Disentangling Task Influence and Synergist Muscle Contributions to Evaluate Neurophysiological Mechanisms of the Bilateral Deficit Phenomenon

by

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The bilateral deficit (BLD) phenomenon is an inability to maximally contract bilaterally compared to the summed unilateral contractions. The mechanism is unknown but presence of bilateral homologous (BH) BLD opposed to bilateral non-homologous (BNH) contractions suggests BLD reflects differences in corticospinal control. Yet the influence of methodological factors such as BLD calculation technique, task familiarity, and differences in synergist muscle contributions have received less attention. **Purpose:** Examine corticospinal and methodological contributions to BLD to determine its mechanistic basis. **Methods:** Eleven healthy adults (6 women/5 men, 25.6±3.7years; 171.81±11.44cm; 74.4±21.2kg) participated in a counterbalanced repeated measures study. Sessions one and seven, transcallosal inhibition (TCI) and voluntary activation were assessed with transcranial magnetic stimulation during maximal BH, BNH, and dominant flexion (DF) of the proximal elbow. Sessions two through six, bilateral and unilateral isometric contractions were performed repetitively with electromyographic measures of agonists, antagonists, and scapular stabilizing muscle activity. **Results:** BH BLD was present sessions 2-7 while BNH displayed no BI. Corticospinal measures did not differ between contractions or sessions. Task practice increased all measures of maximal force, but without translation to BH and BNH BLD performance, with poor reliability across test sessions. BLD varied as a function of task-specific stabilization practices. Specifically, BNH and DF were stabilized by upper extremity horizontal rotation, resulting in greater forces compared to BH, which was stabilized through the

sagittal plane. **Conclusion:** The results of this study indicate BLD reflects subtle differences in muscle stabilization during BH, BNH, and DF contractions, over differences in corticospinal control or task familiarity. Synergistic muscle co-activation during maximal isometric BNH and unilateral contractions likely improves stability, increasing force. The most significant finding of the study, however, is the poor reliability of BH and BNH BLD measures, which raises the need to consider the thresholds used to determine the presence of BLD.

Table of Contents

List of Figures

List of Tables

Preface

This work is to be submitted for the degree of Doctor of Philosophy in Rehabilitation Science at the University of Pittsburgh. This dissertation is a culmination of work which would not be possible without the support I received from my family, friends, and teachers, past and present.

When I was younger, I was diagnosed with an injury that a cast and crutches for 9 months, all concluding into a surgery and physical therapy. Marlene DeRosa was my physical therapist, and she is the person who inspired me to be in the field of sports medicine rehabilitation due to her positive and caring attitude, her ability to make painful work fun, and her goals to make me better. Marlene – I set out goals to be exactly like you when I grew up. Although things have changed, and I decided PT was not for me, you helped start me on the path to where I am today just by being you. Thank you so much for being such a big part of my life.

At Creighton University as an undergrad, I was truly challenged to grow as an adult, student, and teammate. For teaching me, and forcing me to grow, I would like to thank all of my rowing teaming, professors, and athletic trainers. These people taught me everything and forced me to grow when I failed. Thank you for teaching me and inspiring me in the world of exercise science and athletic training. Without your support, ridiculously hard classes, and requirements, I would not have been set up to succeed.

My master's degree was completed at the University of Nebraska at Omaha, earning my degree in Athletic Training. My advisor was Dr. Melanie McGrath, set my on the path to get into a PhD program by encouraging me to complete a masters' thesis. Thank you for being there through my panics and encouraging me to succeed. Through my master's program, however, I was

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My first full time job was as an athletic trainer at Belmont Abbey College, working with men's soccer, women's basketball and baseball teams. Through this busy schedule, my bosses and colleagues were my support system. Covering me when I couldn't be there, discussing injuries, and assuring me to keep going when eleven simultaneous shoulder rehabilitations seemed too much. You made me a better clinician. Yet, another thank you needs to go to the coaches, who tested me to get the athletes cleared sooner, but respected my decision to keep them back. I know I could not have asked for better coaches, those who cared about their team beyond performance and consistently challenged them to be better. You have inspired me to do research to reduce and rehabilitate sport injuries.

There are always those people who support you in the time you are with them, but then there are people who are in your life forever. I would like to start by thanking my second family, the Strathman clan. I met them when I was in high school, but they have been a huge support system since then. From this family, I would like to especially thank my best friend, and the smartest person I know, Brian Strathman. As you know, you were my sanity through high school and you have kept me grounded since then. I can't imagine my life without you, so I hope you move back west soon.

Of my life friends, I want to thank my college roommate, best friend, and matron of honor, Sarah Mooney. You know exactly how much I love you, and if I continue to write and thank you then it will be longer than the dissertation itself. You make me a happier and better person all the time. There are ten million things I could not have survived without you, literally. I also want to thank my amazing friends, Bre Bell and Ashley and John Erny, who all have kept me sane with daily pep talks. Thank you for your friendship, despite my dissertation obsession and insanity.

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take me outside my panic cycles and research mind, and maintain any glimpse of social life I could ever have. I was so lucky to find you at the beginning of this process and even luckier that you stayed and supported me through it. I love you. I also need to sneak in a thank you to my pups, Campbell, Diesel, Emmy, and SoCo. These furry guys were my therapy dogs through it all, and I could not be more grateful to have them in my life.

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directly inspired and shaped my future as a researcher. Chris, you are the reason that I am a researcher. Your guidance, red ink, support, life lessons, tough love, and weird stories somehow got me through it, despite our initial beliefs. There are no words to thank you for what you have done for me, and for all the other students at the lab. We recognize your hard work and passion to help the next generation of researchers. I just hope I will have your finesse to guide a student similar to myself through their PhD, but it is likely I will need your help and guidance to get through that as well. Thank you for making me into who I am today and giving me the confidence to reach even further.

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Each of these individuals have shaped my life by teaching, challenging, and supporting me. It is not without a community that any person can achieve such a feat on their own, and I am so grateful for mine. Thank you all.

1.0 Introduction

Originally discovered in 1961, Henry & Smith described a 3% deficit in bilateral handgrip strength, compared to the sum of the unilateral contractions, in an attempt to demonstrate neural overflow theory [1]. Currently known as the *Bilateral Deficit* (BLD) phenomenon, it is an inability to maximally contract bilaterally as compared to the sum of the corresponding unilateral contractions [2-4]. When the bilateral force is greater than the sum of individual contractions, bilateral facilitation (BLF) is evident [2]. This phenomenon is variable between and within subjects, ranging from BLD to BLF, and is reported as a percent range, known as Bilateral Index (BI); with negative (positive) percentages indicative of BLD (BLF) [2, 5].

Several theories followed Henry & Smith, guided by the potential influence of psychological factors, task characteristics and familiarity, and physiological limitations [5]. Many of these theories have been refuted, but some can be described as a methodological error rather than an underlying mechanism. For example, greater unilateral force production may reflect contributions from surrounding musculature to improve stabilization [6, 7]. Alternatively, BLD may result from low task familiarity and was thus be reduced or eliminated with task-specific practice [2, 8, 9]. *Without consideration of these methodological concerns, vexed researchers have not come to a consensus of the phenomenon underlying mechanism.*

One concept, however, has been consistent: BLD is present when maximal bilateral contractions are symmetric (homologous: BH) [10, 11], while otherwise similar asymmetric (non-homologous: BNH) contractions produce comparable bilateral and unilateral forces (considered no BI) [2, 12, 13]. Mechanistic basis of this concept is unknown but theorized to be caused by altered neural control, specifically ipsilateral motor cortex hemisphere suppression from the

contralateral hemisphere, termed transcallosal inhibition (TCI). As a response of redundant activity from the ipsilateral hemisphere, TCI is theorized to improve efficiency and precision of motor processes [14-16], due to prior increased and diminished TCI presentation during BH and BNH tasks, respectively, as compared to unilateral [17].

Although considered the predominant theorized mechanism for BLD [2, 12, 17-19], evidence of altered TCI between BH, BNH, and unilateral tasks originates from submaximal contractions [17, 20]. Transcallosal inhibition between BH and unilateral maximal voluntary isometric contractions (MVIC) remained ambiguous [18], but theorized to diminish descending neural drive and resultant voluntary activation (VA) [21]. Assessment of VA has revealed varied results [12, 18, 21-24] between the unilateral and BH tasks due to the inherent complexity of corticospinal measures within MVICs. Therefore, to properly assess within maximal isometric contractions, differences in BH and BNH activation patterns, as well as influence of task familiarity, must be properly evaluated to accurately assess neurophysiological control upon the BLD phenomenon.

1.1 Theoretical Underlying Mechanisms

1.1.1 Neurophysiological

Until the early 1960s, the distal extremities were theorized to be controlled solely by the contralateral hemisphere [25, 26]. Since then, neurons of the ipsilateral motor cortex have been identified as active during regular unilateral contractions in healthy adults, and capable of influencing the opposing hemisphere through transcallosal fibers [27, 28]. Such connections may

support the hemispheric integration needed for fast and efficient task execution [27, 29, 30], but differences in the contributions of such activity during unilateral and bilateral maximal contractions is unclear [31].

Several approaches have been used to investigate the role of the ipsilateral hemisphere during unilateral and bilateral tasks [14, 31, 32].

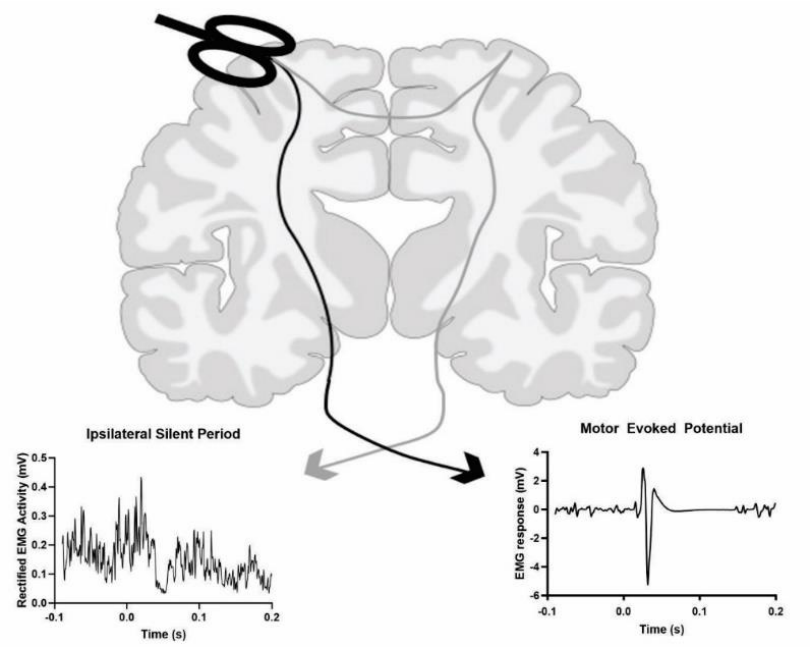


Figure 1. Ipsilateral Silent Period using TMS

TMS pulse travels through the hemispheres, known as the corpus callosum, sending a signal to the ipsilateral EMG, but the silent period is a mark of the signal's inhibition.

Bi-hemispheric neuronal activation patterns were explored through BH and unilateral tasks using encephalogram (EEG) and magnetic resonance imaging (MRI). Suppression of motor potential [19, 33-35] and diminished supplementary motor area [36] were reported, respectively, during maximal BH compared to unilateral contractions. Although contributions to BLD are unclear during bi-hemispheric neural activity, more granularity can be made with measures of the ipsilateral silent period (iSP), evoked with single pulse transcranial magnetic stimulation (TMS; Figure 1) [37-41].

As a research tool, TMS facilitates the characterization of corticospinal system function *in vivo*, enabling the neural basis of BLD to be further examined through resultant muscle responses [17, 18, 21]. When TMS is delivered to subjects with corpus agenesis or corpus callosum lesions, iSP is absent [39, 41, 42]. Furthermore, when measured at known stages of corpus callosum transformation, including age [43-48], fine motor control [49], and physical activity [48, 50], the length and/or area of iSP is highly correlated with callosal connections.

Previous studies have demonstrated iSP was increased during BH and decreased with BNH compared to submaximal unilateral contractions [17, 20]. These results have not been repeated during maximal isometric tasks [5, 18] with consequential unknown TCI influence upon maximal force. Yet, only one study has attempted to do so, using BH and unilateral isometric knee extension tasks, and omitting BNH [18]. Previous research also suggested bilateral training may be the BLD overriding mechanism, producing BLF [2]. Therefore bilateral (weightlifters and powerlifters; N=7), unilateral (high jumpers and long jumpers; N=5), and untrained (N=5) subjects were recruited. Nevertheless, no differences were evident in BLD or iSP between BH and unilateral contractions, which might have reflected small group sizes or trial numbers [18].

Using TMS, decreased VA was evident during a BH task, in a population with no BI [21]. Although this study did not directly measure TCI, VA might have resulted from decreased neural drive [2, 4, 21, 22, 24, 34-36, 51, 52]. Measures of VA are common in BLD literature, but have yielded inconsistent results [12, 18, 21-24, 53]. These alterations may have been influenced by difference in task, activation patterns, and population, and should be assessed to properly evaluate neural influences underlying the BLD phenomenon, warranting further research.

1.1.2 Task Familiarity

Maximal voluntary isometric contractions (MVIC) are highly reliable over multiple days, with interclass coefficient correlation (ICC) values $\geq$ 0.96 [54, 55]. The reliability of BLD is currently unknown, but inter-day differences in BLD of 17% are evident when assessed with isometric knee extensions [8]. Since BLD is expressed as the ratio of bilateral to the summed unilateral MVICs, a slight change in either input may substantially alter BLD estimates.

When a new task is learned, movement patterns are highly variable, with efficiency and precision developed after practice [56, 57]. Yet, formerly learned movements can either interfere with, or facilitate, the development of the new motor skill through previous spatial (in)familiarity and task variability [58]. Accordingly, consistent practice of bilateral and unilateral tasks can lead to bilateral facilitation (BLF) and BLD, respectively [2, 52]. Demonstrated in bilaterally, unilaterally, and untrained subjects BLF was observed in the former and BLD in the latter two [2]. This may be due to the prerequisite for *the bilateral group only*: familiarity with bilateral knee extension [2]. Yet, BLF was no longer evident when measured with peak average force across three trials, but the unilateral and untrained BI remained the same [2]. These transformed BI results may be due to familiarity of the tested task in combination of bilateral power training and developed strategy to achieve peak bilateral force. Nevertheless, attempts to replicate this study were unsuccessful, with no BLF in any group [8, 18], which may be due to differences in specific task training.

1.1.2.1 Measures of Maximal Force

Bilateral deficit is typically calculated based on the ratio of *peak forces*. Yet, the definition of maximal force is inconsistent, and has *yet to be addressed as a methodological concern*. Most

studies assess BI using the absolute peak of each the unilateral and bilateral force [2, 4, 8, 9, 18, 23, 52, 59-62]. Yet, a single maximal point may be prone to error or bias [63], and therefore other measures have been proposed, including the averaged peak force [63-65], peak of force plateaus [6, 10, 21, 33-35], and the average of the force plateaus [2, 22, 66]. Each represents a different variable within the MVIC, and can alter BLD estimates [2].

Although peak values may be prone to error and bias, use of the average values may not be appropriate to assess maximal strength, as it is not a true representation of maximal values. Thus, one could argue averaged values are appropriate to measure force during submaximal or fatigue tasks, where overall loss of force production is appropriate. Consequently, as seen in Figure 2 (section 2.2), variability of MVIC plateau over the full maximal contraction is evident, and error may still occur with an average force analysis. Averaged forces, therefore, may not be more optimal to measure BLD than peak force, specifically if the decision relies upon the argument of bias and error.

1.1.2.2 Rate of Force Development

The strategy to achieve maximal force may be better elucidated with the analysis of force slopes from movement initiation to force plateau or peak, known as rate of force development (RFD) [67]. This has recently become a popular measure to characterize strength and explosive adaptations to training, over measures of maximal force [68, 69]. The magnitude of RFD slope is thought to be dependent on the motor unit contractile properties, with low thresholds recruited prior to large threshold motor units [70, 71]. Consequently, the early RFD slope (<75ms) is altered due to neural adaptations [67, 72, 73], as latter slope (> 75ms) is theorized to be influenced by the speed related properties of the muscles, with maximal muscle strength accounting for 52-81%

RFD variance [73]. Consequently, mechanisms which alter RFD are not fully understood, due to difficultly in reliable and valid evaluation [69]

Rate of force development may represent a biomarker of BLD, with a 13% reduction in bilateral knee extensor RFD compared to its unilateral counterpart [22]. While BI was not reported in this study, unilateral and bilateral VA as evoked by tetanic stimulation, presented with 94% and 89% VA, respectively [22]. Yet, slope was measured over the course of full force development, and therefore the cortical mechanism contributing to the RFD decrement is unknown [22]. Within a population presenting with no BI, RFD was analyzed at 0-50ms, 50-100ms, and 100-150ms, reporting BLD at 50-100ms of the RFD slope [63]. Mechanisms to these bilateral RFD decrements are unknown in terms of maximal force, but changes observed over the course of several trials may reveal contractile properties related to BLD.

1.1.3 Synergistic Musculature

Bilateral deficit could be the result of added contributions of surrounding musculature to stabilize unilateral tasks. While commonly theorized, there is little evidence to support different patterns of core or synergist muscle activation during unilateral contractions. Thus far, only differences in force between unilateral and BH plantar flexion have been directly related to increased contralateral hip torque during unilateral MVIC [6], as assessed with valid and reliable closed and opened kinetic chain device [74], to simultaneously observing all lower extremity torque during the BH and unilateral tasks.

Other study of synergistic muscle contributions has been observed based on electromyography (EMG), which can be used to assess the magnitude and timing of muscle activation during different tasks. For example, the rectus abdominis and external obliques are

active during dynamic leg press exercises, but not handgrip strength [66]. BLD in the former, but not the latter, was theorized to be due to core activation, but was limited by lack of other lower extremity muscle activation observation [66]. As other studies have observed unilateral squats are completed with altered activation from bilateral tasks [7], assessment of agonist, antagonist, and synergist muscle activity are necessary to establish altered strategies to produce unilateral and bilateral maximal force.

