their observations.

Calvo-Merino et al., 2006.

This study was critical for demonstrating that mirror neuron activity elicited

through action observation is highly dependent on the familiarity of the motor act. The

authors showed this by having expert male and female ballet dancers observe either sex

perform a familiar dance routine while fMRI scans were performed. The authors

demonstrated heightened levels of activity in the premotor, parietal, and cerebellar

circuits when the dancers observed routines from their own motor repertoire. These

findings are important because they showed that we not only process the visual input of

a motor act, but we understand the specific act through internal motor representations.

In other words, these results show that motor familiarity, not visual familiarity,

underlies the physiological basis of the mirror neuron system during action observation.

An interesting finding of this study was that there was no activation of the superior

temporal sulcus during observation, leading the authors to suggest that this system is

more involved with visual processing.

Tsutsumi et al., 2011.

This is the only study that has examined the influence of mirror visual feedback

on the development of fatigue. The authors had the participants (n = 12 males, all right

hand dominant) perform 60, 1-second isometric handgrips of their left hand with and

without mirror visual feedback. Before and after the fatiguing intervention the maximal

handgrip force for both hands was determined. The results showed that handgrip forces

for the contralateral hand were significantly reduced following fatigue, but there were

no differences between visual feedback conditions. The novel finding of this study was

that mirror visual feedback attenuated the magnitude of force loss for the fatigued hand

after the fatiguing protocol. Although novel, this study has several limitations that

severely limit the interpretations of its results. For instance, the fatiguing protocol

employed in this study is questionable. Although it used a 50% duty cycle, the short

duration of each contraction (1 second) and total duration (1 minute) is likely

insufficient to observe meaningful centrally mediated changes in performance, it may

even be that the repeated 1-second contractions produced a potentiation like effect.

There were no measurements other than isometric grip strength, and the authors only

reported pre- and post-fatigue MVC data. Additionally, the others didn't provide any

relative measurements for a more robust extrapolation of their data. Although

interesting, this study provides a very limited view of the effects of mirror visual

feedback on the progression of fatigue.

Gatti et al., 2013.

This study was important for delineating the similar and yet unique aspects of

motor imagery versus action observation in regard to acute motor learning. The authors

compiled a short review of the shared physiology of these types of interventions and

then presented original data which showed that action observation was superior to

motor imagery for the acquisition of a novel motor task. The authors discuss how two

experimental designs are typically used to study motor learning: 1) motor sequence

learning and 2) motor adaptation models. Importantly, both of these types of

assessments distinct motor learning phases may be distinguished into time-dependent stages: 1) acute, 2) consolidation; 3) slow; 4) automatic; 5) and retention phases. The authors point out that little is known about the most optimal way to start the motor learning process (i.e., acute motor learning phase) and therefore investigated two well-established strategies, action observation, and motor imagery, on the performance of a novel motor task. The participants (n = 45) were required to move their right hand and foot in the same angular direction while at the same time moving their left hand and foot in the opposite direction. The participants were randomly divided into three groups (i.e., action observation, motor imagery, control) and performed their respective protocol for 7 min. Importantly, the action observation group was shown a video of a male and female performing the novel motor task from four different planes (right and left, cranial and caudal). Kinematic data were recorded from the wrist and ankles during the execution of the movements and error time, the frequency of movement, and range of motion was compared between groups after the respective intervention. The results showed that action observation resulted in significantly less error time compared to motor imagery (3.3 ± 7.6 versus 20.1 ± 14.5 s; p = 0.002). The authors suggest that although the mirror neuron system underpins both motor imagery and action observation, the visual input delivered through action observation likely results in greater excitation of the system as the premotor cortex directly receives visual input. In summary, this was the first study to directly compare the efficacy of action observation versus motor imagery in the acquisition of a novel motor task. The authors suggest that action observation has a major role in motor learning, sports training, and neurorehabilitation.

Buccino, 2014.

This review focused on the utility of action observation as a neurorehabilitation tool. The author specifically analyzed the role of the mirror neuron system in relation to the beneficial functional outcomes resulting from action observation treatment. Neuroimaging evidence shows that action observation activates the same cortical structures involved during the actual execution of the observed action. As a neurorehabilitation tool, patients typically observe ~20 specific actions on a video that is ~12 minutes in duration, and importantly, different perspectives (i.e., lateral, frontal) are provided. This type of intervention builds a motor engram in healthy and clinical perceivers and is likely the wellspring of the functional adaptations that result. The author decomposed the findings of neuroimaging studies on stroke and Parkinson patients that underwent action observation treatment. The studies observed significant increases in the bilateral ventral premotor cortex, superior temporal gyrus, supplementary motor area, and the contralateral supramarginal gyrus after training. The functional improvements in these patients together with the increased activity of these cortical structures following action observation treatment shows that this type of intervention may reorganize neural circuits within frontal and parietal lobes that link to the motor cortex. It is important to consider that the activation of the mentioned cortical structures is dependent on the perceiver's familiarity with the observed action (i.e., motor repertoire). This was illustrated in a study (Calvo-merino et al., 2005) that showed higher cortical activation in professional dancers who viewed their respective style of dance compared to another style. Interestingly, however, action imitation also activates neural elements in the mirror neuron system (i.e., pars opercularis, rostral posterior parietal lobe, and Broca's area) that also correspond with areas responsible for

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motor learning (i.e., premotor cortex, dorsolateral prefrontal cortex). Finally, the author suggests that the relative magnitude and spatial distribution of cortical activation are largely determined by the depth of the immersive experience during action observation.

Graham et al., 2014.

This study is one of the few that have investigated mental imagery and fatigue responses. The authors randomized participants into either an imagery (n = 25, 16 female) or control (n = 25, 16 female) group. Both groups performed MVCs of their dominant wrist flexors and then sustained 50% MVC until task failure. After failure, the participants in the imagery group were instructed to imagine performing the same fatigue protocol again. The control group simply rested. Importantly, the recovery period for either group was 3 minutes and their arm was in the same position as it was during the fatigue task. After this period, the participants performed the exact same fatigue protocol again. EMG was collected from the flexor carpi radialis during both trials. The results showed that the imagery group had a significantly greater reduction in endurance time (-18.7% versus -4.6%, p = 0.003, d = 0.87) compared to control. Interestingly, when normalized to total endurance time for the second fatigue task, EMG amplitude was greater at baseline and 25% of endurance time for the imagery group compared to the control. Overall, this study showed that motor imagery during recovery exacerbates fatigue during an endurance task.

Deconinck et al., 2015.

This systematic review sought to coalesce the existing knowledge on the neurophysiology of mirror visual feedback with three general hypotheses regarding its clinical utility. The authors describe that the concept of reafference, the integration of perception and action, likely provides the basis for the cortical plasticity observed with

mirror visual feedback. Specifically, the generation of a motor command produces a paralleled efference copy of the expected sensory feedback. This efference-afference loop can be compromised in amputees, stroke patients, unilateral orthopedic, pain and motor disorders, and cerebral palsy. Mirror visual feedback may provide a means to attenuate the cortical restructuring that occurs in these conditions. The three hypotheses that have been put forth for the utility of mirror visual feedback relate to 1) the mirror neuron system; 2) activation of ipsilateral motor pathways, and 3) increased spatial activation of cortical structures brought about by increased observational attention. Importantly, these hypotheses are not mutually exclusive and all three are likely to be involved. The studies that were analyzed in this review showed that compared to control conditions, mirror visual feedback induces greater activity in ipsilateral and contralateral attention, motor, and mirror neuron system networks. Specifically, the activity of the ipsilateral occipital and parietal cortex, and the superior temporal and precentral gyrus is enhanced. In addition, activity in contralateral areas (i.e., posterior parietal and cingulate cortex, premotor cortex) involved with visuospatial processing and the acquisition of motor skills are elevated with acute and chronic mirror viewing. The analyzed studies show that unilateral versus bilateral mirror viewing likely produces unique activation of the involved cortical structures. Yet, the combined evidence strongly supports that mirror visual feedback produces beneficial performance adaptations through reductions in interhemispheric and intracortical inhibition. Altogether, the evidence presented in this review supports the combined involvement of all 3 hypotheses for the transfer of motor function through mirror visual feedback.
Di Rienzo et al., 2015.

This is one of the few studies that have examined the effects of motor imagery on force and EMG responses. Specifically, the authors examined MVC of the elbow flexors and EMG amplitude of the biceps brachii and anterior deltoid following 1) motor imagery of full muscle activation; 2) motor imagery of full muscle relaxation; 3) and a control condition. The results showed that motor imagery of muscle activation resulted in higher MVC values compared to motor imagery of relaxation (2.1%) and the control condition (3.5%). Interestingly, it was observed that motor imagery of muscle relaxation resulted in higher MVC values compared to the control condition (1.9%). There were no significant differences for EMG amplitude values between conditions. These results suggest that motor imagery alone may result in priming of the motor circuits involved in the intended action.

Zult et al., 2015.

The purpose of this study was to examine whether mirror-viewing of the right wrist at rest and during contraction influenced corticospinal excitability (MEP) and intracortical inhibition (SICI) of the ipsilateral motor cortex. The participants (n = 27, 5 female, all right-handed) arms were placed in a box so that they could only see the image of the mirror-illusion of the contracting (right) arm overlaid onto their left arm. Wrist flexions were performed at 20°/s and corresponded to 60% MVC. To assess corticospinal excitability and SICI of the ipsilateral motor cortex, TMS was delivered at rest and during contraction of the right wrist, with and without mirror viewing. The MEP and SICI were recorded from the left flexor carpi radialis and extensor carpi radialis for all conditions. The authors observed that corticospinal excitability of the left flexor carpi radialis was greater during contralateral (right) wrist flexion than at rest, but mirror viewing had no influence on the amplitude of the MEP. Interestingly, SICI for

the left flexor carpi radialis was reduced ~9% when the participants were mirror

viewing the contracting (right) wrist. In summary, this study showed for the first time

that action observation via mirror illusion of a limb reduces inhibition of the resting

contralateral muscle group. The absence of any effects for the extensor carpi radialis

suggests that mirror viewing primarily affects the agonist homologous projections, not

the antagonist. The authors speculate that mirror viewing of the contracting hand creates

a synchronous bimanual movement illusion in the ipsilateral motor cortex that may

result from interhemispheric interactions or from areas upstream of the motor cortex.

Importantly, these findings show that reduced SICI of the ipsilateral motor cortex may

be a mechanism that accentuates interlimb strength transfer during mirror training and

possibly action observation.

Zult et al., 2016.

This was the first study to examine the hypothesis that mirror training may

augment the cross-education of strength. The authors hypothesized that action

observation via mirror-viewing would augment the strength transfer via visual input to

the mirror neuron system, a network of neurons that are active during action

observation, thereby enhancing elements of the untrained motor cortex. Participants

were divided into a mirror training (MG, N = 11) and a non-mirror training group

(NMG, N = 12) and the participants performed 640 concentric contractions of the right

wrist flexors at 80% MVC during 15 training sessions across 3 weeks. The authors

examined maximal strength and specific markers of neuronal excitability via TMS

before and after the training intervention. The findings showed that the trained wrist

flexor MVC increased 72% across groups, but the cross-education of strength in the

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MG (61%) was greater than the NMG (34%, p = 0.047). The two TMS metrics that

showed training-induced changes were the contralateral silent period duration and

interhemispheric inhibition. The MG exhibited a reduction (15%) in the duration of the

contralateral silent period (cSP) during contraction of the left wrist flexors (flexor carpi

radialis) and the NMG showed an increase (12%, P < 0.03). Interestingly,

interhemispheric inhibition measured from the trained to the untrained primary motor

cortex, increased in the MG (11%), yet decreased in the NMG (15%, P = 0.048) when

measured at rest in the mirror setup. The increased corticospinal and motor cortical

excitability from the untrained motor cortex during dynamic contractions of the trained

wrist flexors and the lack of changes in corticospinal and motor cortical excitability for

the trained motor cortex supports the hypothesis that the untrained motor cortex is

involved in the cross-education of strength. The lack of changes in SICI further support

that hypothesis and add to the notion that $GABA_A$ receptor circuits have little role in

strength training. The interhemispheric inhibition data are challenging to reconcile but

indicate that the interhemispheric plasticity contributes to cross-education and adapts in

a training-specific manner. The authors speculated that the stimulus of the contralateral

motor cortex suppressed the activity of the ipsilateral motor cortex and may explain the

greater interhemispheric inhibition for the MG and suggest this to be studied further

specifically in stroke patients where interhemispheric inhibition maintains a critical

impairment. The authors discussed how the change of cSP provides the strongest

support for the mirror-training enhancement of cross-education, and that diminution of

this inhibitory path is fundamentally linked to $GABA_B$ – mediated intracortical

inhibitory circuitry and the cross-education of strength.

Ruddy et al., 2016.

This study presented two separate experiments which examined whether changes in corticospinal excitability or muscle activation were associated with the degree of cross-education during acute unilateral training of the nondominant limb with three unique vision conditions. Specifically, 3 groups of participants completed 300 rapid wrist flexion contractions of the nondominant arm with visual feedback of 1) the mirrored reflection of the training limb; 2) no visual feedback of either limb; 3) the inactive limb. The dominant (untrained) limb performance for the same task was tested before, halfway through, and following the training. The primary outcome variables were peak acceleration of the wrist flexion task, the rate of rise for EMG of the flexor carpi radialis, and the AURC of the MEP of the flexor carpi radialis to assess corticospinal excitability. These variables were measured for both limbs. The authors observed significant increases in peak acceleration for the training limb for the mirror (median = 36.84%), no vision (median = 27.88%), and inactive limb (median = 48.33%) groups, yet these improvements were significantly different between groups (p = 0.07). Importantly, the magnitude of cross-education, calculated as the change in performance of the untrained limb expressed as a percentage of the change in performance of the training limb, was significantly increased for the mirror (median = 146.5%; CI = 102.3 – 214.1%), no vision (median = 81.0%; CI = 16.4 – 102.%), and inactive limb (median = 52.3%; CI = 19.3-89.1%) groups, and the improvements for the mirror group were significantly greater (p < 0.01) compared to the no vision group. The EMG rate of rise was significantly shortened (i.e., improved) for both limbs and for both visual feedback conditions (i.e., mirror versus no vision). Moreover, for the

untrained arm, the decrease in the period of flexor carpi radialis EMG onset to maximum rate of rise was negatively correlated ($r = -0.46$, $p < 0.01$) with the degree of cross-education. In addition, the association between the pre to post changes in the maximum EMG rate of rise and the degree of cross-education approached significance ($r = 0.22$, $p = 0.08$). The authors found that the AURC for the trained flexor carpi radialis was increased for all groups, yet there was no evidence that corticospinal excitability was elevated in the contralateral flexor carpi radialis following training or associated with the degree of cross-education. When the datasets were combined for the 2 experiments and collapsed across groups, the degree of cross-education (expressed as a percentage of the change for the trained limb) was 82.44%. Interestingly, in the first experiment, the authors found that the degree of cross-education was greatest for the group that focused on the visual feedback of the training limb provided by a mirror, yet this finding was not replicated in the second experiment. The authors speculated that the association between the improved EMG rate of rise and the degree of cross-education may reflect adaptations in areas upstream of the motor cortex, likely the cortical areas involved with the initiation of movement (i.e., motor planning centers). An important aspect of this study was the recognition that the degree of cross-education is individual and task-dependent, as individuals may demonstrate a large variation in their capacity for motor imagery and likely their responsiveness to augmented visual feedback. Altogether, this study showed that the neural adaptions associated with cross-education express their training-related plasticity of brain areas upstream of the motor cortex.