1.2 Definition of the Problem

A consensus on the veracity and cause of BLD is lacking. Ambiguous results may reflect differences in research approaches contributed by methodological factors such as synergist muscle contributions, low or variable task familiarity, and the technique used to determine maximal force. Nonetheless, there is evidence to support the contention that BLD reflects differences in interhemispheric communication during BH, BNH, and DF contractions [3, 5, 13, 18, 21, 22]. In this case, increased TCI may impair coordinated maximal force production during BH contractions, as evidenced by submaximal VA and the presence of BLD [17, 20]. Nevertheless, given extensive technological requirements [2, 10, 19, 24, 33, 35, 51] and heterogeneous study populations [18], this theory is untested. An assessment of BLD that incorporates the influence of calculation technique, familiarity, and synergist muscle contributions is, therefore, necessary and would provide the context needed to interpret the potential neurophysiological basis of BLD.

1.3 Purpose

The purpose of this study is two-fold: (1) to determine the relationship between neurophysiological activity and BLD, and (2) to assess the influence of task familiarity, synergistic muscles, and force calculation technique on BLD estimates. This research approach will address technical sources of variability and comprehensively assess potential neurophysiological contributions to the BLD phenomenon.

1.4 Specific Aims and Hypotheses

Specific Aim 1:

Assess neurophysiological basis of BLD

Hypothesis 1a: Transcallosal inhibition will be greater (lower) during BH (BNH) compared to DF

Hypothesis 1b: Voluntary activation will be lower for BH compared to BNH and DF

Hypothesis 1c: Transcallosal inhibition and voluntary activation will strongly relate to BH and BNH BI

Hypothesis 1d: Task familiarity will be associated with changes in VA and TCI, regardless of contraction type.

Specific Aim 2:

Examine changes in strategy to achieve maximal force with increased movement task familiarity

Hypothesis 2a: Coefficient of Variation will decrease with increased task familiarity

Hypothesis 2b: Rate of force development will increase with increased task familiarity

Specific Aim 3:

Examine relationship between non-primary agonist muscle activation and BLD

Hypothesis 3: Bilateral and unilateral MVICs will produce similar muscle activation patterns

1.5 Study Significance

Several isolated lines of effort have attempted to explain the BLD phenomenon based on neurophysiological factors, task familiarity, and contributions from surrounding musculature. Disparate approaches have led to conflicting results with no resultant consensus. This study will comprehensively assess the contributions of leading theoretical causes of BLD, including physiological and methodological factors. To accomplish these goals, the research will combine purpose-built muscle testing equipment, advanced neurophysiological techniques, and sensitive/large-array sensing capabilities. Observation of BNH will be added as a secondary level of analysis to capture measures of no BI and altered neurophysiological and physiological strategies to achieve BNH from BH MVIC. This comprehensive investigation will capture inherent methological errors of maximal force measures to progress comprehension of the BLD underlying mechanism.

2.0 Review of Literature

Several theories to explain BLD have been developed since its original discovery, guided by psychological, physiological, and practical considerations [5]. Many of these theories have been refuted, but some theoretical mechanisms may represent technical factors such as differences in task familiarity [2, 8, 9], synergist muscle contributions [6, 7], and force calculation technique. *Without consideration of these methodological concerns, researchers have not come to a consensus of the underlying phenomenon.* One concept has been consistent: homologous bilateral contractions (BH: e.g. both biceps brachii), are associated with a BLD [10, 11], while non-homologous contractions (BNH: e.g. one biceps brachii and other triceps brachii) produce no BI (BI = 0) [2, 12, 75]. Currently, the only understanding of this difference is through altered neural control between hemispheres, considered TCI. This section will discuss the current body of research on BLD, exploring potential influence of common methodological differences between BH and BNH with concurrent study of neurophysiological differences which may exacerbate the BLD phenomenon.

2.1 Psychological

Initially, BLD was theorized to be due to lack of psychological fortitude to achieve maximal BH force. Concepts include prior knowledge of BLD phenomenon, perceived exertion, and division of attention. Although each of these may play a role in contraction force, the

contribution of these factors to BLD is inconsequential. Nevertheless, there are interesting findings that are relevant to the BLD literature base.

The perception and *knowledge* of forces acting on, and by the body, are influenced by previous expectations [76]. This is exemplified with decreased perception of impact with the knowledge of an incoming tackle, as well as an increase in force production, overcoming a previous maximal force. Although based upon unilateral and bilateral maximal forces, the BLD phenomenon is not reportedly affected by knowledge of the phenomenon [60, 77]. To assess, a single population was given none, fake, and correct BLD information on different testing days, but no BI differences were reported during an isometric leg press task [60]. Differences during a single session, when half of the participants were informed of the phenomenon, also yielded no BI differences [77]. Although results suggest no differences in BI based upon phenomenon knowledge, real time feedback during maximal contractions were not given. As subjects were able to compare to previous trials or experiences, and able to quantify the current trial based off the previous [76].

Perceived exertional bias was theorized to decrease bilateral force due to the increased loads, as compared to the unilateral [3]. To test, bilateral and unilateral isometric elbow flexion at 25, 50, 75, and 100% MVIC were compared, reporting decreased bilateral strength at all levels [10, 11, 78]. Interestingly, as exertional levels increased, BI reportedly decreased [78] and increased [11] with no explanation as to why this occurred. Therefore, differences in submaximal BI may indicate different mechanisms from maximal contractions and should be interpreted with caution.

Decreased bilateral force has additionally been hypothesized to be due to a *division of attention*. Initially tested using elbow flexion BLD was present during BH but not BNH

contractions [13]. Researchers suggested this to be due to altered strategies of neural interaction within the cerebral hemisphere, differing between performance of BH and BNH voluntary movements [13]. Similar results were observed in later re-evaluated using elbow flexion with knee extension [2] and elbow flexion with thumb adduction [12]. These differences identified that maximal voluntary neural drive is not limited by contralateral activation, but is specific to homologous muscle contractions.

2.2 Familiarity

Task familiarity is the most understudied methodological factor in the BLD literature, with a single report of a 17% BI difference between testing days [8]; BI of 80 ± 2.5% (BLD) was reported on the first day, and 97 ± 2.9% (no BI) on the second, tested with isometric knee extension [8]. Familiarization trials have been implemented in some studies, but the criteria have not been standardized, typically serving as a warm-up prior to testing [6, 18, 79, 80]. This common methodological practice may be due to maximal isometric force reliability over multiple days [54, 55]. Yet, the strategies to produce maximal bilateral and unilateral contractions differ between subjects and may change based on tested tasks (ie lower versus upper extremity or uni- versus multi-articular tasks), thereby altering BI [5].

When learning a new task, the human brain generates highly choreographed patterns of muscle activity, which are altered by practice and experience [56]. As a result, the network of organized motor controllers adjusts to optimally achieve the new motor skill, also known as motor learning [57]. Initial higher task-relevant variability has been deemed highly important, predicting faster learning rates through explorative affordances [81]. Yet, tasks formerly learned can either

interfere with, or facilitate, the development of the new motor skill through previous spatial (in)familiarity and task variability [58]. This can be exemplified through differences in weightlifter and cyclist BI [2] as well as bilateral and unilateral specific weight training [52]. Through consistent practice of bilateral and unilateral tasks, the production of maximal force can be biased to the spatial familiarity [58], presenting as BLF and BLD, respectively [2, 52]. Though, comparison with different tasks within the same population may reveal different BI due to lack of previous practice.

This is exemplified in Figure 2 representing BH and BNH MVIC the first test session, where the BNH MVIC (dotted line) still presents with more variability and decreased RFD than the BH (solid black line), suggesting greater initial BH task familiarity than BNH. Although the present MVIC are not representative of the whole population, similar patterns are expected with the current study. Differences in averaged and maximal force measures will, therefore, result in altered BI. With task practice, it is theorized the plateau will become less variable, similar to the BH MVIC, resulting in less variability in all measures of averaged and peak force.

Practice of isometric tasks increases maximal force and RFD over the course of several training sessions [72]. When compared to an untrained control group, two weeks of training resulted in increased maximal isometric plantar flexion torque and RFD [72]. Interestingly, maximal torque and RFD were highly correlated ($r=0.95$, $p<0.001$) and were increased by the third test session [72]. Rapid adaptations have been reported elsewhere [82, 83], and likely reflects adaptations in the neuromuscular system, rather than changes in muscle structure [72, 82, 83].

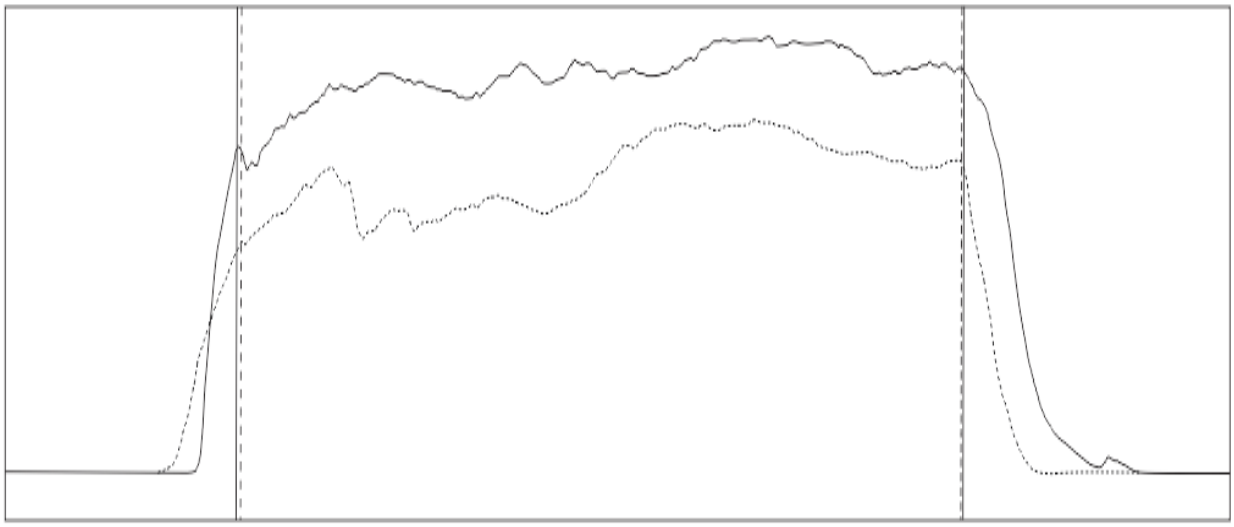


Figure 2. BH and BNH MVIC Plateau Variability

BH (solid line) and BNH (dotted line) MVIC plateau were pulled from a subject the first test session. The coefficient of variability (CV) of the plateau, marked with solid (BH) and dotted (BNH) lines, was calculated as the (SD/average)*100. Collected at 2000Hz, the CVs for BH and BNH plateaus were 5.6% and 9.6%, respectively.

2.3 Influence of Task

Tasks to assess BLD vary based on joint, range of motion, and type of contraction. Each of these factors affect maximal force production [3], but the influence on the ratio of unilateral to bilateral force is unknown. Unpredicted factors between unilateral and bilateral maximal force production, such as familiarity and differences in synergist muscle activation, can result in an inaccurate BI. Therefore, this section will explore the differences in tasks, clarifying how these variances may change the current understanding of BLD.

2.3.1 Isometric vs. Dynamic

Currently, isometric and dynamic tasks have been used to test the BLD phenomenon, but have presented with different BI: *dynamic BI* of -11.7 ± 9.7% (upper extremity: −5.8 ± 3.5%; lower extremity: −13.2 ± 10.3%) vs. *isometric BI* of -8.6 ± 8.5% (upper extremity: −9.0 ± 8.0%; lower extremity: −8.1 ± 9.2%) [5]. Some hypothesize these differences may be due to altered underlying mechanisms [5], muscle coordination patterns [65], or due to the measurement of maximal force, differing from isometric tasks. Specifically, maximal jump force or height [59, 64, 84, 85] peak torque [86-88], work [85], individual joint peak torque [85], and ground reaction forces [85] have been used. Although these measures can be clinically relevant, the maximal force is not similar to isometric tasks, which is matched by joint angle.

It is also theorized a biomechanical advantage during unilateral dynamic movements is apparent, considered the force-velocity relationship [64, 85, 89]. Differing between concentric and eccentric contractions, the force-velocity relationship is, respectively, inversely and directly related [90-92]. Exemplified with a squat jump or bench press throw, the bilateral dynamic task produces greater velocity as compared to the unilateral, resulting in reduced force generation from each joint [59, 93].

To attempt control of the force-velocity relationship, body weight was accounted for during a horizontal leg press jump. Measuring individual joint power using inverse dynamics and ground reaction force, 50% and 100% body weight during unilateral task was compared with 100% and 200% body weight during bilateral tasks, respectively. Joint maximal power measures revealed evolving BI within each joint through the full movement, but overall BLF in the knee and BLD in the ankle and hip. Analysis of the task ground reaction force revealed an overall BI of -13%, but consistently evolved through the task [85].

This variation is suggested to be due to increased muscle activation of the soleus, medial gastrocnemius, biceps femoris, vastus medialis, rectus femoris, and gluteus maximus during the unilateral jump, as compared to the bilateral [85]. Additionally, the complex dynamic movements consistently change the force produced [59, 65, 85], without the capability to account for muscle specific force contributions. Thereby consideration of the BLD underlying mechanism is questionable during dynamic tasks due to lack of BI consistency and major mechanistic variations.

While similar BI is present in dynamic and isometric tasks, the use of dynamic contractions to determine the underlying mechanism is considered *inherently flawed*. The remainder of this review will, therefore, focus on isometric tasks to understand the BLD underlying mechanism.

2.3.2 Synergist Muscle Activation

Compared to single joint and upper extremity tasks, multi-joint and lower extremity tasks are consistently associated with BLD [5], which may reflect minimized contributions of surrounding muscles during more isolated tasks [5, 6, 23, 66, 85, 94]. This is exemplified with reports of increased unilateral planter flexion due to contralateral hip torque, measured using a closed kinetic chain device [6, 74]. Of importance, the same task completed in the open chain device revealed no BI, as the apparatus was uncoupled from the body, allowing localization of plantar flexion without other joint measures [6, 74]. Yet, researchers are still uncertain if contributions from supporting musculature are the cause of BLD.

Consistently, activation of the biceps femoris is equal during isometric bilateral and unilateral knee extension [2, 18, 23, 63, 95], which is consistent with other tasks [5]. Yet, synergist and core muscle activation, as measured with electromyography sensors, is reportedly increased during unilateral multi-articular movements [7, 23, 66]. Specifically, core activation was greater

with unilateral and bilateral leg press than isometric handgrip tasks, reported with BLD and no BI, respectively [66]. These results suggest increased core activation may cause BLD, but inconsistencies in task and measures of contributing synergist muscle activation lead to equivocal conclusions. This is further supported with reports of increased hamstring and gluteus medius activation during unilateral squats, and greater quadriceps activation during bilateral tasks [7, 23].

Activation and control of the upper extremities are distinct from the lower extremities, and therefore may affect the expression and magnitude of BI [96]. Yet, muscle activation in relation to BLD have yet to be observed in the upper extremities. Of importance, shoulder and elbow activation is supported through the scapula [97], involving a complex coordination of muscles which can be altered by training and or insufficient biomechanics [98-100] Therefore, use of an upper extremity closed kinetic device may not provide the proper granularity of synergist muscle contributions. Yet, when observing upper extremity tasks, analysis of unilateral and bilateral muscle activation patterns are necessary to assess BLD or BLF.

2.4 Neurophysiological

Higher order inhibition has been theorized as predominant BLD mechanism [2, 12, 24]. This is supported by the suppression of EEG movement related cortical potentials between motor cortices (C3 and C4) during bilateral contractions, indicative of a shared BH neural drive [33-35]. Recently, TMS has gained prominence as a technique to non-invasively probe the corticomotor system function based on measures such as interhemispheric inhibition and voluntary activation. This section will discuss the role of interhemispheric communication and voluntary activation in

bilateral and unilateral tasks and provide insight into theoretical neural contributions to the BLD phenomenon.

2.4.1 Transcallosal Inhibition

As early as 1966, Gazzangia and Sperry reported faster reaction and completion times during simultaneous task performance in patients without a corpus callosum (callosotomized brain) [101]. The callosotomized brain blocked lateralized information transfer, leading to dissociation between hemispheres and decreased information flow [102]. Yet, during bilateral tasks, the movement was reported to remain with spatial movements isolated to each arm, and therefore *demonstrates the necessity of both hemispheres, and shared control, during a bilateral task* [27].

Communication between hemispheres is largely enabled by the corpus callosum, the largest white matter fiber bundle in the brain [15, 103]. Between motor cortices, fibers are large in diameter, myelinated, and less densely packed compared to other callosal fibers, and these properties enable rapid communication [15, 27, 29, 30, 102, 103]. It is hypothesized these physiological characteristics have led to the human consciousness through learning, continuous neural adaptations, and optimal responses to cognitive and performance tasks over the course of a lifetime [27, 29, 30, 104].

Bi-hemispheric control, during bilateral task, is theorized to cause excess movement and chaos between hemispheres. It is therefore theorized increased TCI during bilateral tasks may act to increase performance by blocking the signal from the opposing hemisphere, so to reduce any unnecessary noise, and optimize completion of the task [102, 105, 106]. This is further supported with reports of inhibition to the opposing motor cortex and surrounding cortical areas during

unilateral tasks, while bilateral movements showed joint inhibition to bilateral hemisphere motor cortex [28].

There is much debate over the model of communication between hemispheres, with arguments for both an inhibitory model and an excitatory model. The inhibitory model suggests independent processing is maintained within the hemispheres, hindering activity to the opposing direction, and thereby increasing unilateral brain function or task execution, known as lateralization [106]. The excitatory model suggests the corpus callosum shares and assimilates information between the hemispheres, producing less lateralization through greater connectivity, and thereby masks independent hemisphere efforts during bi-hemispheric tasks [106]. Currently, the excitatory model seems most prevalent, with evidence of suboptimal hemisphere to enable task completion by the better "performing" hemisphere [102, 105, 106]. This is further supported by task laterality negatively correlated with increased corpus callosum size [105] and surgically split hemispheres [107, 108].

The magnitude of BLD increases with bilateral training and decreases with unilateral training [52, 109]. In parallel, bilateral training lowers TCI, as evident in bilaterally trained musicians [110]. Yet, it is questionable if task familiarity or training can alter TCI, resulting in BLD. To date, the relationship between TCI and BLD has only been explored in a single study, where predominately bilateral- (weightlifters and powerlifters; N=7) and unilateral- (high jumpers and long jumpers; N=5) trained athletes were compared with untrained individuals (N=5) [18]. No BI was produced in any group, and there were no differences in TCI during isometric knee extensions, regardless of task [18]. Solely repeated in unilateral and BH and BNH submaximal contractions of the elbow [17] thumb muscles [20], TCI was greatest in BH and least in BNH,

compared with unilateral. Without evidence of how TCI effects the production maximal force, consideration of TCI as the predominant underlying mechanism remains equivocal.

2.4.2 Voluntary Activation

Voluntary activation is a measure of neural drive from the central nervous system to the muscle [111], and is determined based on responses to electrical stimulation during and before or after contractions using the interpolated twitch technique [5, 112]. The premise of the technique is that stimulation of the peripheral nerve during maximal contractions will create little additional force (in the form of a twitch) if voluntary force production is maximal. [3, 12, 18, 22-24]. The majority of studies indicate that voluntary activation is greater during unilateral contractions [12, 22] although similar [24] or greater VA [18, 23] was found during isometric knee extensions when compared to BH. Such differences may be due to measurement variability [5], as well as the inaccuracy of peripheral electrical stimulation to measure voluntary activation [113].

To assess VA involving the descending corticospinal pathways, TMS protocols were developed and later validated in the biceps brachii, with use of 50%, 75%, and 100% of biceps brachii MVIC to calculate the superimposed twitch [111]. The superimposed twitches were graphed and fitted with a linear regression, resulting in the estimated resting twitch obtained at the point of the y-axis. The following four methods were used: (1) the single linear regression with 10 of each the 50%, 75%, and 100% voluntary contractions, (2) the average of 10 separate linear regression for each of the aforementioned voluntary contractions, (3) the average of five separate linear regressions only using 50% and 100% voluntary contractions, and (4) the average of 5 separate linear regressions only using 75% and 100% voluntary contractions [111]. With the first

considered as the standard, methods 2 and 3 were statistically the same to method 1, but method 4 was not reliable.[111]

Yet, later re-evaluation of the superimposed twitch identified some methodological challenges, stating that knowledge of the pitfalls is necessary to further understand the measure [113]. Specifically, TMS can produce off-target effects, including the excitation of unintended or antagonist muscles. [114, 115]. Furthermore, muscle representation and stimulus intensity at the motor cortex is imperative, as increased stimulus intensity can cause unnecessary stimulation of the musculature surrounding the target muscle, thereby leading to invalid measures [113]. Variability of the measure may also alter the graphing method, at any intensity, as torque to stimulus output may not create an accurate linear regression [113].

To address these methodological errors, many studies have examined the upper extremities due to decreased synaptic pathways, as compared to the lower extremities, decreasing MEP variation and chance of synergist and antagonist muscle stimulation [112]. Nevertheless, only one study has studied BLD using the TMS method, where an isometric knee extension tasks was used with no BI despite a decrease in voluntary activation during the BH MVICs [21]. More research is needed to determine how the motor cortices interact during bilateral and unilateral contractions.

3.0 Methods

3.1 Experimental Design

The study is a repeated measures experimental design. Each participant completed consent prior to seven testing sessions, separated by 24-48 hours.

3.2 Participant Recruitment

Eleven subjects (6 female, 5 male) were recruited from the University of Pittsburgh and surrounding areas using fliers. Interested participants contacted the primary investigator at the Neuromuscular Research Laboratory and completed a phone screen. If all inclusion/exclusion criteria were met, the first visit was scheduled.

3.3 Participant Characteristics

3.3.1 Inclusion Criteria

Included individuals were between the ages of 18 and 35, with normal or corrected vision, right hand dominant, and who were active a minimum of 120 minutes per week. Regular qualifying exercise includes any aerobic, anaerobic, or resistance training workout resulting in substantial increases of energy expenditure.

3.3.2 Exclusion Criteria

Potential participants were excluded from the study if:

1. Suspected or knowingly pregnant
2. Current upper extremity musculoskeletal injury
3. History of upper extremity orthopedic surgery within the past two years
4. Discomfort or unwillingness to complete elbow MVICs
5. Diagnosed with a neurological disorder, epilepsy, cardiovascular, or other major disorders
6. TMS contraindication as indicated by the screening form
7. Current use of central nervous system active drugs or anabolic hormonal substance or growth hormone
8. Alcohol consumption more than 3 drinks/day or 18/week

3.4 Power Analysis

GPower 3.0.10 (Franz Faul, Universität Kiel, Germany) was used to determine sampling requirements with an α error probability of 0.05, power of 0.8, and *a priori* effect size estimate of 1.364 based on previous iSP estimates during BLD contractions by Skarabot et. al. [18]. Therefore, 10 participants were needed for detectable differences on the last testing day.

3.5 Instrumentation

3.5.1 Testing Device

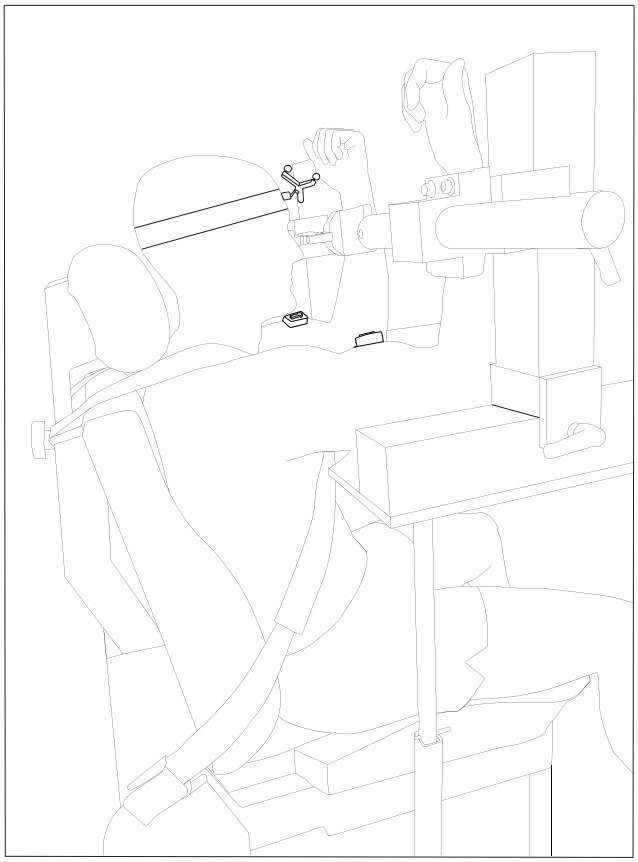


Figure 3. Customized Device Setup in Biodex Chair

Maximal contractions were performed in a commercially-available device (System 4 Pro, Biodex Medical Systems Inc.; Shirley, NY). A customized apparatus was used to test isometric elbow flexion and extension with shoulders at 90^{o} glenohumeral forward flexion and cuffs aligned directly beneath the radius and ulna styloid processes. Designed with 80/20 parts (Grainger Inc., Miami, FL) and a 91 x 122 x 2.5cm steel platform, the device was attached to the Biodex through two legs in the lateral receiving tubes. The platform was stabilized through a third point of contact, connected to the floor. A secondary platform was placed between the vertical posts aligned with

the forearms, which allows elbows to rest without upper arm contact to the main steel platform. This reduced potential counterbalances during MVIC testing. The device was adjusted at platform (1) height and (2) depth, (3) elbows at shoulder width apart on secondary platform, (4) secondary platform depth, and (5) forearm height. The cuffs were also adjustable to allow quick transition between elbow flexion and extension. Participants were secured in the Biodex chair at the chest and waist to reduce extraneous movement (Figure 3). Device placement was recorded at all joints (mm) to assure accuracy across test days.

3.5.2 Electromyography

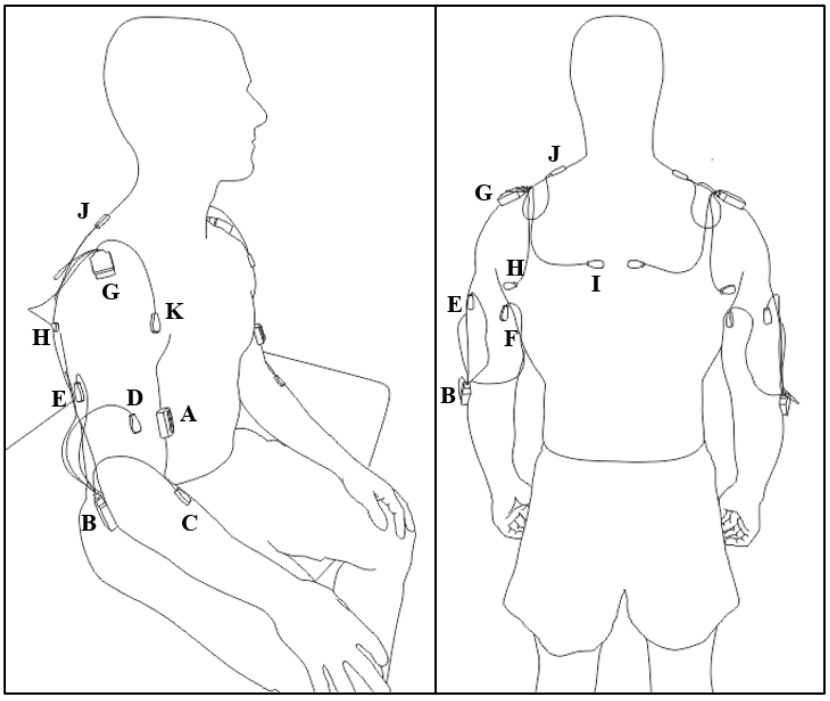


Figure 4. EMG Sensor Placement

A – Bicep Brachii (BB), **B** – Quattro reference sensor 1, **C -** Brachioradialis (BrRa), **D** – Brachialis (BR), **E** – Tricep Lateral Head (TrLa), **F** – Tricep Long Head (TrLo), **G** – Quattro reference sensor 2, **H** – Infraspinatus (IN), **I** – Middle Trapezius (MTr), **J** – Upper Trapezius (UTr), **K** – Anterior Deltoid (AnDe)

The Delsys EMG system (Natick, MA) provideed a noninvasive way to measure the electrical activity of skeletal muscle fibers during muscle contractions and in response to TMS tests, as well as antagonist and synergist muscle activity during MVIC. For biceps brachii analysis, Electromyography (EMG) sensors (Avanti, Delsys, Natick, MA; interelectrode distance: 10mm, Noise: 750nV) were placed after skin preparation using SENIAM guidelines. Delsys Quattro sensors (Delsys, Natick, MA, USA; interelectrode distance: 10mm, Noise: 750nV) measured activity in all other muscles. Quattro reference sensors were placed bilaterally on the (1) lateral epicondyle and (2) acromion with sensor heads on the (1) triceps long head (TLo), triceps lateral (TLat), brachialis (BR), and brachioradialis (BrRa), (2) middle trapezius (MTr), upper trapezius (UTr), infraspinatus (IN) and anterior deltoid (AnDe)(Figure 4). SENIAM recommendations were used for placement, when applicable. A certified and trained clinician used manual muscle tests and palpated the muscle belly to determine optimal sensor placement for IN, BR, and BrRa [116], where SENIAM guidelines are not provided. Indelible ink was used to make all sensor placement to assure accurate measures between test days.

3.5.3 Force Transducers

SM-250 load cells (Interface, Scottsdale, AZ) connected to the 3D printed cuffs in the customized device. Load cells were wired with a 3-pinLemo circular style connector to mate with Trigno Load Cell Adapters (Delsys, Natick, MA). Data was digitized, collected at 2000Hz at a gain of x1000, filtered with butterworth low pass (40dB/dec), and averaged every 20 data points (0.01s). Dominant and non-dominant limb force data were collected using Labchart analysis software (Colorado Springs, CO), and summed to measure bilateral MVICs.

3.5.4 Transcranial Magnetic Stimulation

A Magstim Rapid^2 was used for single pulse TMS (Magstim Company Limited, Spring Gardens, UK). A 70mm figure-of-eight coil (Magstim D70^2) will deliver electromagnetic nerve stimulation.

3.5.5 Neuronavigation

Participants' skulls were calibrated to the Montreal Neurological Institute (MNI) brain atlas using a frameless neuronavigation platform (Brainsight v.2, Rogue Research Inc., Montreal, Quebec, Canada). Infrared markers facilitated calibration of the coil and participant forehead (Figure 3) using an optical system (Polaris Vicra, Northern Digital Inc., Waterloo, Ontario, Canada). Upon marking the motor cortex hotspot, coil X, Y, and Z coordinates, as well as rotation and angle were monitored and recorded for each TMS delivered.

3.5.6 Labchart

Created by AdInstruments (Colorado Spring, CO), Labchart was used to acquire and analyze EMG, TMS, and force signals. Using this software, force data was also shown to participants in real time, without measures of force, to provide internal motivation to complete MVICs.

3.6 Testing Procedures

Subjects participated in 7 testing sessions separated by 24-48 hours (Figure 5). To assess the influence of task familiarity on BLD and neurophysiological function, TCI and VA was assessed on visit one and seven. Maximal isometric contractions were practiced test sessions 2-6 to examine changes in MVIC with increased task practice.

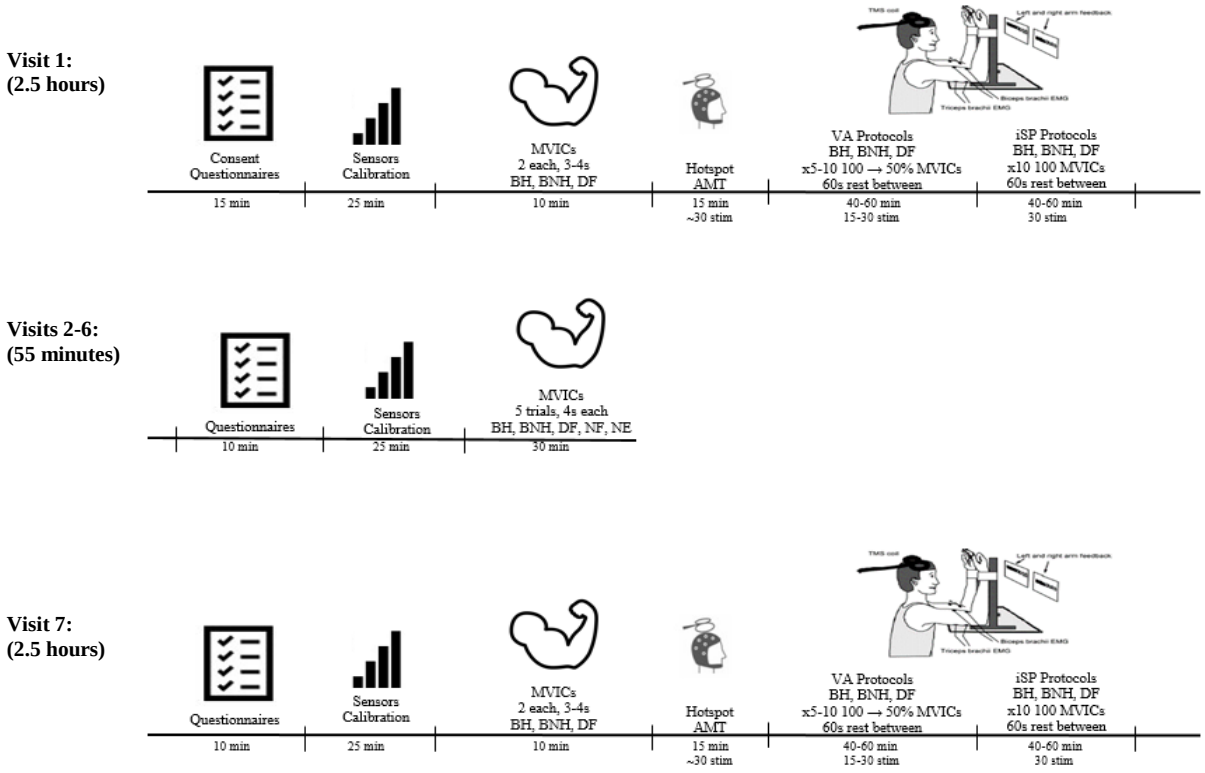


Figure 5. Study Procedures

Subjects took part in 7 test sessions. Sessions 2-6, subjects participated in 25 MVICs each session. Sessions 1 and 7, subjects completed neurophysiology sessions with TMS.

3.6.1 Randomization

Maximal voluntary isometric contractions were randomized in the following or reversed order for each subject, and remained the same for each visit: BH, NE, DF, NF, and BNH. This order optimized muscle-specific rest between tasks. MVIC randomization order were determined based on order of entry into the study.

3.6.2 Questionnaires

Once consent was obtained, participants proceeded through a series of questionnaires to comply with consensus of TMS guidelines, including the following (Appendix A):

- Screening questionnaire for TMS candidates
- Edinburgh Dominant Handedness and Footedness Questionnaire
- International Physical Activity Questionnaire
- 24-hour Diet Log (completed each visit)
- Sleep Quality and Quantity Scale (completed each visit)

Once completed, participants were familiarized with the testing protocol as referenced in Visit 1 of Figure 5. Participants were allowed to ask any questions to assure they felt comfortable for the entirety of the session.