2.3.1. Summary.

In the early 1990s, breakthrough advancements in our understanding of the visuomotor system and the plasticity of the adult human brain were made, subsequently paving the way for low-cost therapeutic interventions. In a classic experiment, the utility of mirror visual feedback was demonstrated when amputees whom exhibited phantom limb pain, a condition characterized by aberrant sensations (i.e., pain, ownership, movement) of the amputated limb (Ramachandran and Altschuler, 2000), placed their arm in a mirror box which provided the illusion of synchronized bilateral limb movements. Fascinatingly, some patients had instant relief, yet it took several training sessions for others, and for a few there was unfortunately no reprieve (Ramachandran and Rogers-Ramachandran, 1996). Since, MVF has been successfully used as a therapeutic modality for hemiparesis from stroke (Altschuler et al., 1999; Dohle et al., 2009), peripheral nerve complications (Rosen and Lundborg, 2005), and has recently been shown to augment the magnitude of cross-education in healthy individuals (Zult et al., 2016). Although the exact mechanisms that bring about these favorable outcomes are unknown, recent neuroanatomical evidence has provided some exciting insight.

The discovery of mirror neurons by Rizzolatti and his lab (Di Pellegrino et al., 1992) was critical for showing the influence of visual feedback on the properties of motor learning and action recognition. First documented in the primate brain, it was observed that mirror neurons in the ventral portion of the premotor cortex were active not only during the execution of a goal-directed motor act but also when observing others (primate or human) perform the same motor act. This groundbreaking discovery

showed that these neurons possessed both sensory and motor properties, and even more, *encoded* specific motor actions. Brain imaging techniques have since demonstrated the existence of a mirror neuron system within the human brain (Rizzolatti et al., 1996; Grafton et al., 1996; Molenberghs et al., 2012). This network is distributed across the visual areas of the occipital, parietal, and temporal lobes, with connections in the premotor, supplementary motor areas, and even the primary motor cortex (Rizzolatti and Craighero, 2004; Catteaneo and Rizzolatti, 2009; Rizzolatti and Fabbri-Destro, 2010). Together, the mirror neuron system integrates the visual, somatosensory, motor planning, and execution of observed goal-directed actions (Rizzolatti and Craighero, 2004). The combined evidence strongly supports the hypothesis that the mirror neuron system facilitates motor learning and skill acquisition through observation and imitation (Di Pellegrino et al., 1992; Rizzolatti et al., 1996; Grafton et al., 1996). It should be noted that mirror neuron system is distributed across the right and left hemispheres of the brain (Rizzolatti and Craighero, 2004; Howatson et al., 2013; Zult et al., 2014). Being so, both action observation and motor imagery (Jeannerod, 2001) bring about bilateral activation of motor planning, somatosensory, visual, and even language networks (Molenberghs et al., 2012). This bilateral cortical activation may very well be the crux of the interlimb facilitation mediated through MVF (Ramachandran and Altschuler, 2009; Cattaneo and Rizzolatti, 2009; Howatson et al., 2013; Zult et al., 2014).

The mirror neuron system lays the foundation for the efficacy of MVF as a therapeutic tool. Three general hypotheses have been suggested regarding the mechanisms that could mediate the positive functional outcomes of MVF (Deconinck et

al., 2014): (1) the action observation derived from MVF activates the mirror neuron system and reinforces the internal motor command for that action, (2) MVF may recruit the ipsilateral descending pathways (Benecke et al., 1991; Ramachandran and Altschuler, 2009), and (3) the illusionary MVF increases the level of attention dedicated to the hidden limb which may augment cortical excitability (Dohle et al., 2009). These hypotheses are not mutually exclusive, and it is likely that each one exerts an independent influence during MVF.

It should be acknowledged that several factors modulate the activation of the mirror neuron system and thus the effectiveness of the intervention: 1) the familiarity of the motor act, 2) the visual feedback (i.e., unilateral versus bilateral) delivered to the participant, 3) the interlimb proprioceptive congruence, 4) inter-individual differences in the capacity for motor imagery, 5) the immersive input provided, and 6) the attention towards the motor act (Calvo-Merino et al., 2006; Gatti et al., 2013; Buccino, 2014; Deconinck et al., 2014; Ruddy et al., 2016). For instance, different magnitudes of brain activation have been observed between professional dancers when observing their respective style of dance versus another (Calvo-Merino et al., 2006). In addition, the direct visual input delivered with action observation produces greater activation of the mirror neuron system compared to motor imagery, though the combined use has been suggested to augment the reinforcement of the internal motor command (Gatti et al., 2013; Buccino, 2014; Deconinck et al., 2015).

The few studies that have assessed the effects of MVF on brain activation and excitability have shown unique, yet conflicting, activation patterns of the contralateral and ipsilateral hemispheres compared to control conditions (Deconinck et al., 2014;

Zult et al., 2014; Ruddy et al., 2016). The most consistent observation reported with acute and chronic MVF is the increased activation and excitability of the ipsilateral motor cortex (Garry et al., 2005; Fukumura et al., 2007; Nojima et al., 2010; Tominaga et al., 2011; Hamzei et al., 2012). The limited data regarding interhemispheric and intracortical inhibition with MVF vary considerably between studies. There are reports of increased levels (Zult et al., 2016) and no change (Nojima et al., 2010; Läeppchen et al., 2012) of interhemispheric inhibition from contralateral to ipsilateral hemispheres, and decreased levels (Läeppchen et al., 2012; Zult et al., 2015; Zult et al., 2016) or no change (Nojima et al., 2010; Carson and Ruddy, 2012) of intracortical inhibition. Importantly, the augmented spinal reflex excitability that occurs with acute (Gandevia et al., 1997) and chronic (Grosprêtre et al., 2018) motor imagery may also be involved with the positive effects mediated through MVF, though this remains to be established. The remarkable effects of MVF on ipsilateral motor cortex excitability and possibly intracortical inhibition clearly demonstrate the clinical utility of this subtle, low-cost intervention.

An attractive aspect of MVF interventions relates to the increased activity it produces in regions that are also involved with cross-education. Indeed, a neuroanatomical link is hypothesized (Howatson et al., 2013; Zult et al., 2014) between the cortical structures that adapt with cross-education and their overlap with the mirror neuron system. A recent study (Zult et al., 2016) in healthy participants has supported this hypothesis as the group who trained with MVF experienced a ~27% greater magnitude of cross-education compared to the group that did not receive MVF, though the acute effects of MVF are still not established (Tsutsumi et al., 2011; Ruddy et al.,

2016). Collectively, the findings that bilateral motor, somatosensory, and visual networks are activated during action observation together with the increased ipsilateral motor cortex excitability through MVF suggests that elements of the mirror neuron system may be exploited for optimal rehabilitation design.

CHAPTER 3: METHODS

3.1. Participants.

This study was approved by the University of Oklahoma Institutional Review Board for Human Subjects (Appendix A). Thirty healthy, right-hand dominant males and females volunteered to participate in this study. The participant demographics are reported in Table 1. Before testing, the participants completed a health history questionnaire (Appendix B) to ensure that no orthopedic or neurological disorders were present, a handedness questionnaire (Appendix C), and they then read and signed an informed consent document (Appendix D). The a priori power calculations were calculated with G*Power software (Version 3.1.9.2) as described by the procedures of Beck (2013) based on the level of statistical significance ($\alpha = 0.05$), the desired power ($1 - \beta = 0.80$), and a conservative effect size ($f = 0.25$) for the design of the present study.

Table 1. Participant characteristics.

Group	Age (years)	Height (cm)	Body mass (kg)
Male (n = 15)	24 ± 4	183.7 ± 4.9	84.7 ± 10.6
Female (n = 15)	24 ± 4	165.2 ± 9.7	69.6 ± 18.6

Data are presented as mean ± standard deviation.

3.2. Research Design.

This study used a pseudo-randomized crossover design that required five visits to the lab. The experimental visits were separated by a minimum of 72 hours and were scheduled at the same time of day (± 2 hours). The first visit was used as a familiarization session. The participants completed the necessary paperwork and

performed the same testing procedures that were required during the experimental visits. The next four testing visits (i.e., mirror, no-mirror, non-dominant, control) were completed in a pseudo-randomized order with a modified Latin square design. An overview of the testing order for all participants is provided in Table 2. This was performed to control for order effects. During two of the experimental visits, the participants performed a series of repeated maximal voluntary handgrip contractions of the right (dominant) hand under two different visual feedback conditions (i.e., no-mirror and mirror). Another experimental visit required the participants to perform the fatiguing protocol with the left (non-dominant) hand with no mirror visual feedback. The participants also completed a control visit where they performed the pre- and post-fatigue strength testing measurements but rested quietly for the same duration (6 minutes) as the fatigue protocol between pre- and post-measurements. Figure 1 provides a schematic representation for the procedures of the experimental visits.

Table 2. The order of testing for each participant in the male and female group.

Participant no.	Male group	Female group
Participant 1	R, C, R$^+$, L	R, C, R$^+$, L
Participant 2	C, R$^+$, L, R	C, R$^+$, L, R
Participant 3	R$^+$, L, R, C	R$^+$, L, R, C
Participant 4	L, R, C, R$^+$	L, R, C, R$^+$
Participant 5	R, C, R$^+$, L	R, C, R$^+$, L
Participant 6	C, R$^+$, L, R	C, R$^+$, L, R
Participant 7	R$^+$, L, R, C	R$^+$, L, R, C
Participant 8	L, R, C, R$^+$	L, R, C, R$^+$
Participant 9	R, C, R$^+$, L	R, C, R$^+$, L
Participant 10	C, R$^+$, L, R	C, R$^+$, L, R
Participant 11	R$^+$, L, R, C	R$^+$, L, R, C
Participant 12	L, R, C, R$^+$	L, R, C, R$^+$
Participant 13	R, C, R$^+$, L	R, C, R$^+$, L
Participant 14	C, R$^+$, L, R	C, R$^+$, L, R
Participant 15	R$^+$, L, R, C	R$^+$, L, R, C

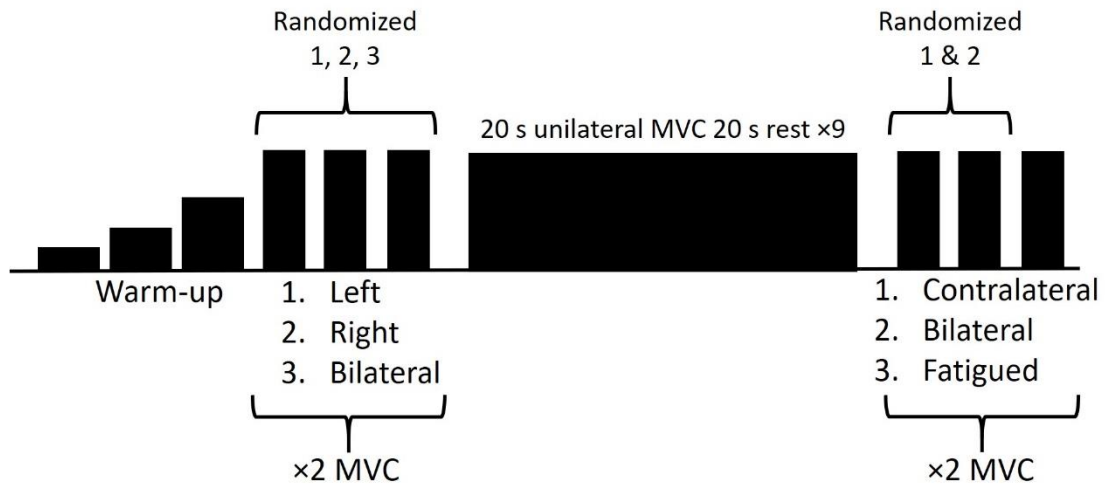R = no-mirror fatigue visit; C = control visit; R$^+$ = mirror fatigue visit; L = non-dominant fatigue visit.

Figure 1. Schematic representation for the testing procedures of the experimental visits.

3.3. Instrumentation and Procedures.

3.3.1. Isometric Strength Assessment

All strength testing was performed in a custom-built strength testing apparatus. The participants were seated in front of the apparatus and both arms were placed on a pad in front of them. The participants gripped a modified handgrip dynamometer that was attached to a tension-compression load cell (Model SSM-AJ-500, Interface Inc., Scottsdale, AZ.) with a neutral handgrip position (i.e., palms facing each other). Before strength testing, the participant performed 3, 5-second isometric contractions of the handgrip muscles at ~25, 50, and 75% of their perceived maximum force. Strength testing was performed before and after the fatigue intervention. Each (non-fatiguing) maximal voluntary contraction was 3 seconds in duration with 30 seconds of recovery provided between attempts. The strength measurements before the fatigue protocol were

exactly the same for each visit but were performed in a randomized order: (1) maximal

unilateral handgrip contractions of the right hand (×2), (2) maximal unilateral handgrip

contractions of the left hand (×2), and (3) maximal bilateral handgrip contractions for

both hands (×2). Each contraction was performed twice. After the fatigue intervention,

the order of strength testing was randomized between the contralateral and bilateral

MVC, the fatigued hand was tested last (Figure 1). Standardized verbal instructions to

"squeeze as fast and hard as possible" were provided to the participants for each

strength assessment.

3.3.2. Fatigue Intervention

The fatigue protocol required 3 minutes of maximal activity, and was

interspersed into nine, 20-second maximal voluntary contractions with a 50% duty cycle

(i.e., 20 seconds on, 20 seconds off). At the conclusion of each visit, the participants

were asked to provide their rating of perceived exertion for the entire session (Appendix

E).