3.6.3 Sensor Set-Up

Participants were fitted with Delsys wireless electrodes on the target muscles (Figure 4). Skin preparation consisted of alcohol cleansing, removal of excess hair with a shaving razor, and skin abrasion with medical tape followed by an additional alcohol rub.

3.6.4 Device Set-Up

Participants sat in the Biodex chair, strapped at the chest, and waist to reduce excessive movement. The customized elbow contraction device was fit into the chair, and adjusted based off torso height and upper and lower arm length. Subjects were placed in the bicep force cuffs, with the lateral part of the cuff directly beneath the styloid processes of the radius and ulna (Figure 3).

3.6.5 Warm-Up and Familiarization

Participants completed a standardized warm-up of 50% and then 100% MVIC, of each task, to ensure adequate preparation for maximal elbow contractions.

3.6.6 Maximal Voluntary Isometric Contractions Protocol

For sessions 2-6, all MVICs were completed 5 times for 4 seconds: (1) bilateral elbow flexion (BH), (2) non-dominant elbow extension (NE), (3) dominant elbow flexion (DF), (4) non-dominant elbow flexion (NF), and (5) dominant elbow flexion with simultaneous elbow extension (BNH). This order allowed rest of the flexors and extensors and reduced effects of fatigue. Prior

to each MVIC, subjects were instructed to keep the jaw open and relaxed to reduce excess muscle activation superior to the glenohumeral joint. Subjects saw force produced on a screen in front of them to maintain internal motivation, and were verbally encouraged through the full four second contraction. Approximately 60-90 seconds of rest was given between each MVIC. All force and EMG activity was recorded in LabChart software.

3.6.7 Neurophysiological Testing Protocol

The following protocol was completed on visits 1 and 7, using TMS to assess VA and TCI during maximal isometric BH, DF, and BNH contractions of the elbow muscles.

3.6.7.1 Maximal Isometric Contractions

Mimicking the aforementioned MVIC protocol, participants completed 3 MVICs for each contraction type in the previously assigned order. Participants were instructed to keep the jaw open and relaxed to reduce excess muscle activation superior to the glenohumeral joint. Maximal contractions lasted 4 seconds, with 60-90s rest between. The peak force of BH, DF, and BNH tasks were used to determine 100% (and 50%) force for VA and TCI measures.

3.6.7.2 Hotspot

The primary motor cortex biceps hotspot was determined for each subject, bilaterally, to test VA (left hemisphere) and TCI (right hemisphere). Using Brainsight neuronavigation, single pulses TMS was delivered by a figure-of-eight 70mm^2 coil (Magstim D70^2 coil and Super Rapid^2 Stimulator, Magstim, Carmarthenshire, UK), placed tangential to the scalp with the handle oriented 45^o in the posterior-lateral direction to induce a posterior-anterior/anterior-posterior

current along the precentral gyrus [117]. Single TMS pulses was initially delivered 5cm lateral and 1cm anterior to the vertex, considered the typical hotspot of the biceps brachii [118]. Coil position was then adjusted in 0.5cm increments to establish the position that produces the largest peak-to-peak MEP responses, and this position was marked and labeled as the hotspot for all subsequent tests and visits. The bilateral hotspots were reassessed during visit 7 to assure consistency between test days.

3.6.7.3 Active Motor Threshold

Active motor thresholds (AMT) was determined with the parameter estimation by sequential testing (PEST) technique [119]. Single-pulse TMS was applied to the left (VA) and right (TCI) hotspots while participants contracted the target bicep at 20±5% MVIC. Stimulation started at 45% stimulation output and was adjusted until AMT was determined based on a peak-to-peak MEP response of 200uV [120, 121]. For VA and TCI, stimulus intensity was set to 140% AMT [118]. VA AMT was reassessed session seven to assure consistent stimulus output based upon task-specific strength post training.

3.6.7.4 Voluntary Activation

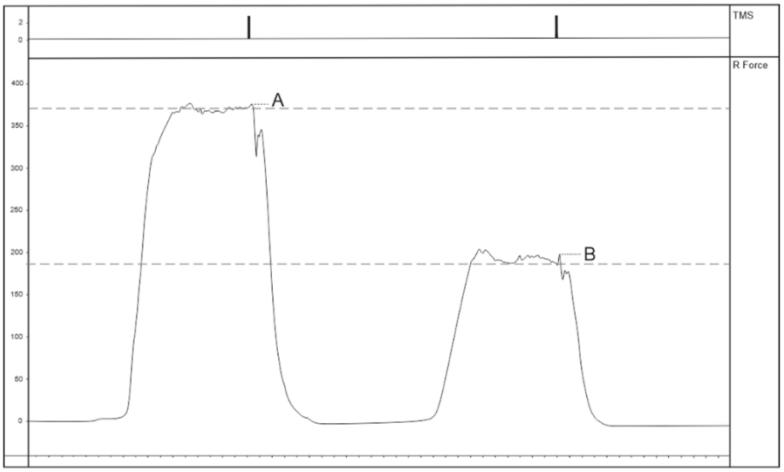


Figure 6. Voluntary Activation Trial

Vertical TMS lines depict timing of TMS pulse, A – difference in force between dotted lines depicts 100% superimposed twitch (SIT), B – difference in force between dotted lines depicts 50% superimposed twitch. Force at time of TMS and SIT, at 100% and 50% MVIC, will be graphed to estimate the resting twitch.

3.6.7.5 Transcallosal Inhibition

TMS was delivered to the right hemisphere (non-dominant limb) to assess TCI of the dominant bicep in BH, DF, and BNH tasks, in the previously assigned order. Lines depicting maximal MVIC, for each respective task, were shown to the participants, so maximal force could be achieved every test session. Once maximal force was reached, a TMS pulse was delivered to the right hemisphere. Participants were given 90-120s rest between contractions. A total of 10-15 MVIC of each task, in the previously assigned order, was completed to assure 10 MVICs of each task reached maximal force.

3.7 Data Reduction

3.7.1 Maximal Force

Maximum force was assessed for each test session, using the *four methods of force* calculation previously reported in BLD research. For each individual MVIC, force was defined based on peak and plateau force measures. Peak force was defined as the maximal point of each MVIC. Plateau force was defined with use of a first order derivative of MVIC force averaged every 3.75ms, with onset defined at 0N/s after force incline and offset defined as the last 0N/s point before force decline. The mean force between the onset and offset was used to calculate force plateau. For each test session, *absolute* maximum for (1) peak and (2) plateau, as well as *averaged* (3) peak and (4) plateau measures were calculated.

3.7.2 Bilateral Index

BI was calculated using the following equation 1, with negative (positive) values indicative of BLD (BLF). BH BI (%) was assessed with BH over the summed DF and NF tasks, where BNH BI (%) was assessed with BNH over the summed DF and NE tasks. BH and BNH BI were calculated using absolute and averaged peak and plateau forces, resulting in eight measures of BI for each test session.

$$BI\% = \left(100 \text{ x } \frac{\text{Bilateral Force}}{\text{Right Unilateral Force + Left Unilateral Force}}\right) - 100 \quad (1)$$

3.7.3 Task Familiarity

Task specific variability was assessed for each MVIC using CV and RFD, and tracked over all testing sessions. Raw data, collected at 2000 Hz, was used in LabChart to identify each MVIC force onset and plateau. MVIC onset was defined as the last point of 0N/s prior to force incline using a first order derivative averaged every 3.75ms. Plateau force was defined with the same first order derivative of MVIC force, with plateau onset defined at 0N/s after force incline and offset defined as the last 0N/s point before force decline. RFD was defined by change in force divided by change in time, from point of force initiation to (1) 75ms (2) force plateau (3) maximal force, as well as (4) 75-150ms. CV was calculated for each MVIC plateau to track variability of plateau force, using the equation (SD/mean)*100.

3.7.4 Electromyography Signal

Digitized EMG signals were collected at 2000Hz. Avanti sensor EMG data was captured with LabChart analysis software (version 8, ADInstruments, Colorado Springs, CO, US) and Quattro sensor EMG data was collected with EMGWorks (Version 4, Delsys Inc., Natick, MA, US). All signals were bandwidth filtered at 20-450 Hz and converted to root mean square (RMS) 1000ms prior to force onset and ±500ms surrounding the point of maximal force to assess EMG activity at baseline and maximal force, respectively. Data collection between the two programs were synced with a trigger, but due to differences in sensor transmission, scales between Avanti and Quattro sensors differed. As EMG between the two types of sensors were not compared, scale adjustments were not completed.

3.7.5 Voluntary Activation

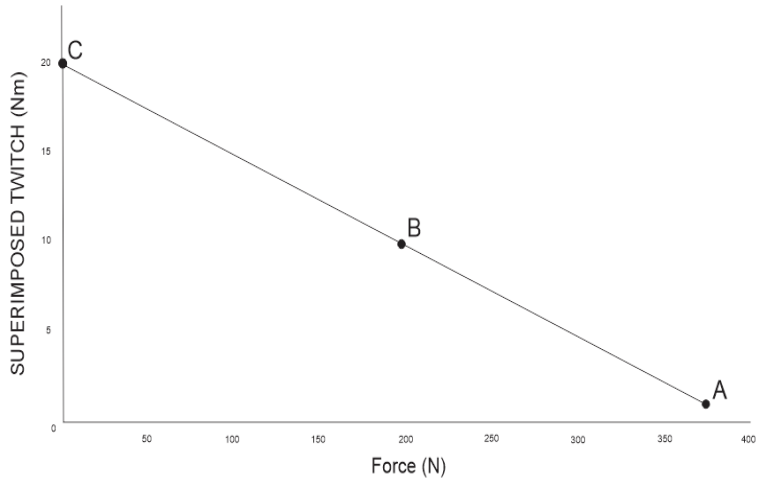


Figure 7. Voluntary Activation Analysis

Graphed points are pulled from Figure 6 **A:** Point of voluntary maximal force (373.58) and maximal SIT (1.02) **B:** Point of voluntary 50% MVIC force (187.32) and 50% SIT (10.04) **C:** y-intercept of linear points A and B, considered the estimated resting twitch (19.9). VA = (1-1.02/19.9)*100 = 94.9%

Voluntary activation (VA) was determined during BH, DF, and BNH where VA equals (1-maximal superimposed twitch/estimated resting twitch) x 100. Superimposed twitch (SIT) was considered the excess force evoked by stimulation of the motor cortex during voluntary contractions in relation to maximal voluntary force. A regression line was fitted to SIT forces produced at 50% and 100% MVIC to estimate resting twitch force (Figure 7) [111, 113]. The most maximal VA, within session, was used for analysis.

3.7.6 Transcallosal Inhibition

TCI was assessed for each individual trial. For each task and test session, EMG activity was rectified and averaged for measure of activity 90ms prior to TMS signal. Any signal less than the averaged rectified EMG, starting between 25 and 60ms post-TMS and lasting 10ms or longer, was

included as a valid measure of TCI [122]. Onset of all TCI present trials was aligned based off TCI onset, to calculate depth and normalized area [17, 123]. Depth was calculated from the mean EMG activity during the iSP, expressed as a percentage of the mean of the pre-stimulus EMG, and then subtracted from 100 [123]. The iSP area was calculated using the following formula: [iSP area = (mean pre-stimulus EMG) x (iSP duration) - (area under the curve during iSP)] and then normalized against the level of contraction for measure of area normalized [iSP area normalized to contraction iSP area/(area under mean EMG preceding stimulus) [122].

3.8 Statistical Analysis

Data was evaluated for normality at an alpha level of 0.05. If data was not normal, the non-parametric statistical test was used for analysis. Descriptive data, including means ± SD was reported. For Specific Aim 1, hypotheses 1a and 1b, paired t-tests was used separately to analyze iSP and VA differences between BH, BNH, and DF MVIC at pre- and post- task-specific training. For hypothesis 1c, a series of Pearson correlations was used to explore the contributions of iSP and VA to both BH and BNH BI. For hypothesis 1d a series of paired t-tests was used to assess differences in BH, BNH, and DF VA and iSP pre to post testing. For Specific Aim 2, multiple repeated measures ANOVAs was used to analyze RFD and CV measures between and within testing sessions for each BH, BNH, DF, NF, and NE MVIC. For Specific Aim 3, repeated measures ANOVA was used to assess across test days for each muscle tested, within each MVIC task. If differences were determined between test sessions, muscle activation patterns were assessed within each test session. If no differences were evident between test session, EMG data ware combined and muscle activation patterns were assessed using paired t-tests to compare (1)

unilateral versus bilateral tasks at point of maximal force (±500ms), (2) unilateral task inactive limb baseline versus maximal force, (3) unilateral active versus inactive limb at maximal force, and (4) dominant limb BH versus BNH at point of maximal force. Dominant and non-dominant limbs were individually analyzed for each of the following muscles: biceps brachii, triceps long head, triceps lateral head, brachialis, brachioradialis, anterior deltoid, upper trapezius, and middle trapezius.

4.0 Manuscript 1: Inconsistency of Bilateral Deficit Reflects Low Reproducibility of Estimates Based on Voluntary Force

4.1 Introduction

In 1961, Henry & Smith described a 3% deficit in bilateral handgrip strength when compared to the sum of the unilateral forces [1]. This *bilateral deficit* (BLD) phenomenon is evident in different movements, contraction types, anatomical joints, and populations [5]. Theorized mechanisms include psychological factors, such as inadequate task familiarity, and limitations in voluntary activation capacity [4, 5], although varying approaches and mixed results have produced contradicting interpretations. Moreover, little attention has been given to the potential influence of reliability. If BLD is an epiphenomenon that reflects variable or low methodological precision, individuals who perform maximal bilateral activities can do so knowing that all contractile resources are available. Alternatively, if BLD is real, counteractive training strategies are warranted.

Bilateral deficit is typically calculated as an index (BI, see Equation 1) based on voluntary maximal force. Where maximal voluntary force is highly reliable (ICC $\geq$ 0.96) [54, 55], force ratios are sensitive to subtle differences within and between contractions [8]. In addition, maximal force is defined a number of ways, with non-trivial consequences for BI measures. For example, peak force is absolute and easy to interpret, but a single maximal measure may be prone to error from ancillary muscle activity, sudden postural adjustments, or instrument noise [2, 4, 18, 23, 52, 63]. Maximal force plateaus may be more robust, but reflect the ability to maintain near maximal force, and may thus be more sensitive to volitional factors [6, 10, 21, 33-35]. Averaged measures

have a potentially beneficial smoothing effect, but at the cost of reduced sensitivity [2, 22, 63-66]. Thus, different calculation techniques can lead to different conclusions, including the presence or absence of BLD, and occasionally, facilitation (BLF) [2].

The issue of force measurement technique is compounded by the possibility that BLD reflects task familiarity, with repeated practice resulting in its reduction or elimination. Moreover, practice may exert distinct effects on force measurements, and must therefore be considered as a potentially important moderator of BLD estimates. Dependence on task familiarity would not prove that BLD does not exist, but rather, underscore the need for experimental approaches that emphasize neuromuscular, spinal, and supraspinal factors within a motor learning or control framework. Yet before potential mechanisms are investigated, there is a need to determine whether the techniques used to determine maximal force affect BLD estimates, and whether any of the common approaches provide sufficiently robust validity and reliability.

The purpose of this study was to determine the influence of force calculation technique and practice on BLD, and based on these factors, the reliability of BLD estimates. Forces were measured during repeated maximal isometric elbow contractions performed on six occasions. Reliability was determined based on internal consistency, test-retest reliability, and minimal detectable change (MDC). The results of this study will evaluate thresholds to determine the presence of BLD and the amount of task familiarity needed for reliable upper body BLD estimates.

4.2 Methods

Participants

Eleven healthy adults (six women, 25.6±3.7yr; 171.81±11.44cm; 74.4±21.2kg) participated in a counterbalanced repeated measures study. Inclusion criteria included: aged 18-35yr, normal or corrected vision, right hand dominant, and a minimum of 120min physical activity per week. Participants were excluded if they were suspected or knowingly pregnant, had a current upper extremity musculoskeletal injury, history of upper extremity orthopedic surgery within the past two years, unwillingness to complete maximal elbow contractions, or were diagnosed with a neurological, cardiovascular, or other major disorder which might prevent the safe completion of maximal contractions. All procedures were approved by the University of Pittsburgh Institutional Review Board.

Experimental Design

Participants completed six visits separated by 24-72hr (47.3±16.3hrs) within 14 days. Before each visit, subjects completed a 24hr diet log and sleep quality and quantity questionnaire to ensure sleep and nutrition were consistent between visits. The first day was used to calibrate the test device to individual anthropometrics and familiarize subjects to the protocol with three trials of each maximal voluntary isometric contraction (MVIC). MVIC order was counterbalanced with the following contractions: bilateral elbow flexion (BH), dominant elbow flexion (DF), and non-dominant elbow flexion (NF). Test sessions two through six mirrored day one, but involved five repetitions of each MVIC task (15 MVICs per session).

MVIC Equipment

Contractions were performed in a commercially-available device (System 4 Pro, Biodex Medical Systems Inc.; Shirley, NY) with a customized apparatus that positioned the arms at 90^{o} glenohumeral and elbow flexion with resistance provided by cuffs immediately beneath the radius and ulna styloid processes. The apparatus was designed with 80/20 parts (Grainger Inc.; Miami, FL) and a 91 x 122 x 2.5cm metal platform attached by two legs through the Biodex lateral receiving tubes, and a third leg connected from the front of the platform to the floor to provide stability. A secondary platform allowed participants to rest their elbows but avoid upper arm contact with the main platform and thereby reduce counterbalancing postural adjustments during maximal contractions. Platform (1) height, (2) depth, (3) elbow width, (4) secondary platform depth, and (5) forearm height were adjusted for each participant to ensure consistency. Participants were secured at the chest and waist to reduce excessive movement (Figure 8). Device placement was recorded at all joints to assure precise reposition across all test days.