3.3.3. Visual Feedback

During the fatigue visits, a visual divider was placed along the midsagittal plane

of the participant and the contralateral hand was not visible. During the mirror visit, a

plane mirror was aligned to the participant's midsagittal plane and provided a

superimposed mirror image of the dominant hand over the non-dominant hand. In other

words, it appeared as though the inactive, contralateral hand was contracting along with

the ipsilateral hand. During the no-mirror visit, a cardboard divider was positioned in

the same manner as the mirror and the participants were instructed to focus their

attention on an inert visual fixation point that was marked on the cardboard. The non-

dominant visit used the same experimental setup as the no-mirror visit. Importantly, the

contralateral hand was positioned as described above (3.3.1.) and was consistent

between all conditions. An example of each setup is provided in Figure 2.

Figure 2. An example of the experimental setup for the participant during the no-mirror
(1), mirror (2) and non-dominant (3) visit. Picture 4 illustrates the position for the
contralateral limb.

3.3.4. Electromyography

Surface electromyographic (EMG) activity was collected from the flexor carpi

radialis (FCR) and extensor carpi radialis (ECR) of both arms with a bipolar surface

electrode (DE-2.1; Delsys, Inc., Natick, MA.) during all strength testing and fatiguing

contractions. The sensor for the FCR was placed approximately one-third of the distance from the antecubital space to the lateral radial styloid process. The sensor for the ECR was placed approximately one-third of the distance from the lateral epicondyle of the humerus to the lateral radial styloid process. It is important to note, however, that the specific sensor site was determined on a subject-by-subject basis to limit the influence of the innervation zone and cross-talk on the EMG response and ensure maximal signal fidelity. Once determined, the site was cleansed with alcohol and outlined with permanent ink in order to replicate its placement for the subsequent visits. A reference electrode was placed over the seventh cervical vertebrae. Custom-made LabVIEW software was used to process the EMG signals (LabVIEW 13.0; National Instruments). The EMG signals were preamplified (gain, 1000) and band-pass filtered at 20 and 450 Hz. The force and EMG signals were then digitized at 20k Hz with a 12-bit analog-to-digital converter (National Instruments). The maximal voluntary contraction force was quantified as the highest 500 ms average of the 3-second MVC and the corresponding EMG amplitude value was quantified as the highest 500 ms average of the root-mean-square (RMS) value.

3.4. Statistical Analysis.

3.4.1. Maximal Strength

Separate three-way (visit [familiarization, mirror, no-mirror, non-dominant, control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures analyses of variance (ANOVA) tests were used to examine mean differences in MVC force for both the dominant and non-dominant hands. The

justification for this analysis is that it allowed maximal strength values to be compared across visits and between sexes for both hands.

3.4.2. Bilateral Index

A three-way (limb [dominant, non-dominant] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA test were performed on the mean MVC values of the experimental visits. In addition to the absolute MVC force values, the bilateral index (%) was compared between males and females with an independent samples t-test and between the non-dominant and dominant hands with a paired samples t-test. The bilateral index (%) was computed with the following equations (Howard and Enoka, 1991):

$$BLI\% = \left(\frac{(MVC_{Bilateral\ non-dominant} + MVC_{Bilateral\ dominant})}{(MVC_{unilateral\ non-dominant} + MVC_{unilateral\ dominant})} \times 100 \right) - 100$$

$$Non-dominant\ BLI\% = \left(\frac{(MVC_{Bilateral\ non-dominant})}{(MVC_{unilateral\ non-dominant})} \times 100 \right) - 100$$

$$Dominant\ BLI\% = \left(\frac{(MVC_{Bilateral\ dominant})}{(MVC_{unilateral\ dominant})} \times 100 \right) - 100$$

A positive bilateral index (%) indicates bilateral facilitation, while a negative bilateral index indicates a bilateral deficit. The justification for this analysis is that it allowed maximal strength values to be compared between hands across contraction type and to determine whether sex moderated the effects. The analysis of the bilateral index values also permitted a relative comparison between sexes and hands.

3.4.3. Fatigue.

Separate three-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA tests were used to examine mean differences in the percentage change for MVC force and EMG amplitude for the fatigued and non-fatigued hand. The justification for this analysis is that it allowed the relative changes in maximal force (i.e., fatigability) and EMG amplitude to be directly compared for the fatigued and non-fatigued hand across the experimental visits and between contraction type while examining the moderative effects of sex. The percent change (%Δ) in MVC force and EMG amplitude following the respective experimental visit was computed for both hands with the following equation:

$$\%\Delta = \left(\frac{\left(MVC_{post} - MVC_{pre}\right)}{\left(MVC_{pre}\right)}\right) \times 100$$

3.4.4. Rating of Perceived Exertion

A two-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] repeated measures ANOVA test was used to examine the rating of perceived exertion (RPE) across visit and between sex. This analysis allowed a comparison of the rating of perceived exertion between experimental visits and whether there were differences between sexes.

For all repeated measures ANOVA tests, significant interactions were decomposed with simple effects tests with Bonferroni adjustments and significant main effects were examined with Bonferroni pairwise comparisons. The effect size for each ANOVA was examined with the η_p^2 statistic with values of 0.01, 0.05, and 0.07

reflecting small, moderate, and large effects sizes, respectively (Stevens, 2007).

Cohen's *d* was used to examine the effect size between means for variables (e.g.,

contraction and sex) that were central to the research hypotheses. Cohen's *d* values of

0.2, 0.5, and 0.8 were used to characterize small, moderate, and large effects,

respectively, and were computed with the following equation (Cohen, 1988):

$$d = \left(\frac{(\bar{x}_1 - \bar{x}_2)}{\sqrt{\left[\frac{\sigma_{1^2} + \sigma_{2^2}}{2}\right]}} \right)$$

Intraclass correlation coefficients and the standard error of the measurement (SEM)

were computed for the MVC and EMG amplitude values from the test-retest conditions

in the control visit. An alpha level of 0.05 was used to determine statistical significance

for all comparisons.

CHAPTER 4: RESULTS

Table 3, Table 4, Table 5, and Table 6 provide a complete list of the F-statistic,

P-value, and η_p^2 values for the mixed factorial repeated measures ANOVA tests

performed in the present study.

4.1. Maximal Strength.

The results of the separate three-way (visit [no-mirror, mirror, non-dominant,

control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial

repeated measures ANOVA for the dominant and non-dominant MVC values showed

no significant three-way interaction (p = 0.977) for the dominant or non-dominant (p =

0.906) hands, no visit × sex (p = 0.175) for the dominant or non-dominant (p = 0.661)

hands, no visit × contraction (p = 0.514) for the dominant or non-dominant (p = 0.532)

hands, or sex × contraction for the dominant (p = 0.544) or non-dominant (p = 0.875)

hands. There was no main effect for visit for the dominant (p = 0.991) or non-dominant

hands (p = 0.834). Both hands showed a significant main effect for sex (p < 0.001), but

only the dominant hand showed a main effect for contraction (p = 0.001). The follow-up

pairwise comparisons showed that collapsed across visit and contraction, the males had

significantly greater MVC values for the dominant (mean ± standard deviation: 786.9 ±

182.9 N versus 466.7 ± 91.3) and non-dominant (mean ± standard deviation: 608.1 ±

150.1 N versus 355.8 ± 71.3 N) hands compared to the females. The pairwise

comparisons for the dominant hand showed that collapsed across visit and sex, the

unilateral MVC values were significantly greater than bilateral MVC values (mean ±

standard deviation: 639.8 ± 213.0 N versus 613.9 ± 212.2 N; p = 0.001). Table 3

provides the F-statistic, P-value, and η_p^2 for all of these statistical comparisons.

Table 3. The F-statistic, P-value, and η_p^2 for the three-way mixed factorial repeated measures ANOVA test on maximal handgrip strength for both hands between visit, contraction, and sex.

Variable	visit × cx × sex	visit × cx	cx × sex	visit × sex	visit	cx	sex
	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2
Dominant handgrip MVC (N)	0.067 0.977 0.002	0.770 0.514 0.027	0.378 0.544 0.013	1.69 0.175 0.057	0.036 0.991 0.001	**14.042 0.001 0.340**	**40.464 0.000 0.591**
Non-dominant handgrip MVC (N)	0.186 0.906 0.007	0.739 0.532 0.026	0.025 0.875 0.001	0.532 0.661 0.019	0.288 0.834 0.010	2.206 0.149 0.073	**38.089 0.000 0.576**

Visit = no-mirror, mirror, non-dominant, control; cx = contraction = unilateral, bilateral; sex = male, female. Significant interactions and main effects are bolded.

4.2. Bilateral Index.

4.2.1. Force.

The results of the three-way (limb [dominant, non-dominant] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA test for the MVC values of the control visit showed no significant interactions for limb × sex × contraction (p = 0.452), sex × contraction (p = 0.784). However, there was a significant limb x contraction (p = 0.024) and limb × sex (p = 0.001) interaction. Simple effects tests showed that when collapsed across sex, the dominant limb had significantly greater mean MVC values for unilateral (mean ± standard deviation: 639.8 ± 213.0 N versus 486.7 ± 165.7 N) and bilateral (mean ± standard deviation: 613.9 ± 212.2 N versus 477.1 ± 173.9 N) contractions. Simple effects tests also showed that when collapsed across sex, the unilateral MVC values were significantly greater than bilateral MVC values for the dominant hand (mean ± standard deviation: 639.8 ± 213.0 N versus 613.9 ± 212.2 N; p = 0.001), but there was no significant difference between contractions for the non-dominant (mean ± standard deviation: 486.7 ± 165.7 N versus 477.1 ± 173.9; p = 0.149) hand. Figure 3 shows the individual and mean MVC values for both hands and sexes during unilateral and bilateral contractions. Paired samples t-

tests showed that the bilateral index for the non-dominant hand was significantly less than the dominant hand (mean ± SD: -1.9 ± 7.4% versus -4.0 ± 6.2%; p = 0.042; Cohen's d = 0.31; Figure 4). Simple effects tests showed that collapsed across contraction, males had significantly higher MVC values for the dominant (p < 0.001) and non-dominant (p < 0.001) hands compared to females, and both sexes had greater MVC values for the dominant hand compared to the non-dominant hand (p < 0.001). There were main effects for limb (p < 0.001), sex (p < 0.001), and contraction (p = 0.037). Collapsed across sex and contraction, the dominant hand was significantly stronger than the non-dominant hand (p < 0.001). Collapsed across limb and contraction, males showed greater MVC values than females (p < 0.001). Collapsed across limb and sex, the unilateral MVC values were significantly greater than those during bilateral contractions (mean ± SD: 563.2 ± 203.6 N versus 543.5 ± 206.8 N; p = 0.004). On average, the unilateral MVC values were +3.1% greater than bilateral MVC values. There was no significant difference in the bilateral index between males and females (mean ± SD: -2.9 ± 5.3% versus -3.8 ± 6.9%; p = 0.680; Figure 5).

Table 4 provides the F-statistic, P-value, and η_p^2 for all of the statistical comparisons.

Table 4. The F-statistic, P-value, and η_p^2 for the three-way mixed factorial repeated measures ANOVA test on maximal handgrip strength between limb, contraction, and sex.

Variable	limb × cx × sex	limb × cx	cx × sex	limb × sex	limb	cx	sex
	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2
Handgrip MVC (N)	0.583 0.452 0.02	**5.662 0.024 0.168**	0.077 0.784 0.003	**15.378 0.001 0.355**	**279.698 0.000 0.909**	**9.686 0.004 0.257**	**40.415 0.000 0.591**

limb = non-dominant, dominant; cx = contraction = unilateral, bilateral; sex = male, female. Significant interactions and main effects are bolded.
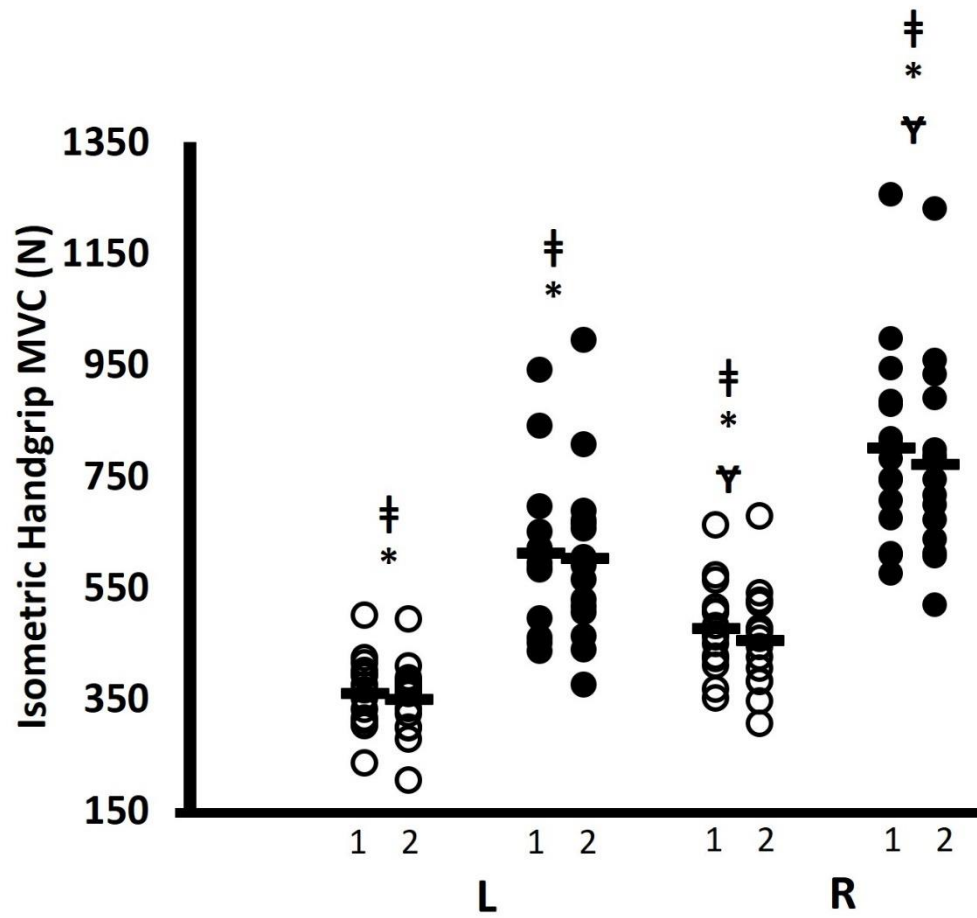
Figure 3. Scatterplot for the mean and individual MVC values for the non-dominant (L) and dominant (R) hands during unilateral (1) and bilateral (2) contractions for the females (open circles) and males (closed circles). *(p < 0.05) between sex; ‡(p < 0.05) between hand; Ⴤ(p < 0.05) between contraction.
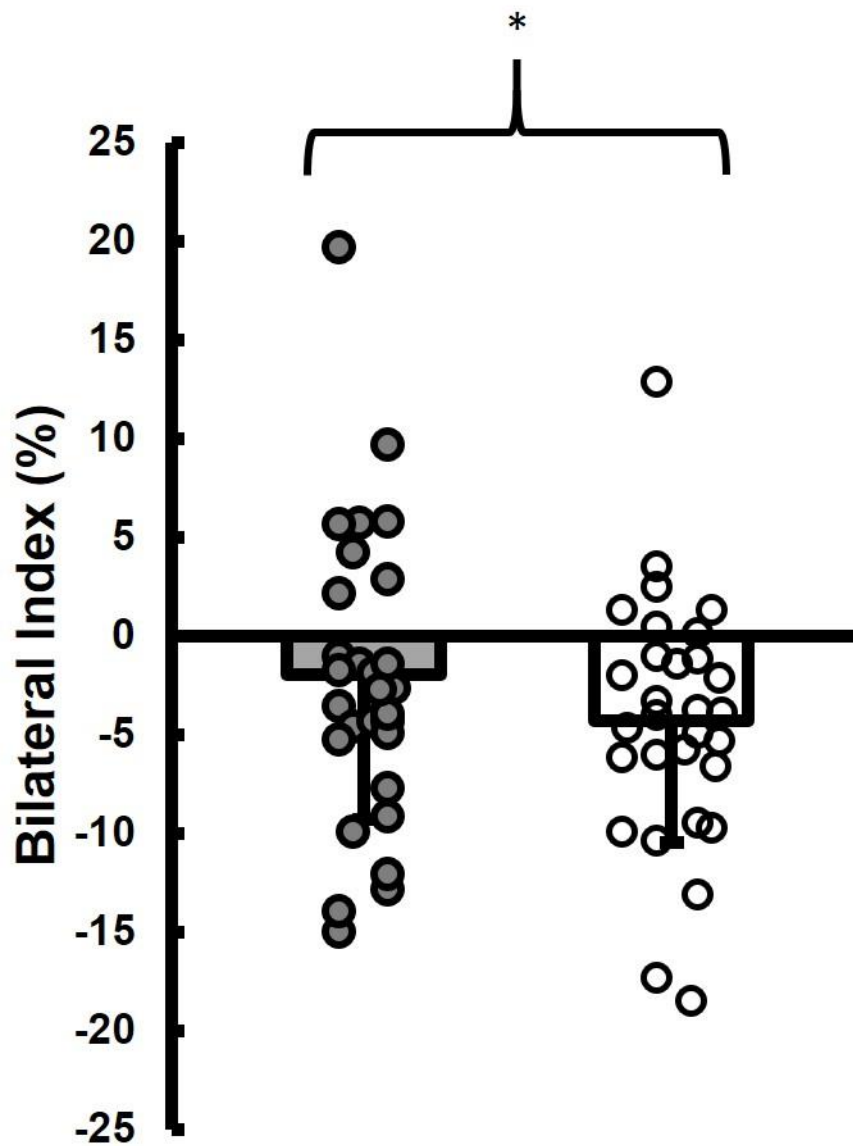
Figure 4. Scatterplot for the mean and individual values of the bilateral index (%) for the non-dominant (filled) and dominant (open) hands. *Significant mean difference (p < 0.05).