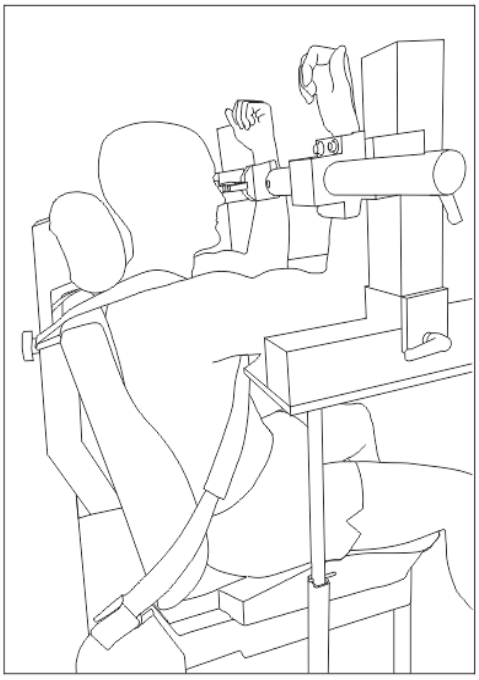


Figure 8. Reliability Customized Device Setup in Biodex Chair

Force Transducers

3D printed cuffs were connected to the device with SM-250 load cells (Interface, Scottsdale, AZ) wired with a 3-pin Lemo connector mated to Trigno Load Cell Adapters (Delsys, Natick, MA). Data were digitized at 2000Hz and a gain of 1000, butterworth low-pass second-order filtered, and averaged every 20 data points (0.01s). Force data were collected using Labchart analysis software (AD Instruments Inc, Colorado Springs, CO).

Maximal Voluntary Isometric Contractions

Prior to each MVIC, subjects were instructed to keep the jaw open and relaxed to reduce excess muscle activation superior to the glenohumeral joint. Subjects were allowed to see force on a screen in front of them for internal motivation, and verbally encouraged during each four second contraction. Task MVICs were completed in the following or reverse order: BH, DF, and NF. 90-120s of rest was given between each MVIC.

Data Reduction

Force was defined based on MVIC peak and plateau force. Peak force was defined as the maximal point of each MVIC. Plateau force was calculated with a first order derivative of MVIC force averaged every 3.75ms, with onset defined at 0N/s after force incline and offset defined as the last 0N/s point before force decline. Mean force between the onset and offset defined plateau force. In addition to the best attempt (absolute maximum), plateau and peak forces were averaged across attempts, resulting in four force measures. BLD was calculated using the following equation, with negative (positive) values indicative of BLD (BLF):

$$BI\% = \left(100 \times \frac{\text{Bilateral Force}}{\text{Right Unilateral Force} + \text{Left Unilateral Force}}\right) - 100 \quad (1)$$

Data Analysis

All analyses were conducted with SPSS Statistics for Windows (Version 24; IBM Corp., Armonk, NY). Peak and plateau force were calculated for each task and trial. Systematic bias was determined using repeated measures ANOVA (RMANOVA). Within session systematic bias was assessed for each MVIC task, based on measures of plateau and peak maximal force. Between session systematic bias was calculated for each MVIC task using all four force measures. If any force measure was identified by RMANOVA as significantly different, the measure was removed from any subsequent reliability analysis. Participant sleep quality, quantity, and nutritional intake based on total kilocalories and grams of protein, fat, and carbohydrates were analyzed with one-way RMANOVA or Friedman's ANOVA, if appropriate.

Force and BLD measures were assessed with Chronbach's α (CA) to determine internal validity, while test-retest reliability was determined using a two-way random effects model of absolute agreement (ICC(2,1)). Based on ICC estimates, SEM and MDC were calculated to determine thresholds for a real BLD. Point of optimal reliability was assessed with an iterative trial inclusion process. Specifically, for within and between sessions, force and BLD were analyzed in a forward (eg. trials 1-2, 1-3, etc), reverse (eg. trials 5-4, 5-3, etc), and a combination of forward and reverse order (eg. 2-3, 4-3). Bilateral index data were categorized as BLD (BI statistically less than 0%), BLF (BI statistically greater than 0%), or no BI (BI=0%) using dependent paired t-tests or Wilcoxon signed-rank (WSR) tests, when appropriate.

4.3 Results

No systematic bias was present for any measure of mean force, BI, sleep, or nutrition, so all were included in the reliability analysis. Within-day, peak and plateau force demonstrated high internal consistency (CA $\geq$ 0.967) and reliability (ICC(2,1) $\geq$ 0.895) during the first two trials. With each additional trial, internal consistency and reliability increased (trials 1-3: CA $\geq$ 0.979, ICC(2,1) $\geq$ 0.901; trials 1-4 (for sessions 2-6): CA $\geq$ 0.992, ICC(2,1) $\geq$ 0.914). The use of all trials (three for session 1 and five for sessions 2-6) provided the greatest internal consistency and reliability (Table 1). Although the first two trials within session were highly reliable, maximal force using absolute peak and plateau measures was achieved across all five trials (Appendix F, Figure 27). All five trials were therefore considered for between session analyses.

Analysis of forces between sessions revealed high reliability ($p<0.05$) but time points of optimal reliability was altered for each MVIC task (Figure 9). For all measures of force BH had increased reliability sessions 3-4 (CA=0.973-0.976, ICC(2,1)=0.952-0.957, $p<0.001$, SEM=28.9-31.9, MDC=82.5-88.4), while NF was more reliable during sessions 2-3 (CA=0.963-0.971, ICC(2,1)=0.934-0.963, $p<0.001$, SEM=18.8-19.8). DF reliability differed between sessions, but was altered based upon measure of maximal force (*absolute peak*: sessions 5-6, CA=0.990, ICC(2,1)=0.976(0.903,0.994), $p<0.001$, SEM=11.2, MDC=31.0; *average peak*: sessions 4-5, CA=0.986, ICC(2,1)=0.962(0.809,0.990), $p<0.001$, SEM=12.6, MDC=34.8; *absolute plateau*: sessions 3-4, CA=0.988, ICC(2,1)=0.975(0.915,0.993), $p<0.001$, SEM=11.2, MDC=31.0; *average plateau*: sessions 5-6 CA=0.991, ICC(2,1)=0.978(0.907,0.994), $p<0.001$, SEM=9.6, MDC=26.5).

Table 1. Within Day Force Reliability

	Plateau				Peak			
Session	CA	ICC(2,1)(95% CI)	SEM	MDC	CA	ICC(2,1)(95% CI)	SEM	MDC
Bilateral Homologous (BH)								
1	0.980	0.901 (0.642,0.975)	33.46	92.75	0.988	0.930 (0.692,0.983)	27.39	75.92
2	0.994	0.973 (0.938,0.992)	22.96	63.64	0.996	0.980 (0.955,0.994)	20.40	56.54
3	0.997	0.983 (0.961,0.995)	19.87	55.06	0.997	0.989 (0.973,0.996)	17.54	48.63
4	0.992	0.959 (0.907,0.987)	24.69	68.42	0.992	0.961 (0.911,0.988)	24.66	68.35
5	0.995	0.971 (0.932,0.991)	23.48	65.09	0.996	0.978 (0.948,0.993)	20.17	55.90
6	0.995	0.970 (0.930,0.991)	20.67	57.29	0.982	0.918 (0.823,0.974)	41.70	115.60
Non-Dominant Flexion (NF)								
1	0.985	0.939 (0.810,0.983)	14.24	39.48	0.984	0.949 (0.866,0.985)	15.29	42.39
2	0.994	0.969 (0.929,0.990)	13.09	36.29	0.994	0.973 (0.938,0.992)	11.66	32.31
3	0.995	0.978 (0.949,0.993)	11.32	31.37	0.994	0.970 (0.930,0.990)	13.01	36.07
4	0.993	0.960 (0.906,0.988)	11.50	31.89	0.996	0.981 (0.957,0.994)	9.46	26.21
5	0.993	0.968 (0.927,0.990)	12.69	35.18	0.994	0.962 (0.909,0.988)	13.37	37.05
6	0.995	0.967 (0.916,0.990)	12.09	33.51	0.996	0.980 (0.954,0.994)	9.30	25.77
Dominant Flexion (DF)								
1	0.984	0.949 (0.866,0.985)	15.29	42.39	0.979	0.932 (0.825,0.980)	18.26	50.60
2	0.994	0.973 (0.938,0.992)	11.66	32.31	0.994	0.973 (0.939,0.992)	12.00	33.27
3	0.994	0.970 (0.930,0.990)	13.01	36.07	0.994	0.974 (0.940,0.992)	12.77	35.40
4	0.996	0.981 (0.957,0.994)	9.46	26.21	0.996	0.981 (0.955,0.994)	10.00	27.71
5	0.994	0.962 (0.909,0.988)	13.37	37.05	0.994	0.967 (0.924,0.990)	13.63	37.79
6	0.996	0.980 (0.954,0.994)	9.30	25.77	0.988	0.945 (0.876,0.982)	18.27	50.64

Chronbach's α (CA), ICC(2,1), SEM, and MDC were assessed for all tested trials (three session 1, five sessions 2-6). High reliability (ICC(2,1) $\geq$ 0.895) was achieved with two trials, and all presented with significance at $p<0.001$, but absolute MVIC was achieved across all trials.

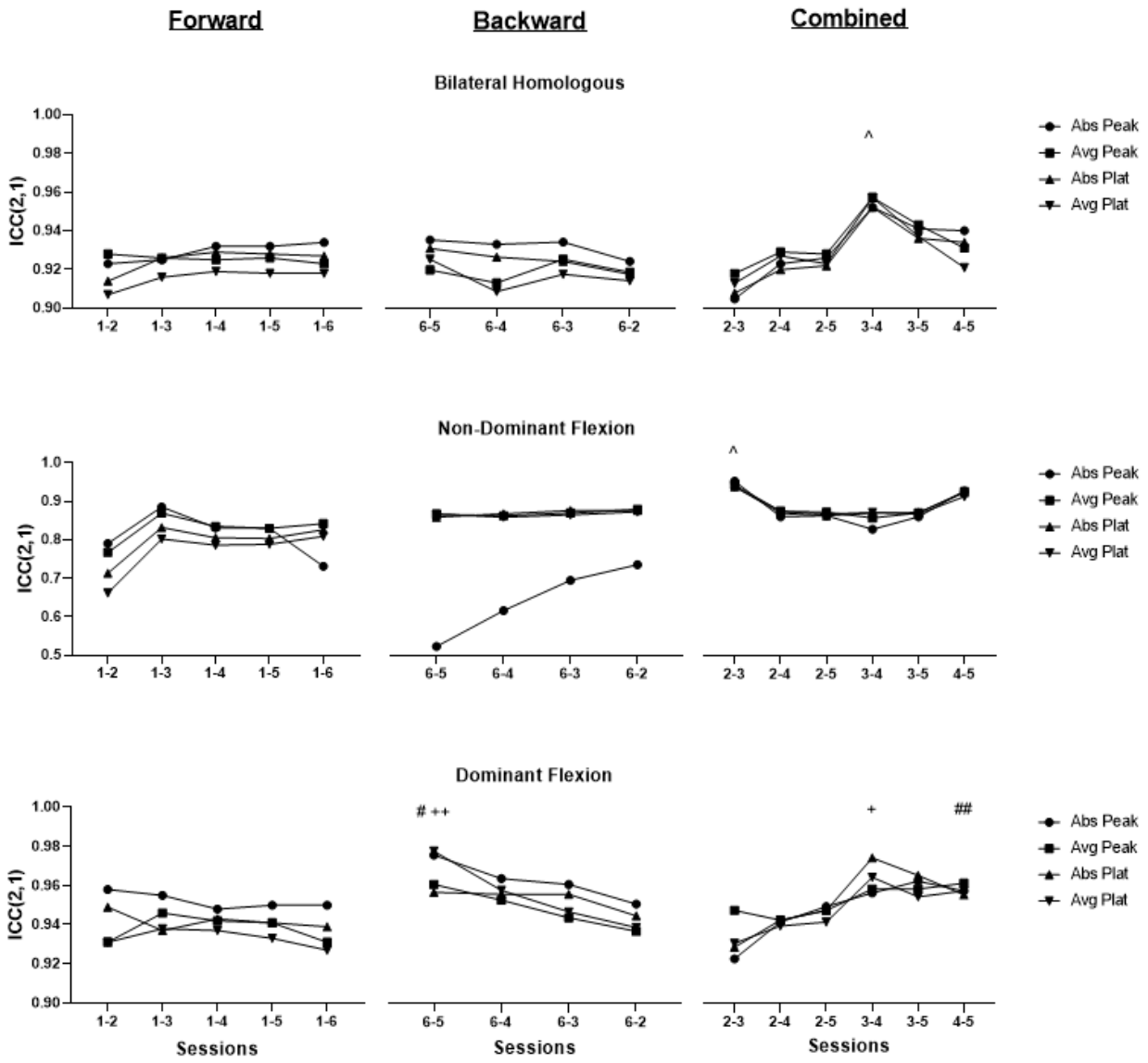


Figure 9. Force Between-Session Reliability

Reliability was assessed using an iterative method (forward, backward, and combined elimination) to assess when force was most reliable between test days. Maximal BH and NF reliability were the same across all definitions of force (denoted by ^), but DF maximal ICCs differed between absolute peak[#], average peak[##], absolute plateau[+], and average plateau[++]. Although maximal reliability varied across tasks, visits 2-3 and 4-5 were the only sessions to consistently produce ICC(2,1) > 0.900 across all tasks and measures of force.

BH had greater SEM and MDC between and within-day due to greater force compared to the unilateral tasks, but was stable across force measures. Sessions 2-3 and 4-5 were the only days to consistently produce ICCs > 0.900 across MVIC tasks and force measures, and were thus considered the most reliable inputs for BLD calculations.

All measures of force indicated a BLD during days 2-6 (Figure 10), but was absent during familiarization (Day 1). BLD was not internally valid or statistically reliable at the same time point when force was considered most reliable (sessions 2-3: CA= -0.079-0.441, ICC(2,1)= -0.041-0.296, $p \geq 0.187$, SEM=4.0-5.4, MDC=11.0-15.0; sessions 4-5: CA=0.070-0.469, ICC(2,1)=0.038-0.319,$p \geq 0.166$, SEM=4.0-5.4, MDC=11.1-15.0) The iterative process to assess the point of greatest reliability was therefore repeated for BLD (Figure 11).

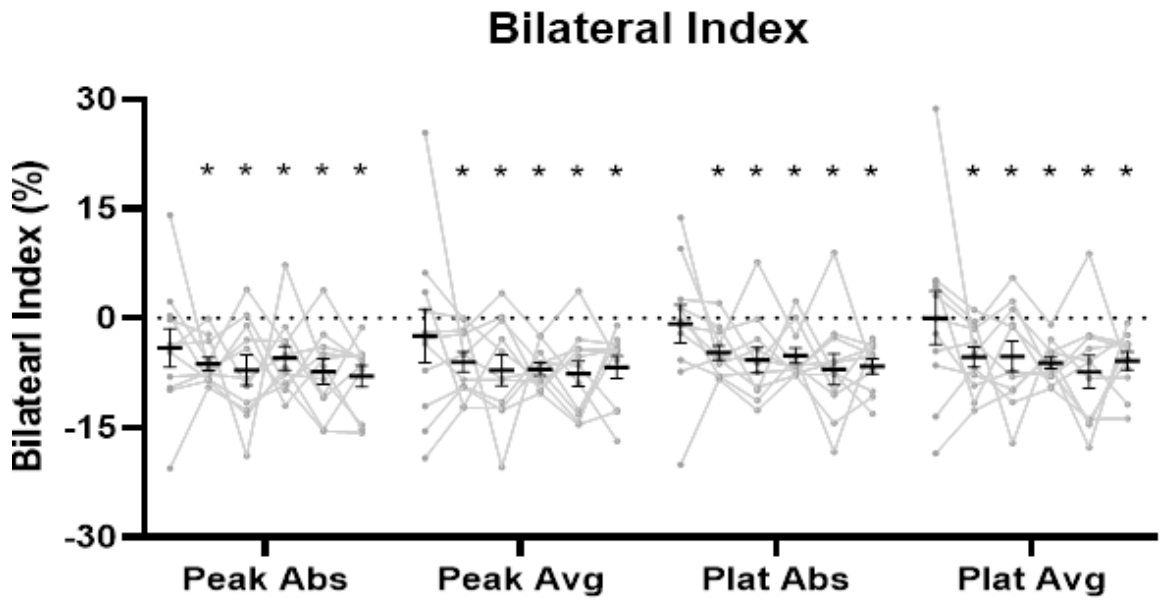


Figure 10. Bilateral Index across All Sessions

All test sessions are presented in consecutive order, for each absolute peak, average peak, absolute plateau, and average plateau. Individual participant data is tracked across all sessions (grey lines), with mean and SEM (black). On sessions 2-6, BH BLD was statistically less than zero (*) indicating the presence of a BLD.

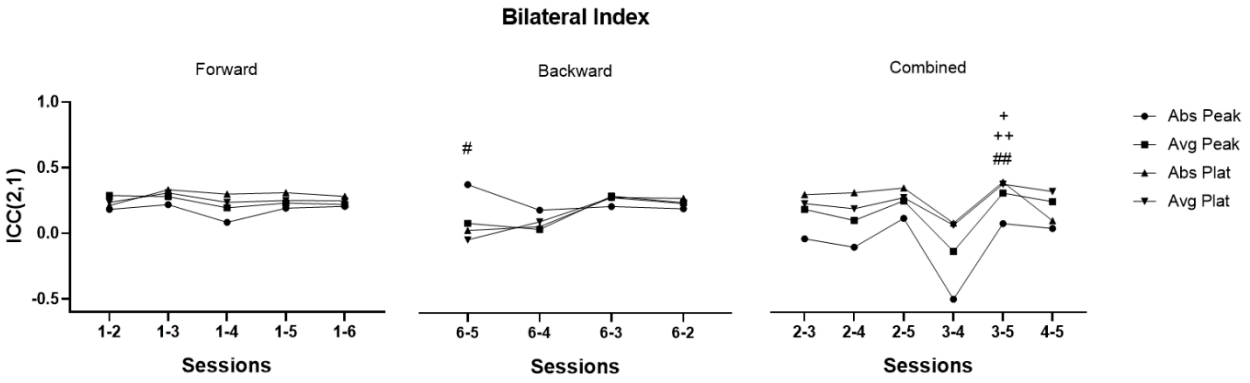


Figure 11. Bilateral Index Reliability

Reliability was assessed in an iterative method (forward, backward, and combined elimination) to assess when BI was most reliable. Unlike between session force reliability, BI maximal reliability was achieved test sessions 5-6 for absolute peak[#] where maximal reliability was achieved 3-5 for average peak[##], absolute plat[+], and average

Estimates of BLD were most reliable between sessions 3-5 for mean peak, absolute plateau, and mean plateau and sessions 5-6 for absolute peak. BLD was least reliable between sessions 3-4 and 5-6 for peak forces and plateau forces, respectively. Yet, when calculated with absolute and mean peak force, BLD was never considered statistically reliable across all session combinations (Table 2).

Table 2. BH Bilateral Index Most and Least Reliable Test Sessions

	Sessions	CA	ICC(2,1) (95% CI)	p-value	SEM	MDC
Most Reliable						
Peak Abs BI	5-6	0.559	0.388 (-0.221,0.786)	0.106	6.9	19.2
Peak Mean BI	3-5	0.549	0.307 (-0.078,0.706)	0.062	4.6	12.8
Plat Abs BI	3-5	0.649	0.392 (0.014,0.752)	0.022*	4.5	12.3
Plat Mean BI	3-5	0.633	0.375 (-0.001,0.742)	0.027*	4.9	13.6
Least Reliable						
Peak Abs BI	3-4	-1.648	-0.501 (-0.941,0.186)	0.930	7.4	20.6
Peak Mean BI	3-4	-0.279	-0.136 (-0.767,0.512)	0.648	5.7	15.7
Plat Abs BI	5-6	0.062	0.035 (-0.642,0.619)	0.460	5.5	15.2
Plat Mean BI	5-6	-0.072	-0.037 (-0.664,0.568)	0.542	6.2	17.1

The most and least reliable BI values were pulled to establish the range of SEM and MDC as thresholds for true changes in BI. Significance was set at $p \leq 0.05$ *

4.4 Discussion

The purpose of this study was to determine the number of trials and test sessions required to obtain reliable BLD estimates. The number of trials, within session, were assessed using internal consistency, reliability, SEM, and MDC with measures of peak and plateau maximal force. All tasks were deemed highly reliable after two trials (ICC(2,1) $\geq$ 0.895), but absolute peak was achieved throughout all five trials (Appendix F, Figure 27), with additional improvements in internal consistency, SEM, and MDC. Therefore, all trials were considered necessary to further assess measures of absolute and mean force and BLD between days.

Maximal task-specific reliability was achieved sessions 3-4 for BH and 2-3 for NF, but DF depended on the force measurement technique. Across sessions 2-3 and 4-5, all MVIC tasks produced ICCs > 0.900, and so two sessions, after a separate familiarity session, were considered to represent the minimum amount of practice necessary for reliable BLD estimates. Yet, when analyzed at these time points, BI reliability was relatively poor. The same iterative process was, therefore, used to determine if reliable BLD estimates could be obtained. When based on absolute and mean plateau force, reliable BLD estimates were attained on/by sessions 3-5, while reliable BLD estimates could not be produced when based on absolute or mean peak force.

Absolute and mean peak and plateau MVICs had similarly high reliability between and within all test sessions, in contrast to prior thought [2, 4, 18, 23, 52, 63]. All measures of force can therefore be used to assess BLD, but as each MVIC force measure reflects a different property of voluntary contractions, the study design and outcome variables should dictate which measure of force to use. Nevertheless, because BLD is considered difference in ability to complete maximal force, peak force should be considered the most externally valid assessment, but never establishes reliability. This variability lends to measures of absolute and mean plateau to assess BLD.

Yet, measures of plateau force indicated reliable presence of BLD sessions 3-5, but never surpassed a quantifiably poor ICC(2,1) of 0.392 [124, 125]. When echoed to prior research, the lack of repeatability introduces a large methodological flaw. The greatest implication of this flaw relates to the use of repeated assessments to test mechanistic theories, as changes in BI may not reflect experimental interventions, but measurement error. Thus, rather than traditional significance testing, MDC should be used to establish changes in BLD.

The least and most reliable time points were presented to provide thresholds for real BLD changes based on isometric elbow flexion and extension. To the best of our knowledge, a single elbow flexion/extension study has exceeded the minimum thresholds, given peak torque BI at 45° (-20.12 ± 17.36) and 90° (-11.35 ± 10.98) were larger than BLD scores at 135° (+20.27 ± 22.77), $p = 0.0001$ [126]. Yet, unilateral force was taken from a single limb, and it was assumed that each limb would produce similar bilateral forces [126]. No other study using elbow MVICs produced values that exceeded the MDC generated in the present study. Nevertheless, it is important to note that these values should serve as a guide for isometric elbow flexion tasks only, as other tasks and contraction types may present different force and BLD characteristics [5].

Due to variability between test days, quantification of true change through altered BI classification (ie BLF, BLD, and no BI) should be questioned. As highlighted in the present study, average peak force BI classifications between sessions one (-2.47 ± 11.5; no BI) and two (-5.96 ± 4.38; BLD) varied but altogether would not be considered different based on the MDC threshold (BI changes greater than 21.39%). This pattern was consistent for every force measure, where BLD classifications changed from session 1 to 2, but never exceeded MDC.

BI was calculated over the course of multiple sessions, as movement patterns are highly variable when new, and become more consistent with practice and experience [56-58]. Subjects in

the current study were considered physically active, with prior experience in elbow flexion and extension, but isometric MVICs with the shoulders at 90^{o} of forward flexion was a new task. Nevertheless, all measures of force were highly reliable within and between test sessions. Therefore, lack of stable BLD, despite high reliability and internal consistency across force measures, is the most important finding of the present study.

The results of this investigation challenge the validity of the BLD estimates in prior work. Specifically, one or two test sessions is common practice, and given our findings, prone to poor reliability. To reduce the risk of errant BLD classifications, studies should be structured to assess mechanisms and emphasize meaningful BLD magnitudes. Specifically, peak isometric knee extension force presented with BLF in a bilaterally trained weightlifting group (BI = 6.6 ± 4.7), no BI in unilaterally trained group (BI = -6.6 ± 7.1) and BLD in an untrained group (-9.5 ± 6.8), suggesting that practicing a different tasks might alter BLD [2]. Yet, true BI differences may not have been reached, as the bilateral, unilateral and untrained populations were mimicked, reporting no BI across all groups (bilateral BI: -11.6 ± 16.0%; unilateral: -11.5 ± 10.5%; untrained: -4.5 ± 13.1%) [18]. Therefore, task familiarity or training does not appear to explain BLD, suggesting prominence of other theories based in physiological, psychological, and neurophysiological concepts. To further investigate, measures of BI minimal detectable difference should be used, over BI classification (measured by statistical difference from zero), to assess true difference and corresponding underlying theories of BLD.

5.0 Manuscript 2: Corticomotor Network Activity Alters Task-Specific Performance but Does Not Contribute to the Bilateral Deficit Phenomenon

5.1 Introduction

The critical role of communication between the two brain hemispheres for everyday function was realized in the 1960s [46, 127-129]. The corpus callosum was subsequently identified as a principal mediator of interhemispheric dynamics [27, 28], with signals carried along transcallosal fibers supporting the bi-hemispheric integration needed to efficiently execute brain functions [27, 29, 30]. Nevertheless, many questions remain about the contribution of transcallosal dynamics to motor control and performance in healthy humans [31].

Interhemispheric dynamics may explain the bilateral deficit (BLD) phenomenon, in which the sum of unilateral contractile forces exceeds those produced during the same contractions performed bilaterally [2, 5]. In this case, diminished forces may reflect interhemispheric processes such as transcallosal inhibition (TCI), resulting in decreased bilateral corticospinal drive [5, 18, 21] and resultant diminished voluntary activation (VA).

In theory, TCI opposes redundant activity from the ipsilateral hemisphere to improve the efficiency and precision of corticomotor processes in the controlling hemisphere [14-16]. Yet with increased inhibition in bilateral homologous (symmetrical; BH), but not bilateral non-homologous (asymmetrical; BNH) tasks, altered transcallosal pathway mediation is theorized to allow a decoupling in BNH tasks [17]. Yet, TCI has only been observed during submaximal [17] and dynamics tasks [20], without understanding the source of inhibition, and therefore further explanation of TCI to BLD, and effect upon volitionally maximal contractions, is necessary.

Through training, TCI has increased through improved corticospinal drive [130], and therefore likely inversely influences VA. Compared between BH and unilateral tasks, to assess BLD and corticospinal drive, VA induced with electrical stimulation has revealed varied results [12, 18, 21-24]. Yet, BLD was present due to diminished BH VA, induced with transcranial magnetic stimulation (TMS).

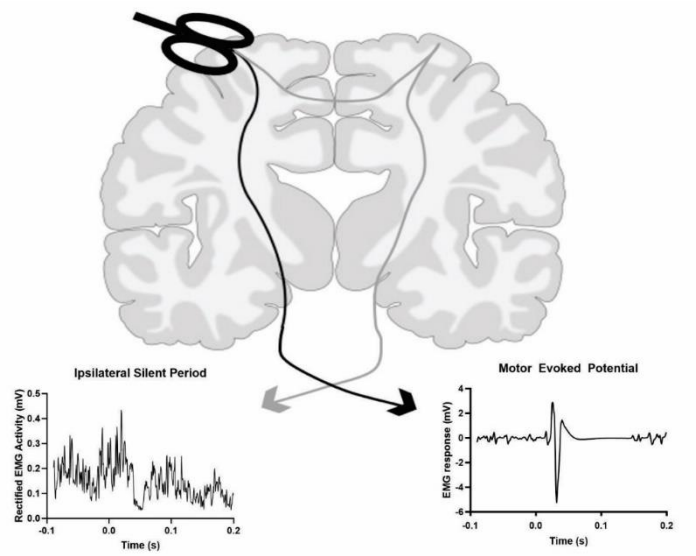


Figure 12. Ipsilateral Silent Period to Measure Transcallosal Inhibition

TMS pulse travels directly to the contralateral bicep, resulting in a MEP, while indirect signal is delivered through the corpus callosum, demonstrated ipsilateral bicep inhibition period (approximately 40ms post TMS)

As a research tool, TMS enables the characterization of corticospinal system function *in vivo* and provides insights into the neural basis of contractile functions based on responses to stimulation in target muscles [17, 18, 21]. VA can be determined measuring the superimposed twitch of maximal force, capturing characteristics of the descending corticospinal drive. Additionally, TCI can be determined with TMS based on ipsilateral silent periods (iSP), measured by the absent signal area and/or depth in the ipsilateral hemisphere (Figure 12). When TMS is delivered to subjects with corpus callosum agenesis or lesions, iSP is absent [39, 41, 42]. Moreover, when measured at known stages of corpus callosum transformation, including aging

[43-48], fine motor control [49], and physical activity [48, 50], the length and/or area of iSP is highly correlated with callosal connections.

In contrast to BH, BNH tasks are not accompanied by BLD [2, 12, 75] and produce reduced TCI during submaximal and dynamic contractions compared to BH and unilateral tasks [17, 20]. This suggests that interhemispheric connections between homologous motor cortex (M1) representations are greater than those of heterologous muscles, reflecting less behavioral use [131]. Yet, task-specific training to improve performance may reduce TCI and thereby eliminate the BLD [2, 9, 52, 131, 132]. Nevertheless, our understanding of the influence of contractile properties on neural drive, and ability to produce voluntary force, remains incomplete, in addition to the contributions of these factors to BLD [18, 21, 70, 71].

The purpose of this study was to explore corticospinal activity during maximal isometric BH, BNH, and unilateral contractions, and the relationship between TCI, VA, and BLD during BH and BNH contractions. Transcollosal inhibition and VA were assessed before and after task training to assess parallel changes in neurophysiological and performance variables. If neurological factors contribute to BH BLD or its absence during BNH contractions, than paralleled changes within neurological and force measures would demonstrate influence upon optimization of human performance and acute training.

5.2 Methods

Participants

Eleven healthy right-handed participants (6 women, 25.6 ± 3.7 years; 171.81 ± 11.44 cm; 74.4 ± 21.2 kg) volunteered to participate in a counterbalanced repeated measures study.

Participants were included if they were between the ages of 18 and 35, with normal or corrected vision, and active a minimum of 120 minutes per week. Participants were excluded if they were suspected or knowingly pregnant, with current upper extremity musculoskeletal injury, history of upper extremity orthopedic surgery within the past two years, discomfort or unwillingness to complete elbow MVICs, and diagnosed with a neurological disorder, epilepsy, cardiovascular, or other major disorders. Prior to testing, participants provided written informed consent and were screened for contraindications to TMS, including current use of central nervous system active drugs, anabolic hormonal substance or growth hormone use, or alcohol consumption more than 3 drinks/day or 18/week. [133]. All procedures were approved by the University of Pittsburgh Institutional Review Board.

Experimental Design

Participants took part in seven visits within 14 days, separated by 24-72hr (47.6±16.2hrs). Prior to all experimental tasks, participants completed a 24-hour diet recall log and sleep quality and quantity questionnaire to ensure that sleep and dietary behaviors were consistent across visits. The first and seventh sessions were used to assess TCI and VA during bilateral and unilateral contractions of the elbow musculature. During sessions two through six, participants performed 25 MVICs five of each (1) bilateral elbow flexion (BH), (2) non-dominant extension (NE), (3) dominant elbow flexion (DF), (4) non-dominant elbow flexion (NF), and (5) dominant elbow flexion and non-dominant extension (BNH). Order of MVIC was counterbalanced based upon entrance into the study, to the aforementioned or counterbalanced order, allowing longer rest times between tasks.

Testing Device

Maximal contractions were performed in a commercially-available device (System 4 Pro, Biodex Medical Systems Inc.; Shirley, NY). A customized apparatus was used to test isometric elbow flexion and extension with the shoulders at 90^{o} glenohumeral forward flexion. The elbows were bent at 90^{o}, and wrist cuffs aligned directly beneath the radius and ulna styloid processes. The device was designed with 80/20 parts (Grainger Inc., Miami, FL) and a 91 x 122 x 2.5cm steel platform, and attached to the Biodex through two legs in the lateral receiving tubes. A third leg connected to the floor, from the front of the platform, to reduce any movements during MVIC. A secondary platform was placed between the vertical posts and aligned with the forearms to allow the elbows to rest without any upper arm contact to the main steel platform so that potential counterbalancing postural adjustments would be minimized during MVICs.

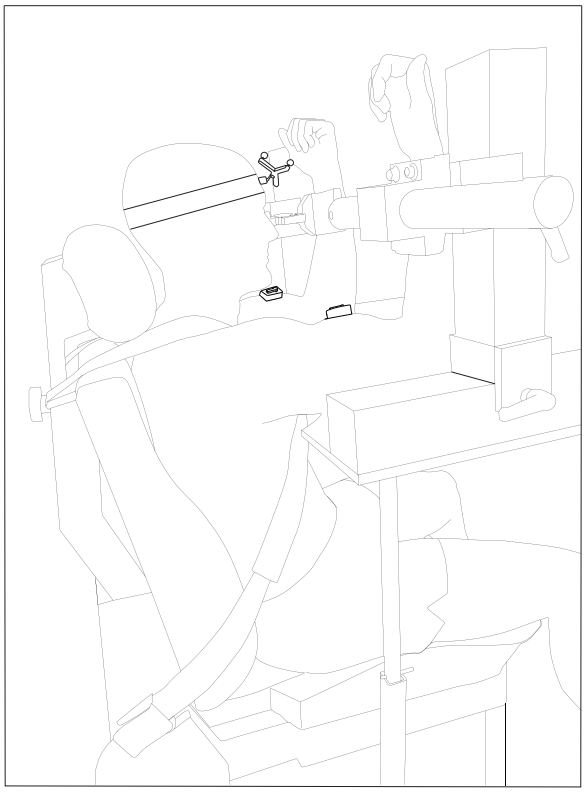


Figure 13. Neurological Testing Chair Set Up

The device was adjustable at platform (1) height and (2) depth, (3) elbows at shoulder width on secondary platform, (4) secondary platform depth, and (5) forearm height. The cuffs were also adjustable to allow for rapid transition between elbow flexion and extension. Participants were secured in the Biodex chair at the chest and waist to reduce extraneous movement (Figure 13). Device placement was recorded at all joints (mm) for consistency across test days.

Force Transducers

SM-250 load cells (Interface, Scottsdale, AZ) connected the 3D printed cuffs to the customized device. Load cells were wired with 3-pin Lemo circular style connectors mated to Trigno Load Cell Adapters (Delsys, Natick, MA). Data were digitized, collected at 2000Hz at a gain of x1000, filtered with butterworth low pass (40dB/dec), and averaged every 20 data points (10ms). Dominant and non-dominant limb force data were collected using Labchart analysis software (Colorado Springs, CO), and summed to determine bilateral MVIC force.

Maximal Voluntary Isometric Contractions

Prior to each MVIC, subjects were instructed to keep the jaw open and relaxed to reduce excess muscle activation superior to the glenohumeral joint. Real-time force was displayed to participants on a computer monitor to provide internal motivation, and verbal encouragement was given. Task MVICs were completed in the following or reversed order with randomized and counterbalanced allocation: BH, NE, DF, NF, and BNH. The selected order was designed to maximize rest for each muscle between tasks. An additional 90-120s of rest was given between each MVIC to avoid fatigue. During sessions one and seven, three MVICs were completed for

each task (15 total) to establish maximal force, used for TCI and VA assessments. During sessions two through six, five of each MVIC task (25 total) was used to provide physical training.

Electromyography

Electromyography (EMG) sensors (Avanti, Delsys, Natick, MA; interelectrode distance: 10mm, Noise: 750nV) were placed on each biceps brachii after skin preparation using SENIAM guidelines. Indelible ink was used for consistent positioning across test days. EMG activity was amplified with a gain of 1000x, digitized at 2KHz, and bandpass filtered from 20-450Hz. Signal quality and baseline noise were assessed prior to testing to assure quality of data.