Figure 5. Scatterplot for the mean and individual values of the bilateral index (%) for the males (filled) and females (open).

4.3. Fatigue.

4.3.1. Force.

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] ×

sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated

measures ANOVA for the relative change in MVC force (%) for the fatigued hand

showed no significant three-way (p = 0.670), visit × sex (p = 0.495), or contraction ×

sex (p = 0.835) interaction. However, there was a significant visit × contraction

interaction (p = 0.009). Simple effects tests showed that when collapsed across sex,

force loss was significantly greater during bilateral versus unilateral contractions for the

no-mirror (mean ± standard deviation: -24.5 ± 11.8% versus -31.9 ± 13.5%; p = 0.003)

and non-dominant (mean ± standard deviation: -26.3 ± 11.9% versus -34.1 ± 12.1%; p =

0.004) fatigue visits (Figure 6). However, there was no significant difference between

unilateral and bilateral force loss values for the mirror (mean ± standard deviation: -27.0

± 10.3% versus -29.7 ± 13.9%; p = 0.257) and control visits (mean ± standard deviation:

-1.9 ± 5.2% versus -0.8 ± 6.7%; p = 0.393). There was a main effect for visit (p < 0.001)

and contraction (p = 0.002), but there was no main effect for sex (p = 0.186; Figure 7).

The pairwise comparisons for visit showed that when collapsed across sex and

contraction, the force loss after the mirror (-28.2%), no-mirror (-28.4%), and non-

dominant (-30.2%) fatigue visits were significantly (p < 0.001) greater than the control
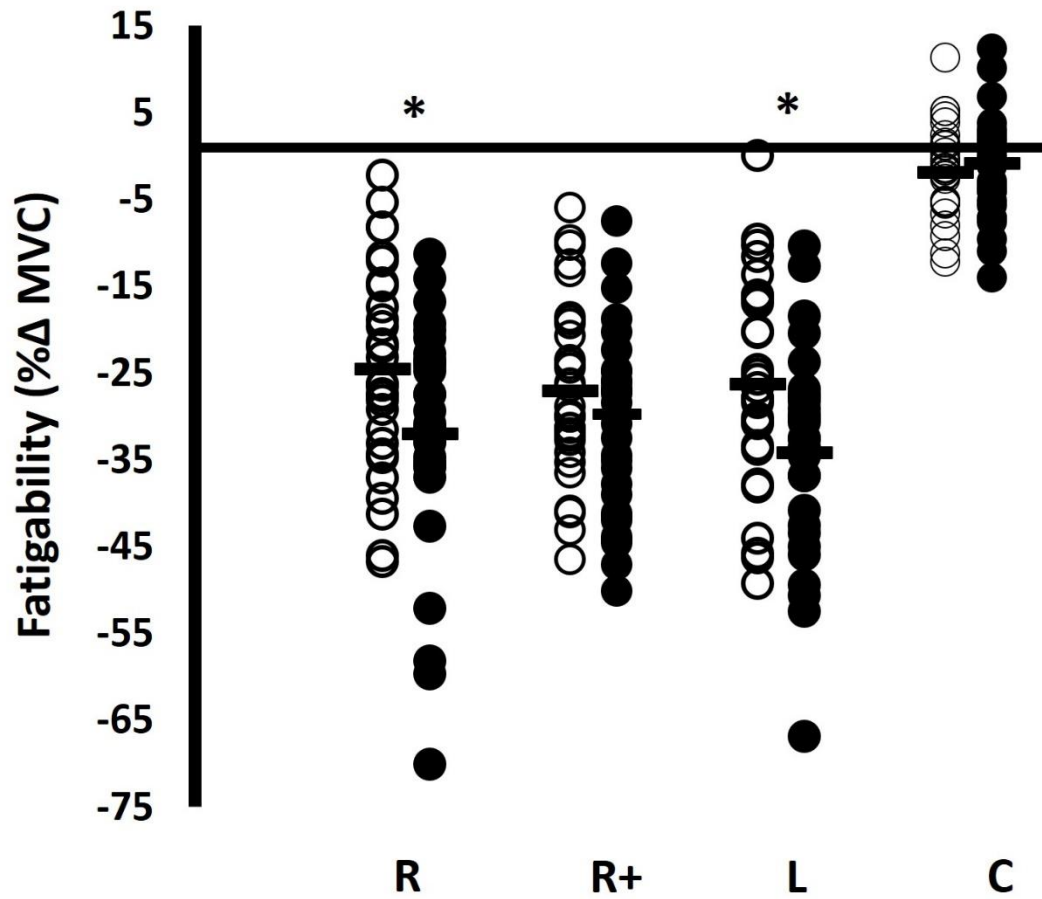
visit (-1.3%).

Figure 6. Scatterplot for the mean and individual values for the relative fatigability (%Δ MVC) of the fatigued hand for unilateral (open) and bilateral (filled) contractions during the no-mirror (R), mirror (R+), non-dominant (L), and control I visits. *Significant mean difference ($p < 0.05$) between unilateral and bilateral force loss.
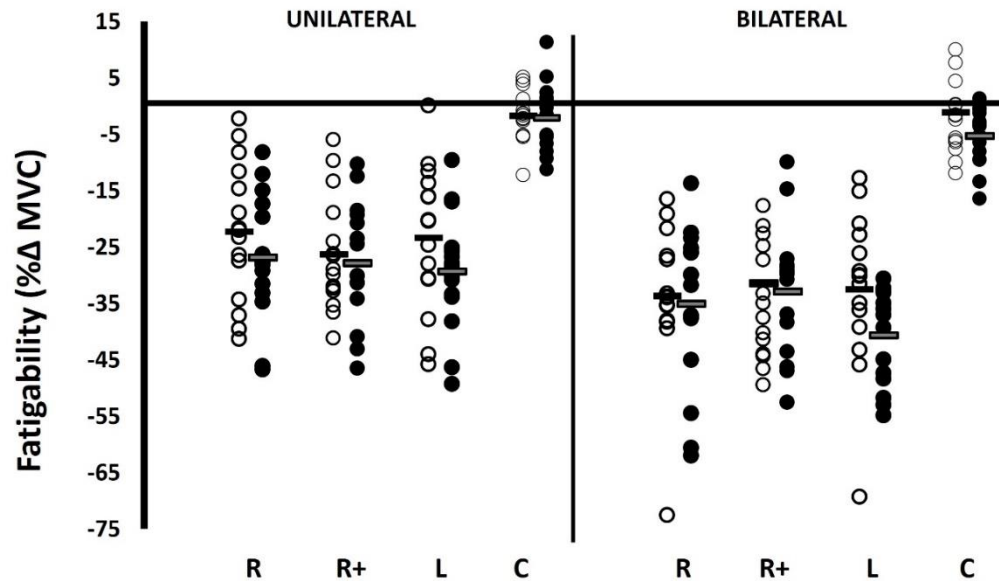
Figure 7. Scatterplot for the mean and individual values for the relative fatigability (%Δ MVC) of the fatigued hand for the females (open) and males (filled) during the no-mirror (R), mirror (R+), non-dominant (L), and control I visits for unilateral and bilateral contractions.

4.3.2. EMG Amplitude.

4.3.2.1. Flexor Carpi Radialis

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA test for the relative change in EMG amplitude (%) for the flexor carpi radialis of the fatigued hand showed no significant three-way (p = 0.403), visit × sex (p = 0.211), visit × contraction (p = 0.131), or sex × contraction (p = 0.211) interactions, and there was no main effect for visit (p = 0.849) or sex (p = 0.130), but there was a main effect for contraction (p = 0.027; Figure 8). Pairwise comparisons showed that when collapsed across visit and sex, the relative change in EMG amplitude was significantly (p = 0.027) greater during unilateral contractions (-11.7%) compared to bilateral contractions (-3.7%).
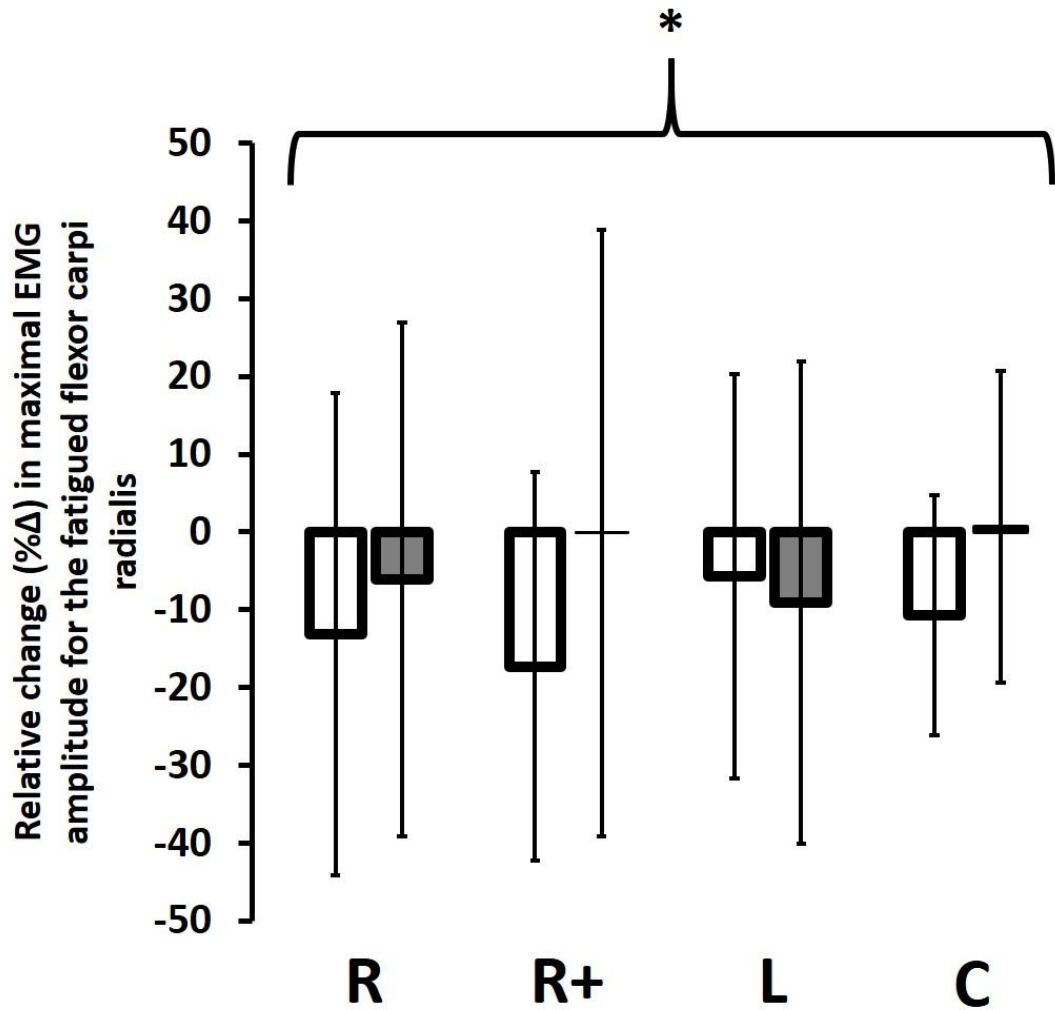
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Figure 8. Mean ± standard deviation for the relative change in maximal EMG amplitude for the fatigued flexor carpi radialis for the no-mirror (R), mirror (R+), non-dominant (L), and control I visit for unilateral (open bars) and bilateral (shaded bars) contractions. *Significant main effect ($p < 0.05$) for contraction.

4.3.2.2. Extensor Carpi Radialis

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] ×

sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated

measures ANOVA test for the relative change in EMG amplitude (%) for the extensor

carpi radialis of the fatigued hand showed no significant three-way interaction (p =

0.648), no visit × sex (p = 0.565), or sex × contraction (p = 0.216) interactions, and

there was no main effect for visit (p = 0.443), contraction (p = 0.917), or sex (p =

0.357). However, there was a significant visit × contraction (p = 0.033; Figure 9)

interaction. Simple effects tests showed that collapsed across sex, the decrease in EMG

amplitude during the unilateral contraction following the no-mirror visit was

significantly greater than control (mean ± standard deviation: -23.6 ± 26.5% versus -9.1

± 22.6%; p = 0.029; Figure 10). There were no significant mean differences for any

other comparisons. Table 5 provides the F-statistic, P-value, and η_p^2 for all of the
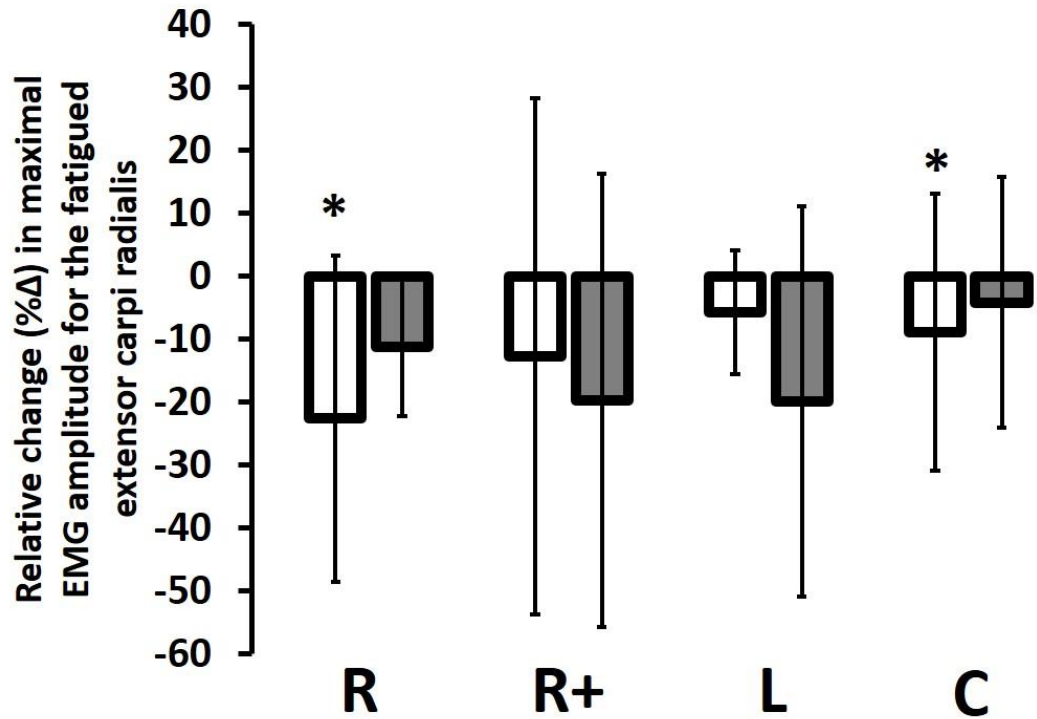
statistical comparisons.

Figure 9. Mean ± standard deviation for the relative change (%Δ) in maximal EMG amplitude for the fatigued extensor carpi radialis for the no-mirror (R), mirror (R+), non-dominant (L), and control I visit for unilateral (open bars) and bilateral (shaded bars) contractions. *Significant mean difference ($p < 0.05$) between visits for the unilateral contraction.
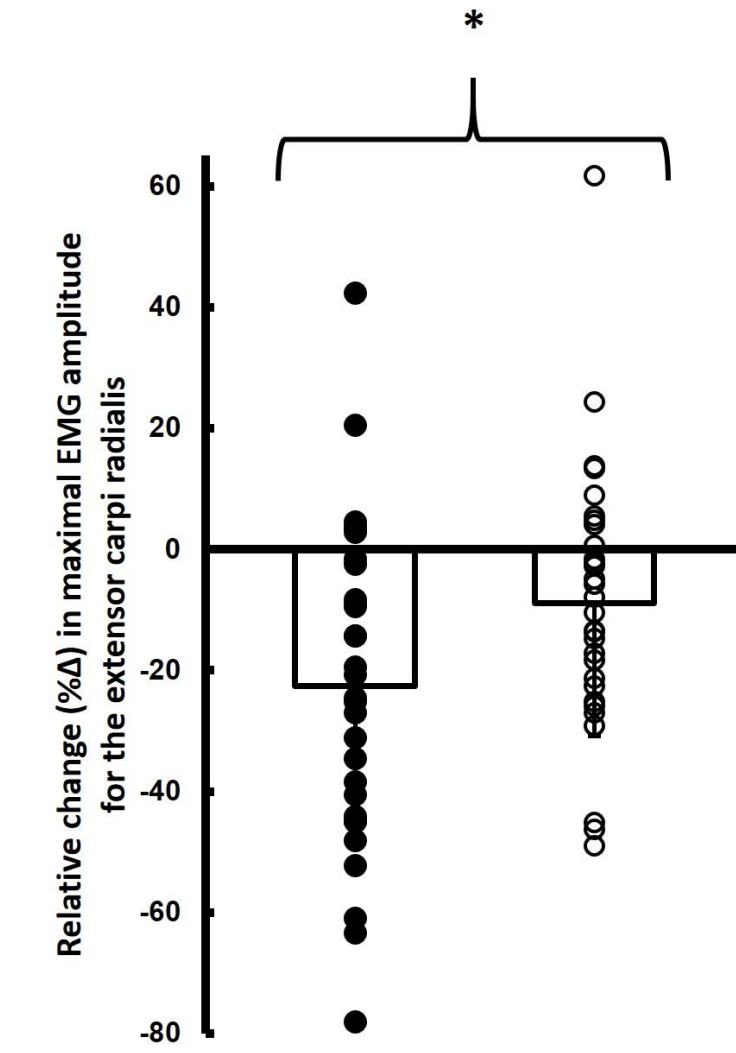
Figure 10. Scatterplot of the mean and individual values for the relative change (%Δ) in maximal EMG amplitude for the extensor carpi radialis during unilateral contraction after the no-mirror (closed circles) and control (open circles) visit. *Significant mean difference ($p < 0.05$).

4.4. Cross-over Effects.

4.4.1. Force.

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA test for the relative change in MVC force (%) for the contralateral, non-fatigued hand showed no significant three-way interaction ($p = 0.799$) and no visit × sex ($p = 0.145$), visit × contraction ($p = 0.160$), or sex × contraction ($p = 0.576$) interaction. There were no main effects for visit ($p = 0.761$) or sex ($p = 0.215$), but there was a main effect for contraction ($p = 0.023$; Figure 11). When collapsed across visit and sex, the pairwise comparisons showed that the mean change in MVC force during the bilateral contraction (-2.9%) was significantly greater than the unilateral (+0.02%) contraction. The effect size for the mean differences, collapsed across sex, between unilateral and bilateral force values for each visit are as follows: no-mirror (Cohen's $d =$ 0.17), mirror (Cohen's $d = 0.24$), non-dominant (Cohen's $d = 0.72$), control (Cohen's d $= 0.18$). A scatterplot is shown in Figure 12 for the changes in bilateral and unilateral force for the non-fatigued hand during the non-dominant visit. Another scatterplot is shown in Figure 13 for the changes in bilateral force for the non-fatigued hand during the non-dominant and control visits.

Figure 11. Scatterplot for the mean and individual values for the relative change (%Δ MVC) in the maximal force of the contralateral, non-fatigued hand for unilateral (open) and bilateral (filled) contractions during the no-mirror (R), mirror (R+), non-dominant (L), and control I visits. *Significant main effect ($p < 0.05$) for contraction.
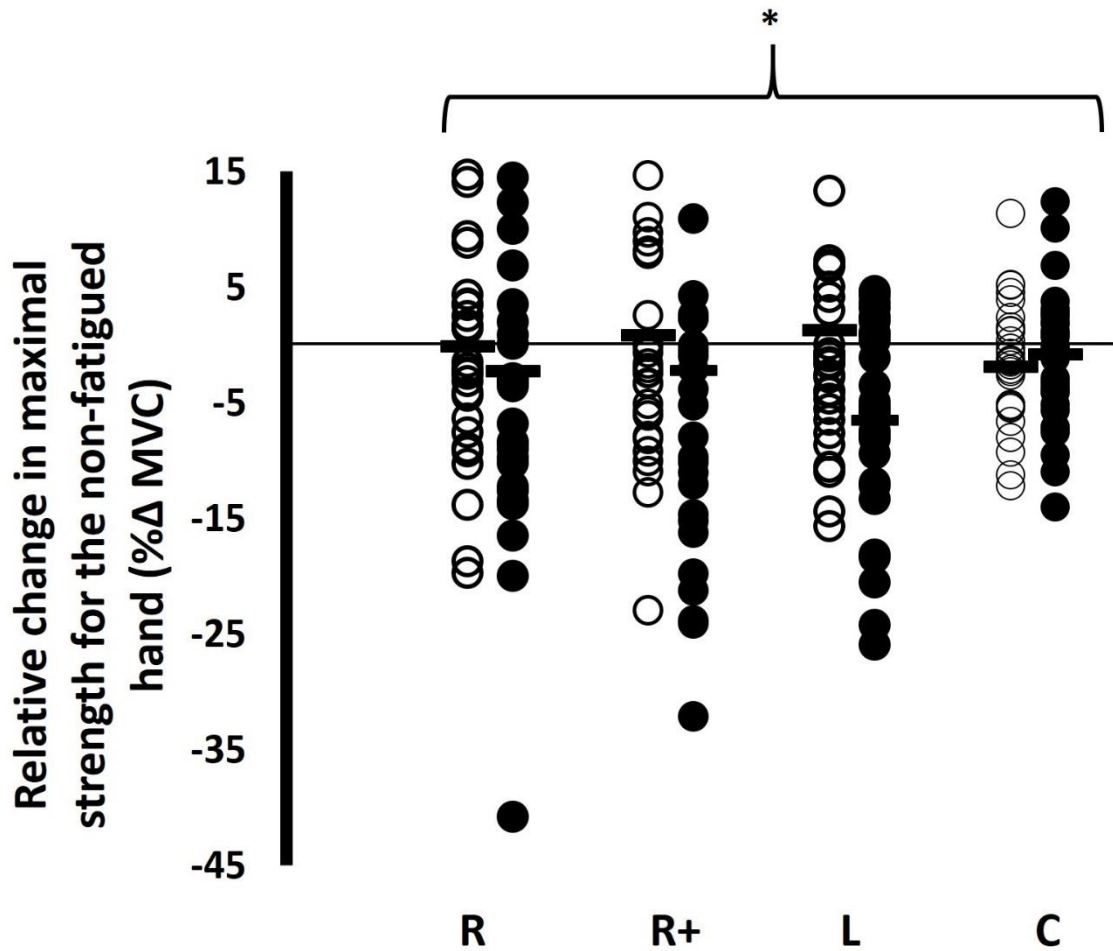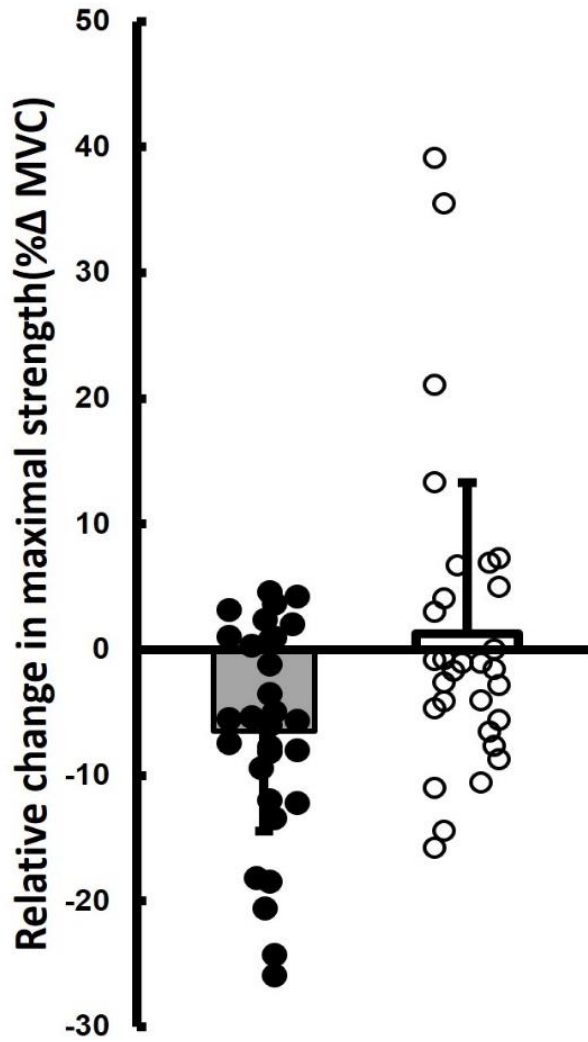
Figure 12: Scatterplot for the mean and individual values for the relative change (%Δ MVC) in the maximal force for the contralateral, non-fatigued hand during the non-dominant visit for the bilateral (filled circles) and unilateral (open circles) contraction.
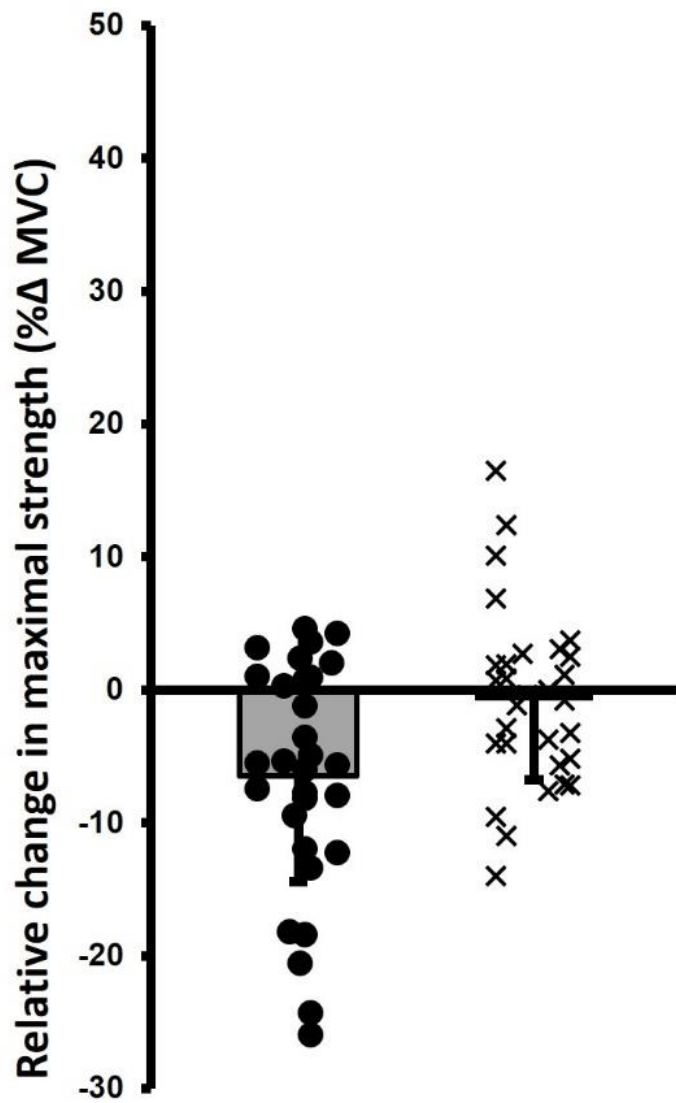
Figure 13: Scatterplot for the mean and individual values for the relative change (%Δ MVC) in maximal force during bilateral contraction for the contralateral, non-fatigued hand following the non-dominant (filled circles) and control (×) visit.