Hotspot

Motor cortex hotspots for the bicep brachii ($M1_{BB}$) were determined bilaterally for VA (dominant hemisphere) and TCI (non-dominant hemisphere). Prior to stimulation, neuronavigation (Brainsight v.2, Rogue Research Inc., Montreal, Quebec, Canada) was used to calibrate subjects to the Montreal Neurological Institute (MNI) brain atlas. Infrared markers were calibrated to the coil and participant forehead (Figure 13) using an optical system (Polaris Vicra, Northern Digital Inc., Waterloo, Ontario, Canada) to track coil and head movement in real time.

A figure-of-eight 70mm^2 coil (Magstim D70^2 coil and Super Rapid^2 Stimulator, Magstim, Carmarthenshire, UK) was placed tangential to the scalp with the handle oriented 45^o in the posterior-lateral direction to induce a posterior-anterior/anterior-posterior current along the precentral gyrus [117]. To locate each $M1_{BB}$ hotspot, single biphasic TMS pulses were applied during unilateral elbow flexion (20±5% MVIC) at 70% stimulator output (SO). Stimulation began 5cm lateral and 1cm anterior to the vertex [118] with the coil moved in 0.5cm increments until the

site that consistently produced the largest peak-to-peak motor evoked potentials (MEPs) (Figure 12) was determined. Responses to stimulation were monitored real-time (Labchart 8, AdInstruments, Colorado Springs, CO, USA). The hotspot point was marked within the neuronavigation software. During all subsequent TMS tests, coil movement in the X, Y, and Z planes as well as rotation and angle were monitored and recorded.

Active Motor Threshold

Active motor thresholds (AMT) were determined with Parameter Estimation by Sequential Testing (PEST) [119]. Single-pulse TMS was applied to the left (VA) and right (TCI) $M1_{BB}$ hotspot while participants contracted the target bicep at 20±5% MVIC. Stimulation started at 45% SO and was adjusted until the AMT was determined based on a peak-to-peak MEP response of 200uV [120, 121]. Each M1 hotspot was relocalized at the beginning of session seven to confirm consistency between test days. Additionally, VA AMT was reassessed to assure differences between sessions were due to true changes in VA and not specific to force.

Voluntary Activation

Maximal voluntary isometric forces for BH, DF, and BNH contractions were used to assess VA. A computer monitor was used to present lines depicting 100% and 50% of maximal force in addition to real time force levels. During each VA trial, participants were instructed to contract the target muscle(s) to match force to the 100% line, relax for five seconds, and then contract the same muscle(s) to match the 50% line.

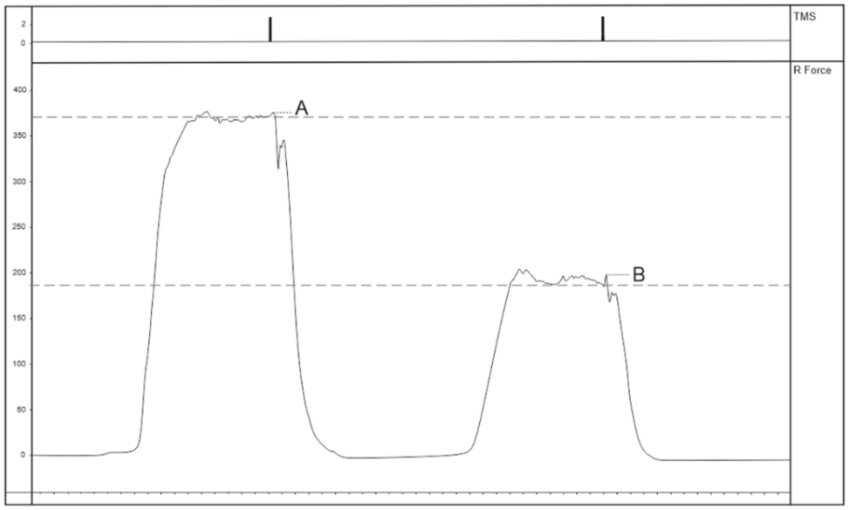


Figure 14. Superimposed Twitch

Screen displays 100% and 50% MVIC, with real-time force. Vertical TMS lines depict timing of TMS pulse, A – difference in force between dotted lines depicts 100% superimposed twitch (SIT), B – difference in force between dotted lines depicts 50% superimposed twitch. Force at time of TMS and SIT, at 100% and 50% MVIC, will be graphed to estimate the resting twitch.

After three practice trials, 10 VA trials (per task) were performed in the assigned order with 90-120s rest between each trial. The TMS coil was placed on the dominant $M1_{BB}$ hotspot with a single pulse delivered at 140% AMT when the target force level was confirmed [118]. Participants were instructed to not relax until after the TMS pulse was delivered (Figure 14).

Transcallosal Inhibition

To assess the influence of TCI on forces produced by the dominant BB, TMS was delivered to the right $M1_{BB}$ at 140% AMT during maximal BH, DF, and BNH contractions. Similar to the VA test, visual feedback was provided to indicate real-time and target force for each contraction type. Once maximal force was confirmed, a TMS pulse was delivered to the right $M1_{BB}$. A total of 10-15 MVICs were completed for each task to ensure a minimum of 10 MVICs reached maximal force. Participants were given 90-120s rest between contractions, which were performed in the previously assigned order.

Data Reduction

Force and Bilateral Index

Peak force was defined as the maximal point for each task per session. BH BLD was calculated by dividing BH peak force by the sum of DF and NF peak forces [2]. BNH BLD was calculated by dividing BNH peak force by the sum of DF and NE peak forces.

Voluntary Activation

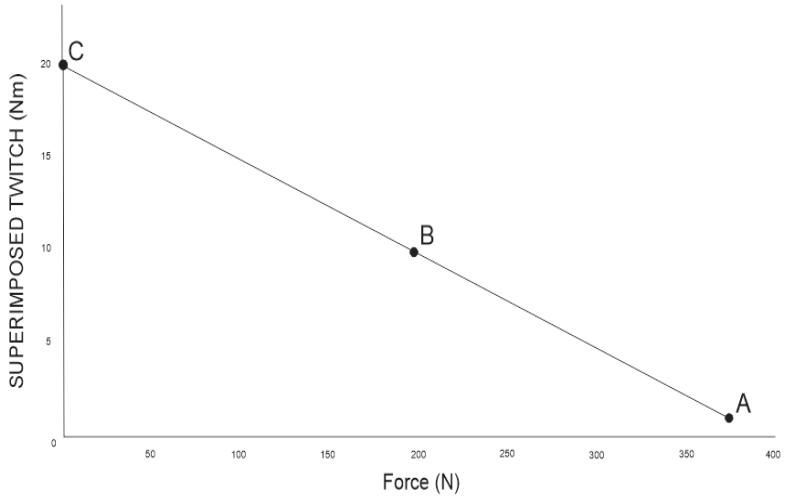


Figure 15. Voluntary Activation Analysis

Graphed points are pulled from Figure 14 **A:** Point of voluntary maximal force (373.58) and maximal SIT (1.02) **B:** Point of voluntary 50% MVIC force (187.32) and 50% SIT (10.04) **C:** y-intercept of linear points A and B, considered the estimated resting twitch (19.9). VA = (1-1.02/19.9)*100 = 94.9%

For each task, VA was calculated as (1-maximal superimposed twitch/estimated resting twitch) x 100. Superimposed twitch (SIT) force represents the excess force evoked by stimulation of M1 during voluntary contractions. A regression line was fitted to SIT forces produced at 50% and 100% MVIC to estimate resting twitch force (Figure 15). The greatest within session VA estimate was retained for further analysis .

TCI

To assess if TCI was present for each individual trial, all trials were averaged with rectified raw EMG during to 90ms pre-stimulus interval used as a threshold. Any individual trial signal that was 1) lower than the pre-stimulus threshold, 2) at least 10ms long, and 3) occurred from 25-60ms post-stimulus was included as a valid iSP [122]. The onsets of all trials with TCI were aligned to calculate depth and normalized area [17, 123]. Duration was considered the time EMG signal was below the 90ms pre-stimulus threshold. Depth was calculated from lowest EMG activity, during iSP, and expressed as a percentage of the mean pre-stimulus EMG, and was then subtracted from 100 [123].

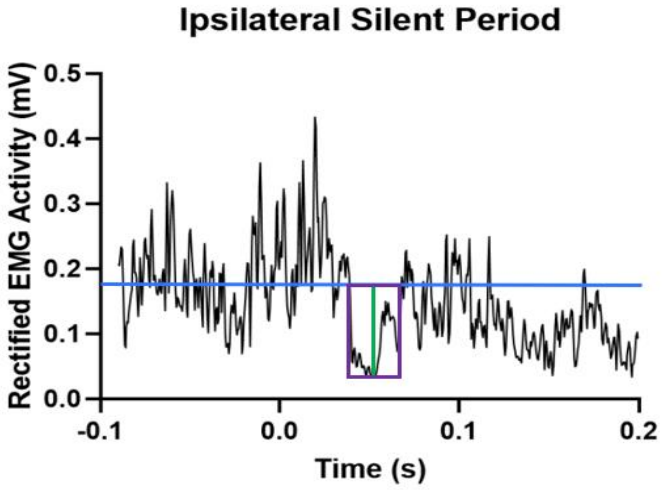


Figure 16. Ipsilateral Silent Period Depth and Area

All EMG activity is rectified, with average activity 90ms prior to TMS stimulus (blue), TCI depth marked as the point from the average to the lowest point (green), and area calculated by the TCI depth*time of TCI(outlined by purple) – the area under the curve

Ipsilateral SP area was calculated as: [iSP area = (mean pre-stimulus EMG) x (iSP duration) - (area under the curve during iSP)] (Figure 16) and normalized to contraction level [iSP area normalized to contraction iSP area/(area under mean EMG preceding stimulus)[122].

Data Analysis

Data are presented as mean (SD) with chi-square (χ^2), Z-score, SEM, MDC, and p-values. All two-sided analyses were conducted with SPSS Statistics (IBM Corp., Armonk, NY). Measures of BLD, TCI, and VA were assessed for normality using Shapiro Wilk's test. Paired t-tests or Wilcoxon Signed Rank (WSR) tests were used to test VA and TCI measures within task and between test sessions. BLD categorization (i.e. BLD, no BI, BLF) was determined with paired t-tests. Pearson or Spearman correlations were used to relate neurological and performance measures. Participant sleep quality and quantity, and nutrition (kilocalories and grams of protein, fat, and carbohydrates) were compared across sessions with one-way ANOVAs. Significance was set a priori at $p \leq 0.05$.

5.3 Results

Peak force was reliable within- ($ICC(2,1) \geq 0.925$) and between-day ($ICC(2,1) \geq 0.730$) for all MVIC tasks (Figure 17; Table 1 and Figure 9, Chapter 4).

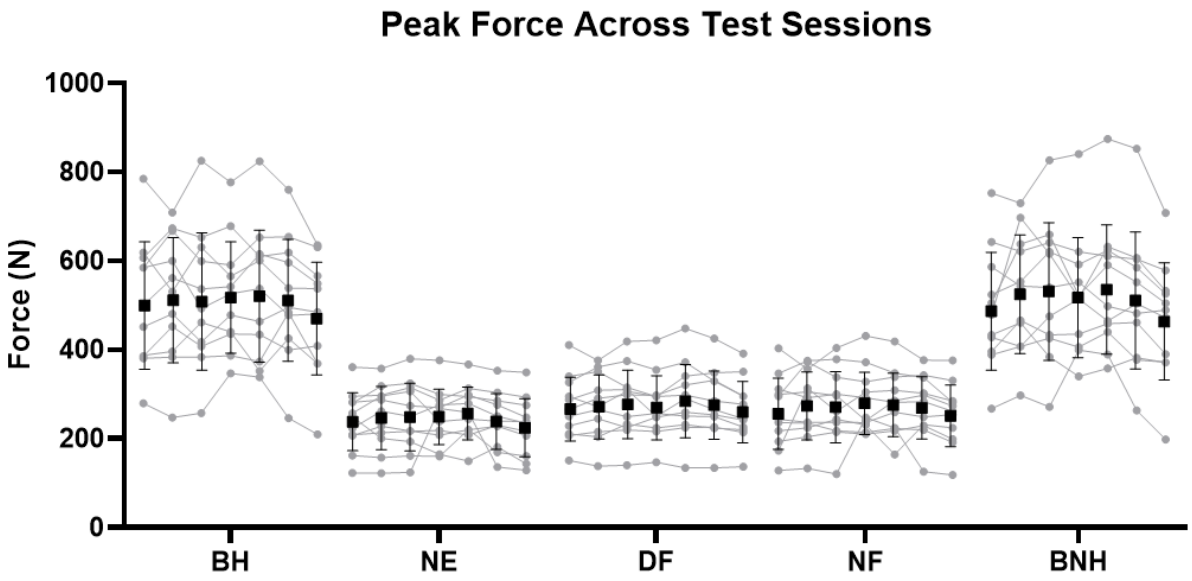


Figure 17. MVIC Peak Forces

Peak MVIC forces for each contraction type are presented in order from session one to seven, with individual data in grey and aggregate mean(SD) in black.

BH BLD was similar each test day ($\chi^2 = 2.03$, $p = 0.971$), but with exception of the first test session (no BI), where BNH produced no BI at any point and did not differ between sessions ($\chi^2 = 4.64$, $p = 0.591$; Figure 18).

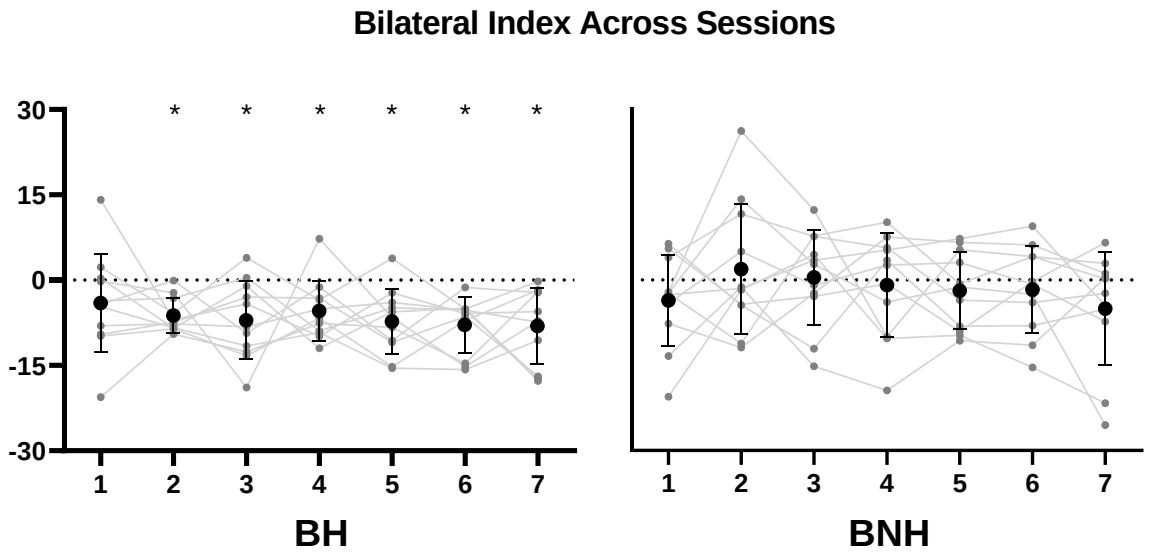


Figure 18. BH and BNH BI across All Sessions

BH and BNH BLD across sessions represented by individual subject data (grey) and mean(SD) in black. Except for day 1, BLD was present on all days for BH, while there was no BLD for BNH . * indicates BLD ($p<0.05$).

There were no differences in VA or TCI between BH, BNH, and DF (Table 3). BH VA decreased from session one to session seven (95.14±4.3 vs. 92.2±4.4 for session 1 vs 7; $t(10)=2.89$; $p = 0.014$), but did not exceed the minimum detectable change threshold (6.47). No other neurophysiological variables differed between session or task (Table 4).

Table 3. Neurophysiological Measures for each Contraction Task

				BH & DF			BH & BNH			DF & BNH		
	BH	**DF**	**BNH**	**SEM**	**MDC**	**sig**	**SEM**	**MDC**	**sig**	**SEM**	**MDC**	**sig**
VA (%)	95.1(4.3)	95.2(5.5)	93.5(5.2)	2.58	7.15	0.637^	4.39	12.17	0.409	4.61	12.77	0.406
TCI Area	0.14(0.08)	0.12(0.08)	0.14(0.13)	0.023	0.062	0.122	0.047	0.130	0.764^	0.047	0.130	0.465^
TCI Depth (%)	59.6(12.5)	54.6(7.4)	56.8(6.6)	6.22	17.24	0.206^	5.65	15.65	0.638^	4.24	11.75	0.248

^indicates non-parametric variable, determined using WSR analysis

Table 4. Contraction-Specific Changes in VA and TCI From Session 1 to 7

	N	Session 1 Mean (SD)	Session 7 Mean (SD)	SEM	MDC	sig
Voluntary Activation (%)						
BH	11	95.14(4.3)	92.27(4.4)	2.33	6.47	0.016*
DF	11	95.23(5.5)	93.69(4.5)	3.34	9.25	0.304
BNH	11	93.53(5.2)	91.50(7.2)	4.72	13.09	0.338
TCI Area Normalized						
BH	11	0.140(0.08)	0.149(0.14)	0.063	0.18	0.819
DF	11	0.124(0.08)	0.100(0.06)	0.032	0.09	0.162
BNH	11	0.141(0.13)	0.133(0.08)	0.032	0.09	1.000
TCI Depth (%)						
BH	11	59.56(12.5)	55.97(8.0)	5.73	15.87	0.172
DF	11	54.56(7.3)	54.22(8.8)	6.49	18.00	0.905
BNH	11	56.78(6.6)	56.46(10.8)	5.77	16.01	0.900

Voluntary activation for BH ($r = -0.655$; $p = 0.039$) and DF ($r = -0.636$; $p = 0.035$) was inversely related to BLD for BH on session one. No other neurophysiological measure was correlated with BLD for BH or BNH. Peak BH ($r = -0.627$, $p = 0.039$) and BNH ($r = -0.682$, $p = 0.021$) forces were inversely related to TCI area on session seven, but DF was not ($r = -0.391$, $p = 0.235$). Measures of VA and TCI depth were not correlated with peak force (Table 5). Sleep quality, quantity, and nutrition (calories, carbohydrates, protein, and fat) were equivalent across all test days.