4.4.2. EMG Amplitude.

4.4.2.1. Flexor Carpi Radialis.

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] ×

sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated

measures ANOVA test for the relative change in EMG amplitude (%) for the

contralateral, non-fatigued hand showed no significant three-way ($p = 0.396$), visit ×

sex ($p = 0.092$) or sex × contraction ($p = 0.845$) interaction, but there was a significant

visit × contraction interaction ($p = 0.007$; Figure 14). Simple effects tests showed that

when collapsed across sex, the relative change in EMG amplitude during the mirror

visit was significantly different between unilateral and bilateral contractions.

Specifically, the mean percent change in EMG amplitude during the unilateral

contraction increased whereas during the bilateral contraction there was a decrease

(mean ± SD: +6.4 ± 32.1% versus -10.9 ± 28.1%; $p = 0.007$). In addition, the mean

percent change in EMG amplitude during the unilateral contraction of the mirror visit

was significantly greater than control values (mean ± SD: +6.4 ± 32.1% versus -10.7 ±

15.5%; $p = 0.05$; Figure 15).

Figure 14: Mean ± standard deviation for the relative change (%Δ) in maximal EMG amplitude for the non-fatigued flexor carpi radialis for the no-mirror (R), mirror (R+), non-dominant (L), and control I visit for unilateral (open bars) and bilateral (shaded bars) contractions. *Significant mean difference ($p < 0.05$) between contraction; ‡significant mean difference ($p < 0.05$) between R+ and C for unilateral contraction.
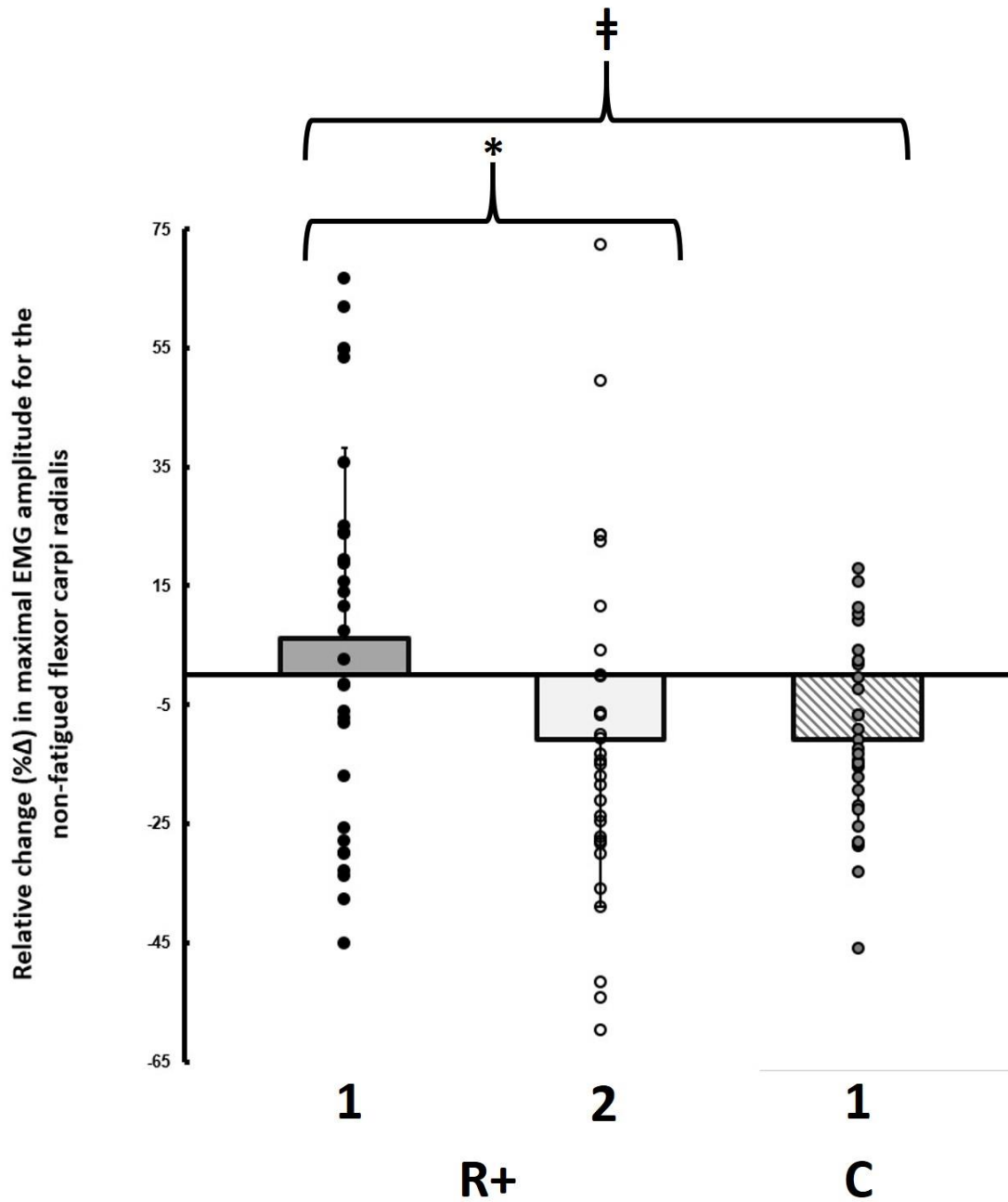
Figure 15: Scatterplot of the mean and individual values for the relative change (%Δ) in maximal EMG amplitude for the contralateral, non-fatigued flexor carpi radialis during unilateral (1) and bilateral contraction (2) for the mirror (R+) visit and the values for unilateral contraction (1) during the control (C) visit. *Significant mean difference (p < 0.05) between contraction; ‡significant mean difference (p < 0.05) between R+ and C for unilateral contraction.

4.4.2.2. Extensor Carpi Radialis

The results of the three-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] × contraction [unilateral, bilateral]) mixed factorial repeated measures ANOVA test for the relative change in EMG amplitude (%) for the contralateral, non-fatigued hand showed no significant three-way (p = 0.396), visit × sex (p = 0.092), visit × contraction (p = 0.150), or sex × contraction (p = 0.845) interactions, and no main effect for visit (p = 0.365), sex (p = 0.155), or contraction (p = 0.123). Table 5 provides the F-statistic, P-value, and η_p^2 for all of the statistical comparisons. Figure 16 shows the mean changes in maximal EMG amplitude for the non-fatigued extensor carpi radialis across the visits.

Table 5. The F-statistic, P-value, and η_p^2 for the three-way mixed factorial repeated measures ANOVA test on the relative change (%Δ) in handgrip strength and EMG amplitude for the fatigued and non-fatigued hands between visit, contraction, and sex.

Variable	visit × cx × sex	visit × cx	cx × sex	visit × sex	visit	cx	sex
	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2
Fatigue MVC(%Δ)	0.568 0.638 0.020	**4.487 0.006 0.138**	0.071 0.791 0.003	0.832 0.480 0.029	**105.21 0.000 0.790**	**11.649 0.002 0.294**	1.870 0.182 0.063
Fatigue EMG FCR(%Δ)	0.987 0.403 0.064	1.927 0.131 0.064	1.639 0.211 0.055	1.128 0.343 0.039	0.268 0.849 0.009	**5.444 0.027 0.163**	2.431 0.130 0.08
Fatigue EMG ECR(%Δ)	0.553 0.648 0.020	**3.047 0.033 0.101**	1.605 0.216 0.056	0.683 0.565 0.025	0.905 0.443 0.032	0.011 0.917 0.000	0.877 0.357 0.031
Non-fatigue MVC(%Δ)	0.336 0.799 0.012	1.768 0.160 0.059	0.321 0.576 0.011	1.845 0.145 0.062	0.389 0.761 0.014	**5.785 0.023 0.171**	1.613 0.215 0.054
Non-fatigue EMG FCR(%Δ)	0.943 0.423 0.033	**4.332 0.007 0.134**	1.262 0.271 0.043	0.465 0.707 0.016	0.139 0.936 0.005	0.047 0.830 0.002	0.035 0.853 0.001
Non-fatigue EMG ECR(%Δ)	1.002 0.396 0.035	1.817 0.150 0.061	0.039 0.845 0.001	2.215 0.092 0.073	1.072 0.365 0.037	2.535 0.123 0.083	2.131 0.155 0.071

Visit = no-mirror, mirror, non-dominant, control; cx = contraction = unilateral, bilateral; sex = male, female. Significant interactions and main effects are bolded.
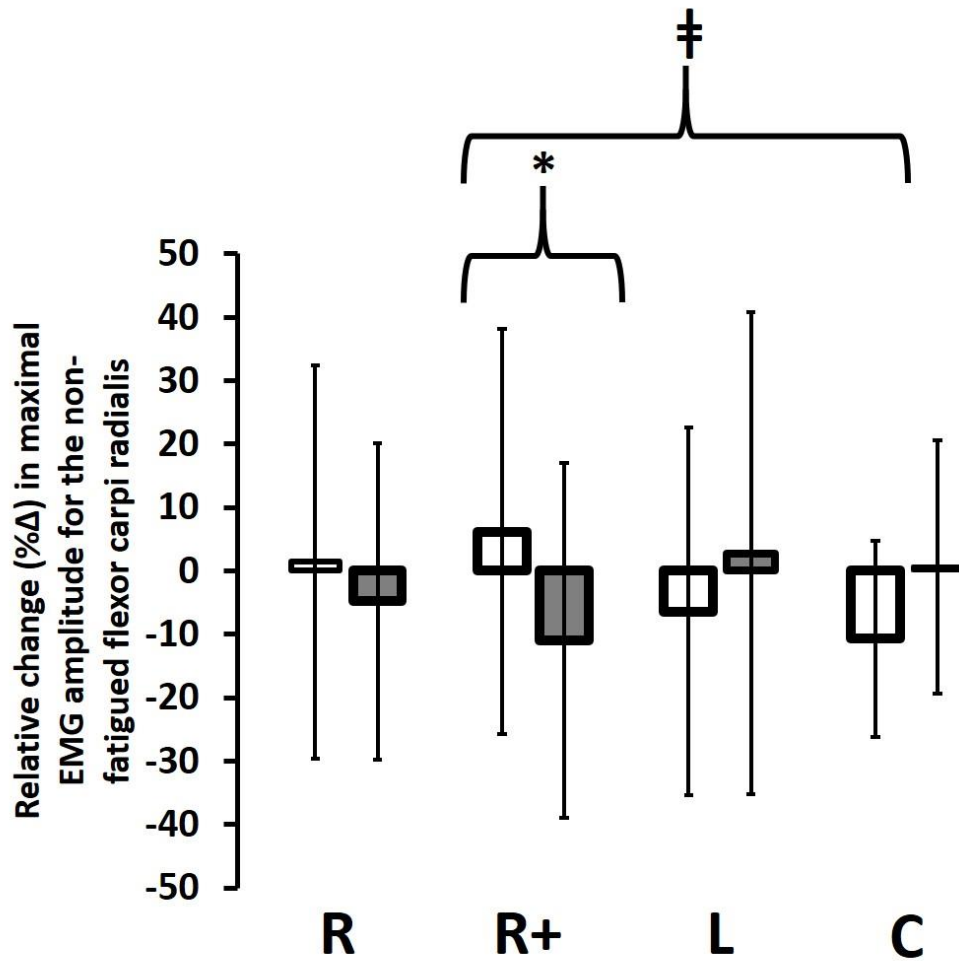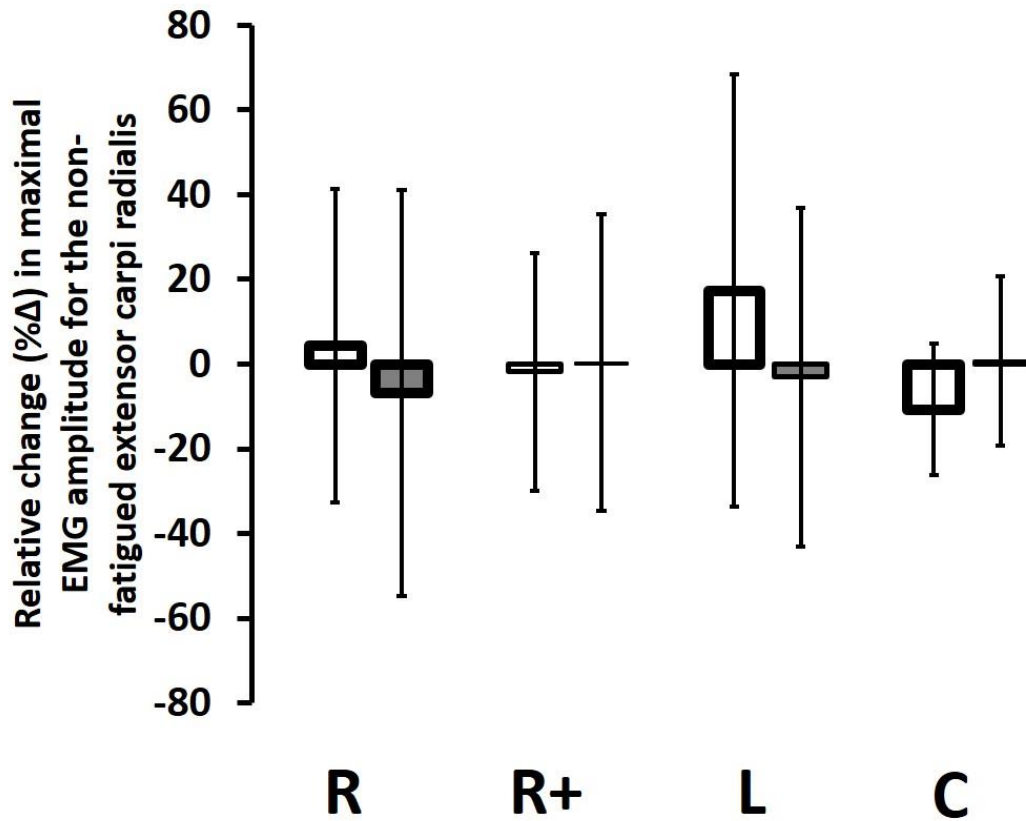
Figure 16: Mean ± standard deviation for the relative change (%Δ) in maximal EMG amplitude for the non-fatigued extensor carpi radialis for the no-mirror (R), mirror (R+), non-dominant (L), and control I visit for unilateral (open bars) and bilateral (shaded bars) contractions.

4.5. Rating of Perceived Exertion.

The two-way (visit [mirror, no-mirror, non-dominant, control] × sex [male, female] repeated measures ANOVA test for the rating of perceived exertion (RPE) showed no significant interaction (p = 0.539), but there was a main effect for visit (p < 0.001). The pairwise comparisons showed that when collapsed across sex, the RPE response for the no-mirror (mean ± SD: 6.1 ± 2.2), mirror (mean ± SD: 6.2 ± 1.7), and

non-dominant (mean ± SD: 6.0 ± 1.8) visits were significantly greater than control

(mean ± SD: 2.5 ± 1.3; Figure 17). There were no significant mean differences for RPE

between sex or the fatigue visits. Table 6 provides the F-statistic, P-value, and η_p^2 for

the statistical comparisons.

Table 6. The F-statistic, P-value, and η_p^2 for the two-way repeated measures ANOVA test on the rating of perceived exertion between visit and sex.

Variable	visit × sex	visit	sex
	F-statistic P-value η_p^2	F-statistic P-value η_p^2	F-statistic P-value η_p^2
RPE	0.872 0.459 0.030	**87.134** **0.000** **0.757**	0.776 0.386 0.027

RPE = rating of perceived exertion; visit = no-mirror, mirror, non-dominant, control; sex = male, female. Significant interactions and main effects are bolded.
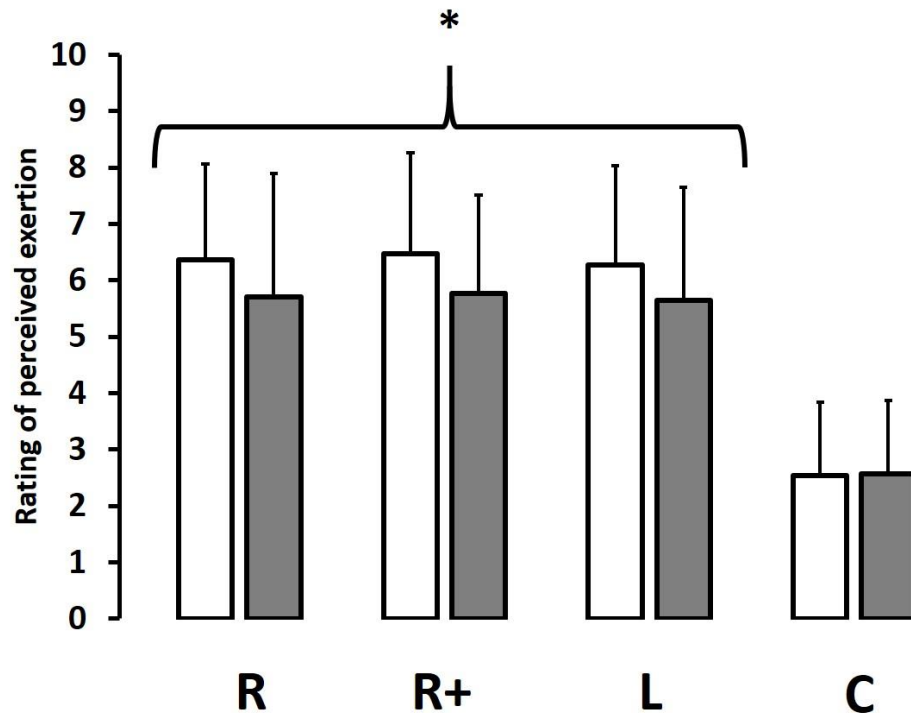
Figure 17. Mean ± standard deviation for the rating of perceived exertion for females (open bars) and males (shaded bars) following the no-mirror (R), mirror (R+), non-dominant (L), and control (C) visits. *Significantly (p < 0.05) different from control.

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4.6. Reliability Statistics.

Table 7. Test-retest intraclass correlation coefficients and the standard error of the measurement (SEM) for the MVC and EMG amplitude values for both hands during unilateral and bilateral contraction of the control visit.

Variable	Limb		Contraction	$ICC_{2,1}$	SEM
Maximal voluntary contraction force (N)	Left		Unilateral	0.956	38.4
			Bilateral	0.911	59.1
	Right		Unilateral	0.979	33.9
			Bilateral	0.921	67.9
EMG Amplitude (μV)	Left	ECR	Unilateral	0.933	20.7
			Bilateral	0.843	34.5
		FCR	Unilateral	0.943	31.2
			Bilateral	0.960	30.2
	Right	ECR	Unilateral	0.741	49.1
			Bilateral	0.929	21.9
		FCR	Unilateral	0.782	128.7
			Bilateral	0.923	64.3

CHAPTER 5: DISCUSSION

This study investigated several different properties of maximal unilateral and bilateral handgrip contractions in males and females. The central research questions that this study addressed were: 1) the bilateral deficit during handgrip contractions, 2) the effects of a unilateral fatigue protocol with the non-dominant and dominant hands on the maximal force and EMG amplitude response during unilateral and bilateral contractions, 3) the effects of unilateral fatigue on the maximal force and EMG amplitude response for the contralateral, non-fatigued hand during unilateral and bilateral contractions, 4) the influence of illusionary mirror visual feedback during unilateral fatigue with the dominant hand for the fatigued and non-fatigued hand, and 5) whether sex moderated the responses for each of the research questions. The main findings regarding the bilateral index, the fatigue responses, and the cross-over effects are presented below and discussed.

The bilateral index data showed that there was a significant bilateral deficit (-3.1%) evident during maximal handgrip contractions, the bilateral deficit was greater for the dominant hand compared to the non-dominant hand (mean $\pm$ SD: -4.0 $\pm$ 6.3% versus -1.9 $\pm$ 7.4%; p = 0.024; Cohen's d = 0.30), and there were no significant mean differences between males and females (mean $\pm$ SD: -2.9 $\pm$ 5.3% versus -3.8 $\pm$ 6.9%; p = 0.680; Cohen's d = 0.15) in the bilateral index. As expected, the males were stronger than the females for the dominant and non-dominant hands, yet there was no significant difference in the bilateral index values. The observation of a significant bilateral deficit for the handgrip muscles is in agreement with one of the first reports on the bilateral deficit (Henry and Smith, 1961) and the magnitude observed here is similar to other

reports on the bilateral deficit during maximal handgrip contractions (Škarabot et al., 2016). Furthermore, our observation that the bilateral deficit was greater for the stronger, dominant hand is an important finding that has been discussed but not consistently observed in the bilateral deficit literature (Henry and Smith, 1961; Ohtsuki, 1981; Howard and Enoka, 1991; Herbert and Gandevia; 1996; Cornwell et al., 2012; Škarabot et al., 2016). Although the data regarding limb dominance towards the bilateral deficit is conflicting (Cornwell et al., 2012; Škarabot et al., 2016), the present data support the notion that the maximal force of the dominant, stronger limb is reduced during bilateral contractions. There is strong evidence (Oda and Moritani, 1994; Oda and Moritani, 1995; Oda and Moritani, 1996; Oda, 1997; Post et al., 2007; Perez et al., 2014) that the inhibitory action between brain hemispheres during bilateral contractions is greater for bilateral contractions compared to unilateral contractions. Further, there is some evidence (Oda, 1997) that the magnitude of this effect is direction-dependent between brain hemispheres. Oda (1997) suggested that the decline in cortical activity has a greater effect on the left (dominant) hemisphere, while Post et al. (2007) observed that the input to the primary motor cortex was diminished for both hemispheres during bilateral contractions compared to unilateral contractions. Nevertheless, the present data and those of others (Henry and Smith, 1961; Ohtsuki, 1981) suggest that the inhibitory action between hemispheres has a larger suppressive effect on the stronger limb (Figure 4). The lack of sex-mediated differences in the bilateral index differs from a recent report (Ye et al., 2019) in which females exhibited a greater bilateral deficit than males for the finger abductors. In the present study, the range of bilateral index values was

large for both males (-16.8% - +2.2%) and females (-12.8% - +16.1%) with the majority

of males (9/15) and females (11/15) demonstrating a bilateral deficit (Figure 5).

The fatigue data for the fatigued hand showed that the force loss for the fatigued

hand was significantly less during unilateral versus bilateral contractions for the non-

dominant (mean ± SD: -26.3 ± 11.9% versus -34.1 ± 12.1%; p = 0.004; Cohen's d =

0.65) and no-mirror (mean ± SD: -24.5 ± 11.8% versus -31.9 ± 13.5%; p = 0.003;

Cohen's d = 0.59) visits, but not during the mirror visit (mean ± SD: -27.0 ± 10.3%

versus -29.7 ± 13.9%; p = 0.257; Cohen's d = 0.22), despite this observation, there were

no significant mean differences in the magnitude of force loss between the fatigue visits

during unilateral or bilateral contractions. However, there was a small effect size for the

mean differences in bilateral force loss between the mirror visit versus the no-mirror

visit (Cohen's d = 0.16) and the mirror visit versus the non-dominant visit (Cohen's d =

0.33). The observations regarding unilateral versus bilateral force loss following

unilateral fatigue present two novel findings. First, the finding that relative force loss is

greater during a bilateral versus unilateral contraction demonstrates contraction-

dependent inhibition following fatigue. It is challenging to reconcile potential

mechanisms that may account for this observation, but it may be speculated that

increased inhibitory actions between hemispheres or within the fatigued hemisphere

contributed to the greater relative force loss for the bilateral contraction. Second,

illusionary mirror visual feedback attenuated the difference between unilateral and

bilateral force losses for the fatigued hand. To date, only one other study (Tsutsumi et

al., 2011) has examined fatigue responses during unilateral fatigue with illusionary

mirror visual feedback. The authors (Tsutsumi et al., 2011) reported that unilateral

fatigue with the mirror illusion attenuated force loss compared to fatigue without the mirror for the fatigued hand. Taken together, illusionary mirror visual feedback appears to slightly attenuate force loss for the fatigued hand during unilateral fatigue. The present study is unable to define the mechanisms responsible for this trend, but when considering previous reports (Garry et al., 2005; Fukumura et al., 2007; Nojima et al., 2010; Tominaga et al., 2011; Hamzei et al., 2012), it may be that the mirror illusion activates the ipsilateral motor pathways and in turn provides greater excitability along the motor pathway for the active motor command. The attenuation of force loss between unilateral and bilateral contractions with illusionary mirror visual feedback indirectly supports this notion.

There were no significant mean differences in the magnitude of force loss between males and females during unilateral (collapsed mean ± pooled SD: -27.9 ± 10.6% versus -23.9 ± 11.7%; Cohen's $d = 0.36$) or bilateral (collapsed mean ± pooled SD: -33.7 ± 12.0 versus -30.1 ± 14.1%; Cohen's $d = 0.28$) contractions. Interestingly, the small effect size between males and females in relative fatigability was dominated by the non-dominant visit for both the unilateral (mean ± SD: -29.3 ± 10.5% versus -23.3 ± 12.9%; Cohen's $d = 0.51$) and bilateral (mean ± SD: -38.2 ± 8.6% versus -30.1 ± 13.9%; Cohen's $d = 0.70$) contractions. The lack of significant sex-based differences in relative fatigability during maximal intermittent contractions is in line with a majority of reports on this topic (Ditor and Hicks, 2000; Hunter et al., 2006; Hunter, 2016; Maughan et al, 1986; Senefeld et al., 2018). However, the larger effect size for the mean difference between sexes in relative fatigability for the non-dominant hand is interesting to consider in regard to the strongest contributor to sex-based differences in fatigue

resistance – muscle fiber type composition (Hunter, 2016). There is evidence that the

chronic preferential use of the dominant limb imparts morphological (Fugl-Meyer et al.,

1982) and functional (Adam et al., 1998; De Luca et al., 1986; Farina et al., 2003)

changes in the dominant muscle compared to the non-dominant muscle. Therefore, the

comparatively higher proportion of fast-twitch muscle fibers in the non-dominant limb

(Fugl-Meyer et al., 1982) may have influenced the larger mean differences in relative

fatigability for the non-dominant limb between sexes. Since females possess smaller

type II muscle fibers and a greater proportional area of type I muscle fibers compared to

males (Larsson et al., 2006; Porter et al., 2002), a smaller proportion of slow-twitch

muscle fibers in the non-dominant limb may have favored the greater fatigue resistance

of the females and therefore contributed to the larger mean differences in relative

fatigability compared to the dominant limb between sexes. However, the larger mean

differences expressed during the bilateral versus unilateral contraction between sexes

suggest a neural influence, which is also unresolved in the literature (Hunter, 2016;

Martin and Rattey, 2007; Senefeld et al., 2018; Yacyshyn et al., 2018; Ye et al., 2018).

Nevertheless, there were no sex-based differences in relative EMG amplitude change

for the flexor carpi radialis or extensor carpi radialis of either arm. The reductions in

maximal EMG amplitude for the flexor carpi radialis were greater during unilateral

versus bilateral contractions, though this effect was dominated by the fatigue-based

reductions for the no-mirror (Cohen's $d = 0.21$) and mirror visit (Cohen's $d = 0.51$).

Whereas for the extensor carpi radialis, the mean reduction in EMG amplitude during

the unilateral contraction of the no-mirror visit was significantly greater than control

(Figure 10).

The cross-over data showed that force loss was significantly greater for bilateral versus unilateral contractions across all visits (-3.0 % versus +0.2 %; p = 0.013), however there was no significant main effect for visit (p = 0.761), but there was a moderate contraction × visit effect size ($\eta_p^2 = 0.059$). Nevertheless, this effect was dominated by the mean difference in the unilateral versus bilateral MVC change during the non-dominant visit (mean ± SD: 1.3 ± 12.5% versus -6.5 ± 8.6%; Cohen's $d = 0.72$). Whereas the effect size for the unilateral versus bilateral force loss was considerably smaller for the no-mirror (Cohen's $d = 0.17$) and mirror (Cohen's $d = 0.24$) visits. The lack of a significant cross-over effect of fatigue in the present study is similar to some reports (Aboodarda et al., 2016; Halperin et al., 2014; Zijdewind et al., 1996), but not others (Halperin et al., 2015; Martin and Rattey, 2007; Post et al., 2008; Rattey et al., 2006; Todd et al., 2003; Ye et al., 2017). The magnitude of mean force loss for the contralateral, non-fatigued hand during bilateral contractions (~2 – 6%) is within a similar range of previous reports (Halperin et al., 2015). However, the mean changes during unilateral contractions for the non-fatigued hand were small (-0.1 – +1.3) and not significantly different than the changes during the control visit. Indeed, many participants, roughly half, showed a facilitatory response for the non-fatigued hand after the fatigue protocol during unilateral contractions (Figure 11). Interestingly, following the mirror visit, the non-fatigued flexor carpi radialis showed a significant mean increase in EMG amplitude during unilateral contraction compared to control values. In addition, the mean increase in EMG amplitude during the unilateral contraction was significantly greater than the mean decline during the bilateral contraction of the mirror visit (Figure 15). These results are interesting for a few reasons. First, significant force

reductions for the contralateral homologous muscle or heterologous non-local muscle groups have been observed following fatigue with the upper limb (Kennedy et al., 2013: Post et al., 2008; Ye et al., 2018), while a majority have not (Aboodarda et al., 2016; Halperin et al., 2014; Halperin et al., 2015). In fact, methodological examination across studies shows that for the upper limbs, maximal force values are not consistently impaired during a single MVC for the non-fatigued limb (Halperin et al., 2014; Li et al., 2018;). Instead, significant cross-over effects manifest after multiple maximal contractions or during a sustained contraction for the contralateral, non-fatigued limb (Halperin et al., 2014; Halperin et al., 2015; Kavanagh et al., 2016; Li et al., 2018: Todd et al., 2003; Zijdewind et al., 1998). Second, the present data suggest that the cross-over of fatigue may be dependent on limb dominance and the mode of contraction. To date, no study has directly compared cross-over effects between dominant and non-dominant limbs nor unilateral versus bilateral force loss for the contralateral, non-fatigued limb. Third, the facilitatory increases in maximal unilateral force for the non-fatigued hand demonstrated by many participants, as well as the increase in EMG amplitude during unilateral contraction of the mirror visit, is in line with similar reports (Aboodarda et al., 2016; Halperin et al., 2015) that have observed significant increases in corticospinal excitability for the non-fatigued limb despite no significant change in MVC force. The lack of a significant change in MVC force for the non-fatigued hand during the mirror visit is similar to the findings of Tsutsumi et al. (2011), however the significant changes in EMG amplitude for the non-fatigued flexor carpi radialis after the mirror visit are entirely novel and may reflect unique illusion-based changes in the excitatory-inhibitory balance along the motor pathway.

CHAPTER 6: CONCLUSIONS

In conclusion, this study observed several novel findings related to bilateral limb interactions with and without illusionary mirror visual feedback. The present observations showed a significant bilateral deficit, and this was primarily expressed by the stronger, dominant limb. The most exciting finding presented here is that illusionary mirror visual feedback attenuated the magnitude of force loss between unilateral and bilateral contractions for the fatigued hand. During the other two fatigue visits, the relative loss of maximal bilateral force was significantly greater than unilateral force loss for the fatigued hand. There were no observations of a significant cross-over effect of fatigue during maximal unilateral contractions of the contralateral, non-fatigued hand. However, the present data suggest that the cross-over effects of fatigue may be contraction and limb dependent. Specifically, the largest cross-over effect was observed during the bilateral contraction following fatigue with the non-dominant hand. The present data also showed no significant sex differences in the bilateral index, EMG amplitude response, or any of the comparisons in relative fatigability. The latter observation is in agreement with many sex-related reports on relative fatigability following maximal intermittent fatigue protocols.

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Appendix – A.

The UNIVERSITY of OKLAHOMA

Institutional Review Board for the Protection of Human Subjects

Approval of Initial Submission – Expedited Review – AP01

Date: May 21, 2018   IRB#:   9346

Principal   Approval Date: 05/21/2018
Investigator: Joshua Corbin Carr   Expiration Date: 04/30/2019

Study Title: An examination of the cross-over effects of fatigue with and without mirror visual feedback

Expedited Category: 4

Collection/Use of PHI: No

On behalf of the Institutional Review Board (IRB), I have reviewed and granted expedited approval of the above-referenced research study. To view the documents approved for this submission, open this study from the *My Studies* option, go to *Submission History*, go to *Completed Submissions* tab and then click the *Details* icon.

As principal investigator of this research study, you are responsible to:
- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations 45 CFR 46.
- Obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB policy.
- Maintain accurate and complete study records for evaluation by the HRPP Quality Improvement Program and, if applicable, inspection by regulatory agencies and/or the study sponsor.
- Promptly submit continuing review documents to the IRB upon notification approximately 60 days prior to the expiration date indicated above.
- Submit a final closure report at the completion of the project.

If you have questions about this notification or using iRIS, contact the IRB @ 405-325-8110 or irb@ou.edu.

Cordially,

Lara Mayeux, Ph.D.
Chair, Institutional Review Board

Appendix – B.

PRE-EXERCISE
TESTING HEALTH &
EXERCISE STATUS
QUESTIONNAIRE

The University of Oklahoma
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

Name _____ Date_____

Home Address_____

Phone _____

Person to contact in case of emergency _____

Emergency Contact Phone _____ Birthday (mm/dd/yy)____/____/____

Gender_____ Age _____(yrs) Height _____(ft)_____(in) Weight_____(lbs)

Does the above weight indicate: a gain_____ a loss_____ no change_____ in the past year?
If a change, how many pounds?_____(lbs)

A.   JOINT-MUSCLE STATUS (✓Check areas where you currently have problems)

Joint Areas
( ) Wrists
( ) Elbows
( ) Shoulders
( ) Upper Spine & Neck
( ) Lower Spine
( ) Hips
( ) Knees
( ) Ankles
( ) Feet
( ) Other_____

Muscle Areas
( ) Arms
( ) Shoulders
( ) Chest
( ) Upper Back & Neck
( ) Abdominal Regions
( ) Lower Back
( ) Buttocks
( ) Thighs
( ) Lower Leg
( ) Feet
( ) Other_____

B.   HEALTH STATUS (✓Check if you currently have any of the following conditions)

( ) High Blood Pressure
( ) Heart Disease or Dysfunction
( ) Peripheral Circulatory Disorder
( ) Lung Disease or Dysfunction
( ) Arthritis or Gout
( ) Edema
( ) Epilepsy
( ) Multiply Sclerosis
( ) High Blood Cholesterol or
     Triglyceride Levels
( ) Allergic reactions to rubbing alcohol
( ) Multiple Sclerosis
( ) Myasthenia Gravis

( ) Acute Infection
( ) Diabetes or Blood Sugar Level Abnormality
( ) Anemia
( ) Hernias
( ) Thyroid Dysfunction
( ) Pancreas Dysfunction
( ) Liver Dysfunction
( ) Kidney Dysfunction
( ) Phenylketonuria (PKU)
( ) Loss of Consciousness
( ) Huntington Disease
( ) McArdle Disease
( ) Peripheral Nerve Disorders

* *NOTE: If any of these conditions are checked, then a physician's health clearance will be required.*

C. PHYSICAL EXAMINATION HISTORY

Approximate date of your last physical examination_____

Physical problems noted at that time_____

Has a physician ever made any recommendations relative to limiting your level of physical exertion? _____YES _____NO
If YES, what limitations were recommended?_____

D. CURRENT MEDICATION USAGE (List the drug name and the condition being managed)

MEDICATION   CONDITION

_____   _____

_____   _____

_____   _____

E. PHYSICAL PERCEPTIONS (Indicate any unusual sensations or perceptions. ✓Check if you have recently experienced any of the following during or soon after *physical activity* (PA); or during *sedentary periods* (SED))

PA   SED   PA   SED
( )   ( ) Chest Pain   ( )   ( ) Nausea
( )   ( ) Heart Palpitations   ( )   ( ) Light Headedness
( )   ( ) Unusually Rapid Breathing   ( )   ( ) Loss of Consciousness
( )   ( ) Overheating   ( )   ( ) Loss of Balance
( )   ( ) Muscle Cramping   ( )   ( ) Loss of Coordination
( )   ( ) Muscle Pain   ( )   ( ) Extreme Weakness
( )   ( ) Joint Pain   ( )   ( ) Numbness
( )   ( ) Other_____   ( )   ( ) Mental Confusion

F. EXERCISE STATUS

Do you regularly engage in aerobic forms of exercise (i.e., jogging, cycling, walking, etc.)?   YES   NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly lift weights?   YES   NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly play recreational sports (i.e., basketball, racquetball, volleyball, etc.)?   YES   NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Appendix – C.

Handedness Questionnaire

Name:_____ Date:_____ Sex:_____

For each of the scenarios below, please indicate (1) which hand you use for that activity, and (2) if you ever use the other hand for that activity.

Activity	Left	No preference	Right	Do you ever use the other hand?
Writing				
Drawing				
Throwing				
Using Scissors				
Using a toothbruth				

Total

Appendix – D.

Signed Consent to Participate in Research

Would you like to be involved in research at the University of Oklahoma?

I am Joshua C. Carr from the Health and Exercise Science Department and I invite you to participate in my research project entitled "The cross-over effects of fatigue with and without mirror visual feedback". This research is being conducted at the Collums building of the Health and Exercise Science Department. You were selected as a possible participant because you are a healthy individual between 18 – 35 years of age. You must be at least 18 years of age to participate in this study.

Please read this document and contact me to ask any questions that you may have BEFORE agreeing to take part in my research.

What is the purpose of this research? The purpose of this research is to examine how mirror visual feedback moderates the development of fatigue within the neuromuscular system. More specifically, we are examining whether fatigue of one arm reduces the force capacity for the other arm, and if mirror visual feedback influences these responses.

How many participants will be in this research? About 30 people will take part in this research.

What will I be asked to do? If you agree to be in this research, you will perform maximal voluntary hand grip contractions (MVCs) of your dominant and non-dominant hand before and after a fatiguing protocol. Two MVCs will be randomly performed with the dominant hand, the non-dominant hand, and both hands, these contractions require maximal effort. During all strength and fatigue testing, two surface electromyography (EMG) sensors will be placed on both of your forearms. These sensors only detect the electrical activity produced by the muscles. The fatigue protocol will require you to perform 9 intermittent fatiguing MVCs sustained for 20 seconds with 20 seconds of rest in-between. In total, 3 minutes of maximal activity will be performed. This protocol will be performed on three separate visits, two will be for the dominant hand, and one will be for the non-dominant hand. For the fatiguing visits, a visual partition will be placed in front of you and you will not see the other (non-fatiguing) hand. More specifically, during one of the fatiguing dominant hand visits 'mirror visit', the mirror image of the fatiguing hand will be superimposed onto the non-fatiguing hand, providing the illusion that both hands are contracting. The other visit for the dominant hand 'no mirror visit' will not use a mirror and instead a blank cardboard divider will be used. This same setup will be used for the fatiguing visit for the non-dominant hand.

How long will this take? Your participation will require 5 visits and will total no more than 4.5 hours.

What are the risks and/or benefits if I participate? The fatigue protocol will induce temporary muscle discomfort which will quickly subside.

What do I do if I am injured? If you are injured during your participation, report this to a researcher immediately. Emergency medical treatment is available. However, you or your insurance company will be expected to pay the usual charge from this treatment.

701-A-1

The University of Oklahoma Norman Campus has set aside no funds to compensate you in the event of injury.

Will I be compensated for participating? You will receive a complementary shirt for your time and participation in this research. You will receive the shirt after completing the study in its entirety.

Who will see my information? In research reports, there will be no information that will make it possible to identify you. Research records will be stored securely and only approved researchers and the OU Institutional Review Board will have access to the records.

You have the right to access the research data that has been collected about you as a part of this research. However, you may not have access to this information until the entire research has completely finished and you consent to this temporary restriction.

Do I have to participate? No. If you do not participate, you will not be penalized or lose benefits or services unrelated to the research. If you decide to participate, you don't have to answer any question and can stop participating at any time.

Who do I contact with questions, concerns or complaints? If you have questions, concerns or complaints about the research or have experienced a research-related injury, contact me or the faculty sponsor at:

Joshua C. Carr   Michael G. Bemben
918 – 232 – 6964   405 -325 - 2717
jc.carr@ou.edu   mgbemben@ou.edu

You can also contact the University of Oklahoma – Norman Campus Institutional Review Board (OU-NC IRB) at 405-325-8110 or irb@ou.edu if you have questions about your rights as a research participant, concerns, or complaints about the research and wish to talk to someone other than the researcher(s) or if you cannot reach the researcher(s).

701-A-1

You will be given a copy of this document for your records. By providing information to the researcher(s), I am agreeing to participate in this research.

Participant Signature	Print Name	Date
Signature of Researcher Obtaining Consent	Print Name	Date

IRB NUMBER: 9346
IRB APPROVAL DATE: 09/12/2018
IRB EXPIRATION DATE: 04/30/2019

Appendix – E.

RATING	DESCRIPTOR
0	REST
1	VERY, VERY EASY
2	EASY
3	MODERATE
4	SOMEWHAT HARD
5	HARD
6	-
7	VERY HARD
8	-
9	-
10	MAXIMAL

Are you interested in science? Fatigue? Mirrors?

VOLUNTEERS ARE NEEDED

Males and females aged 18-35 years who are right-hand dominant may qualify for inclusion.

This study intends to examine the effects of unilateral fatigue on the force capacity of the non-fatigued arm with and without mirror visual feedback.

Five total visits required
(Total time commitment < 4.5 hours)

You will receive a shirt after completing the study.

- Familiarization visit (1)
    - Paperwork + familiarization with procedures
    - ~1 hour
- Control visit (1)
    - Strength testing
    - ~45 minutes
- Fatigue visit(s) (3)
    - Strength testing + fatiguing exercise + strength testing
    - Fatigue will involve intermittent maximal contractions sustained for a total of 3 minutes
    - ~45 minutes

If interested please contact the researcher below:

Joshua Carr, PhD(c), CSCS
jc.carr@ou.edu
(918) 232 6964

The University of Oklahoma is an equal opportunity institution.