Table 5. Correlations between Performance and Voluntary Activation

			DF voluntary activation		BH voluntary activation		BNH voluntary activation	
		N	Corr	sig	Corr	sig	Corr	sig
Bilateral Index								
BH	Day 1	11	-0.655^	0.029*	-0.636^	0.035*	-	-
	Day 7	11	0.039	0.909	0.399	0.224	-	-
BNH	Day 1	11	-0.118^	0.729	-	-	0.384	0.243
	Day 7	11	-0.236^	0.484	-	-	0.536^	0.089
Peak Force								
BH	Day 1	11	-	-	0.036^	0.915	-	-
	Day 7	11	-	-	-0.025	0.941	-	-
BNH	Day 1	11	-	-	-	-	-0.139	0.683
	Day 7	11	-	-	-	-	0.413	0.207
DF	Day 1	11	0.400^	0.223	-	-	-	-
	Day 7	11	-0.526	0.096	-	-	-	-

^analyzed with Spearman Correlations
*significance at $p < 0.05$

Table 6. Correlations between Performance and Transcallosal Inhibition

			DF TCI area normalized		BH TCI area normalized		BNH TCI area normalized		DF TCI depth		BH TCI depth		BNH TCI depth	
		N	Corr	sig	Corr	sig	Corr	sig	Corr	sig	Corr	sig	Corr	sig
Bilateral Index														
BH	Day 1	11	0.182^	0.593	-0.091^	0.790	-	-	-0.219	0.518	-0.227^	0.502	-	-
	Day 7	11	0.400^	0.223	-0.173^	0.612	-	-	-0.060	0.860	-0.186	0.590	-	-
BNH	Day 1	11	-0.145^	0.670	-	-	-0.155^	0.650	-0.527	0.096	-	-	-0.379	0.250
	Day 7	11	0.082^	0.811	-	-	0.136^	0.689	-0.373^	0.259	-	-	-0.345^	0.298
Peak Force														
BH	Day 1	11	-	-	-0.545^	0.083	-	-	-	-	0.136^	0.689	-	-
	Day 7	11	-	-	-0.627^	0.039*	-	-	-	-	0.110	0.748	-	-
BNH	Day 1	11	-	-	-	-	-0.264^	0.200	-	-	-	-	0.202	0.551
	Day 7	11	-	-	-	-	-0.682^	0.021*	-	-	-	-	-0.335	0.314
DF	Day 1	11	-0.373^	0.259	-	-	-	-	0.260	0.440	-	-	-	-
	Day 7	11	-0.391^	0.235	-	-	-	-	0.016	0.963	-	-	-	-

^analyzed with Spearman Correlations

*significance at $p < 0.05$

5.4 Discussion

The purpose of this study was to evaluate the influence of corticospinal drive on BLD before and after regular MVIC task practice. The contributions of TCI and VA to maximal force and BLD was assessed during maximal BH elbow flexor contractions and compared to dominant flexion and BNH contractions of the same joint that displayed no BI. After task-specific training, BH VA was reduced while maximal force was maintained, but without exceeding the MDC. In addition, correlation of BI and peak force to VA and TCI revealed association of session one BH BI with DF and BH VA, session seven BH TCI area normalized with BH peak force, and BNH TCI area normalized with BNH peak force.

Bilateral deficits during BH contractions were evident and comparable to previous reports, but interestingly, no BI was only present in the first session (-4.00 ± 8.70%) compared to BLD in session seven (-8.05 ± 6.66%). In accordance with expectations, BNH produced no BI regardless of visit (session one:-3.66 ± 8.04%; session seven:-5.02 ± 10.02%). Similar to prior work, neurophysiological measures did not explain differences in BLD between tasks and visits. [18] [21]. The results of this investigation calls in to question the extent to which corticomotor factors contribute to BLD during familiar and unfamiliar upper body tasks.

Transcallosal Inihibition

Neurons of the ipsilateral motor cortex act through transcallosal fibers [27, 28] that enable the interhemispheric integration required for rapid and efficient task execution [27, 29, 30]. Several approaches have been used to explain the role of TCI, with consistent reports of greater TCI in bilateral tasks as compared to unilateral [14, 31, 32]. Increased TCI is theorized to be a response

of redundant activity from the ipsilateral hemisphere, acting to improve efficiency and precision of motor processes [14-16]. Yet, it is not understood why TCI is additionally reduced with submaximal BNH, as compared to BH and unilateral tasks [17, 20]. Although evidence is minimal, this inhibition is theorized to result in a diminished BH central neural drive, but not BNH due to the need to decouple movements, subsequently causing differences in BH and BNH corticospinal drive [5] with possible cause of BI [17].

Using submaximal elbow flexion and extension [17] and homologous and non-homologous dynamic thumb movements [20], BH and BNH tasks were reported with increased and decreased TCI compared with the corresponding unilateral task, respectively. Results indicate dynamic regulation of inter-limb interactions, but with ambiguous evidence of how or why this occurs. Examination of why task alters TCI is unknown, but grounded in theories of controlling hemisphere influence [134], activation of altered excitatory pathways [135], and inability to decouple asymmetrical movements [31]. Nonetheless, these hemispheric interactions have not been apparent during maximal force tasks, specifically concerning differences between BH and BNH BI.

To date, only Skarabot et al., examined the relationship between TCI and BI, exploiting the predominantly bilateral and unilateral training history of weightlifters/power lifters and high jumpers/long jumpers, respectively, with additional comparison to untrained controls [18]. Bilateral index increases with bilateral training and decreases with unilateral training [52, 109], yet all groups presented with no BI, nor differences in BH and unilateral TCI during isometric knee extension [18]. In the present study, acute training over the seven sessions did not alter BI after the second session, and with no difference in TCI.

In the present study, TCI was reliably observed during BH, BNH, and unilateral contractions before and after training. Yet, when each of the 66 tests (2 BH, 2 BNH, and 2 DF test sessions for 11 participants) were averaged into a single measure, EMG facilitation rather than inhibition (Figure 16), presented in two thirds of the tests immediately after TMS. Of interest, TCI was more prevalent in the present study than those that used submaximal contractions, where TCI was detected in less than half of participants [17, 136]. We theorize these differences may be due to the increased level of muscle activity prior to TMS during MVICs compared to submaximal tasks, which increased baseline values used for TCI thresholding. This is evident, as TCI measures alter from prior studies, reported a TCI onset average at 40-43ms and depth at 50-60%, as compared to previously reported submaximal contraction onset averaged at 20-25ms and depth at 13-35% [17, 20].

To further investigate differences between trials with and without TCI, independent t-tests were used to assess MEP peak to peak amplitude and force in each elbow as well as TMS positioning error (Table 6). Interestingly, MEP amplitude, force, and TMS error did not present with consistent differences between sessions. Yet, if differences were realized, the trials presenting with no TCI consistently produced smaller MEPs, increased force, and reduced TMS error. These patterns suggest trials without TCI were likley due to muscle activation outside of the targeted biceps brachii, causing excessive noise and measurement error. Previous studies have found diminished TMS error and increased force are likely to increase MEP amplitude [121, 135] but excessive muscle activation has been associated with reduced MEP size [137]. Identification of TCI within BH, BNH, and unilateral MVIC may, therefore, prove difficult.

Table 7. MEP, Force, and TMS Error in Trials with and without TCI

		Day 1					Day 7				
		N	TCI mean(SD)	N	no TCI mean(SD)	sig	N	TCI mean(SD)	N	no TCI mean(SD)	sig
MEP peak-to-peak amplitude (mV)											
BH	ND	94	4.25(3.25)	24	3.70(4.09)	0.481	74	3.85(2.4)	34	5.06(3.8)	0.091
	D		2.88(2.36)		3.24(2.45)	0.507		2.03(1.9)		1.42(0.6)	0.014*
DF	ND	77	1.91(2.6)	41	1.15(1.4)	0.041*	67	2.06(2.7)	40	1.94(3.3)	0.846
	D		3.13(3.0)		2.94(2.0)	0.682		2.02(1.9)		1.57(1.1)	0.183
BNH	ND	77	3.10(3.1)	43	2.18(3.0)	0.122	85	3.20(3.8)	34	1.64(3.3)	0.029*
	D		3.32(3.1)		3.43(2.7)	0.843		2.62(2.1)		1.41(0.8)	<0.001*
Force at time of TMS (N)											
BH	ND	94	201.3(60.9)	24	248.4(97.9)	0.004*	74	208.05(63.8)	34	238.11(71.1)	0.031*
	D		207.3(62.3)		250.4(103.6)	0.010*		217.85(65.0)		256.90(67.9)	0.005*
DF	ND	77	0.10(0.2)	41	0.03(0.3)	0.192	67	0.11(0.6)	40	0.11(0.8)	0.975
	D		231.2(58.1)		248.2(94.8)	0.299		228.6(60.2)		234.9(76.8)	0.657
BNH	ND	77	214.7(56.6)	43	215.9(83.8)	0.937	85	207.2(59.0)	34	185.7(61.5)	0.079
	D		236.7(63.3)		250.3(96.6)	0.412		232.0(59.4)		210.7(76.4)	0.152
TMS Displacement (mm), Yaw (deg), and Pitch (mm) Error											
BH	Dis.	94	5.39(5.3)	24	3.77(3.3)	0.066	74	4.65(5.5)	34	2.58(1.8)	0.005*
	Yaw		4.30(2.2)		3.39(1.7)	0.065		3.64(1.7)		3.43(1.4)	0.529
	Pitch		2.01(4.0)		3.29(2.6)	0.144		2.41(2.5)		1.39(2.2)	0.046*
DF	Dis.	77	4.83(4.4)	41	6.11(4.8)	0.150	67	4.62(5.9)	40	2.63(2.1)	0.013*
	Yaw		3.87(1.8)		3.87(2.2)	0.997		3.12(1.8)		2.57(1.5)	0.100
	Pitch		1.31(3.5)		2.08(2.6)	0.187		2.05(2.1)		1.10(2.2)	0.031*
BNH	Dis.	77	4.61(3.8)	43	4.26(4.0)	0.633	85	5.89(5.8)	34	3.40(2.3)	0.001*
	Yaw		4.11(2.6)		4.57(3.0)	0.377		3.28(1.6)		3.03(2.0)	0.506
	Pitch		1.97(2.7)		2.11(2.8)	0.791		2.15(2.2)		1.61(1.7)	0.205

* indicates significance at $p < 0.05$

ND – Non-dominant limb, TMS targeted muscle; D – dominant limb; Dis.- displacement, or distance, of TMS coil from hotspot (mm); Yaw – angular rotation of TMS coil from hotspot (deg); Pitch – Ant/Post and Med/Lat tilt of TMS coil from hotspot (mm)

Changes from pre- to post-training provide insight of TCI between bilateral and unilateral tasks. Specifically, TCI and BH force were negatively corelated on session one (r_s = -0.545, p=0.083) and seven (r_s = -0.545, p=0.083), with weak DF relation on session one (r_s = -0.373, p=0.259) and seven (r_s = -0.391, 0.235). BNH was accompandied by the largest change from session one (r_s = -0.264, p=0.200) to seven (r_s = -0.682, p = 0.021). These differences are likely a result of training, where BH was familiar, presenting diminished TCI, and BNH unfamiliar with

greater TCI, but reduced with training. Lack of DF correlation is condiered to be due to non-dominant hemipshere inactivation, reducing the necessity to inhibition the opposing limb, with no effect on maximal force. Due to lack of correlation to BI, researchers theorized TCI is not likely the primary mechanism of the BLD phenomenon, but correlations suggest it may influence initial force production.

Voluntary Activation

Electrical peripheral stimulation and TMS cortical stimulation were previously compared during BH and unilateral MVIC knee extensions, with the same result of comparatively greater VA during unilateral contractions. [21]. The present study is the first to examine VA with TMS during BH, BNH, and unilateral elbow contractions, with decreased VA for BH contractions from session one to session seven. Nevertheless, TMS VA measurements did not exceed the MDC, and changes should thus be interpreted cautiously.

Cortical stimulation VA SIT methods previously demonstrated ICC(2,1) = 0.980 [111], but were later reported as a problematic method due to outside muscle activation, ineffectiveness of TMS to maximally activate the corticospinal system, and variability between maximal and submaximal isometric contractions [113]. Due to such challenges to achieve VA, the present study used maximal VA for BH, BNH and DF tasks during each test day. MEP, percent of target force, SIT force, and TMS error (Appendix B, Figure 25) were compared across tasks and contraction levels (100% and 50%) and were comparable. Therefore, data was pooled to examine differences in maximal and non-maximal VA (Table 7). Motor evoked potential, force, SIT, and TMS error mean were altered, at 100% and 50% efforts, demonstrating a need for consistently accurate measures to achieve maximal VA.

Table 8. Maximal and Non-maximal VA Measures

	Non-max N=484	Max N=56	p-value
Voluntary Activation (%)	82.8(13.1)	93.4(5.5)	<0.001^*
MEP (mV) at 100%	4.3(2.6)	4.6(2.8)	<0.001^*
MEP (mV) at 50%	4.7(2.9)	4.6(2.9)	0.001^*
100% target force (%)	91.6(11.1)	94.9(10.2)	<0.001^*
50% target force (%)	50.3(7.6)	51.8(6.3)	0.002*
SIT (N) at 100%	9.7(8.7)	5.5(6.3)	<0.001^*
SIT (N) at 50%	26.5(14.9)	27.7(15.9)	0.001^*
TMS error (mm) at 100%	9.3(4.5)	8.9(4.4)	0.038*
TMS error (mm) at 50%	8.4(4.8)	8.1(4.3)	<0.001^*

^analyzed using WSR test
*significant at $p \leq 0.05$

Bilateral Index

Prior studies suggest bilateral training is the overriding mechanisms of the BLD phenomenon, as bilaterally trained weightlifters produce BLF, while cyclist (unilaterally trained) and untrained subjects demonstrate BLD [2]. As the human brain generates highly choreographed patterns of muscle activity that change with practice and experience [56], the organized motor control network adjusts to optimally achieve the new motor skill [57]. In the present study, researchers used training to assess if changes in force and BLD were correlated with changes in TCI and VA, as neurophysiological factors are believed to determine MVIC force.

Mean maximal forces were steady and reliable across all test sessions but did not translate to BI (see Chapter 4). Mean BNH BLD maintained classification (no BI) across all testing sessions, but BH BLD was statistically similar across test days, but changed from no BI (session 1) to BLD (sessions 2-7). In a similar pattern, BH VA altered with BH BI, deceasing from session one to seven, but showed a high negative correlation with BH BI session one, but not seven. Logical interpretation suggests error within these measures, as results were similar to DF VA, as BH BI

increases with decreased BH force and/or increased DF force. Additional muscle activation to achieve maximal force, outside the BB, is theorized to effect these results due to resultant BI error (Chapter 6). Combined with lack of significant TCI and BI correlation, results suggests neural drive is not the predominant mechanism to dictate BI.

Unlike previous studies, BNH BI was used as a bilateral control to confirm the relationship between TCI, VA, and BLD. Additionally, training was exploited to determine if corticospinal measures were reflective of or responsive to changes in task performance with increased familiarity. Nevertheless, the results of this investigation confirm recent indications that neurophysiological factors do not contribute to BLD. Despite this, TCI was associated with maximal force, and therefore cannot be ruled out as a factor that may contribute to differences in maximal force between BH, BNH, and unilateral contractions.

6.0 Manuscript 3: Altered Stabilizing Muscle Activation Creates the Illusion of the Bilateral Deficit Phenomenon

6.1 Introduction

Maximal force production inherently requires the coordination of activity between numerous muscle groups to achieve peak task performance [138, 139]. To stabilize, muscle activation patterns modify through counterbalances [139], but are altered with practice [140] and type of task demanded [141]. Activation patterns altered with task-specific practice, between bilateral and unilateral tasks, has received nominal recognition as transcallosal inhibition is considered the predominant theory. Overcome by training [142, 143], transcallosal inhibition is delivered from the opposing brain hemisphere to reduce excess neural activity, resulting in increased or diminished BLD with unilateral and bilateral training, respectively. With equivocal evidence of this theory (Chapter 5)[5, 18] and minimal BI reliability (Chapter 4), BLD may rather be a result of stabilizers to achieve greater unilateral maximal force, diminishing with increased task-specific practice to minimize effort.

The required stability to accomplish maximal force tasks is evident with greater BLD reported in multi-joint tasks over single-joints, as well as lower over upper extremity tasks [5]. Only a single study has explored the effect of increased stability upon BLD, resulting in BLD due to contralateral hip counterbalance, which produced greater unilateral ankle plantarflexion force [6]. Further supported using electromyography (EMG), activation of stabilizing muscle groups was increased during horizontal squat jumps when BLD was present, but absent during isometric handgrip contractions without BLD [66].

Isometric elbow flexion and extension are common in BLD research and consistently produce BLD with BH [5, 11, 13, 34, 144]. Of interest, bilateral non-homologous (BNH; asynchronous) contractions present with BI equal to zero, or no BI [2, 12, 13]. Due to complexity of scapular stabilization techniques, it is unknown if unilateral and bilateral homologous and non-homologous upper extremity tasks produce different activation patterns in primary agonist and synergist muscles. Specifically which could explain differences in force and subsequent conclusions about the presence or absence of BLD.

The purpose of the present study was to explore muscle activation patterns during maximal isometric BH, BNH, and unilateral contractions of the elbow musculature, before and after task-specific practice, to determine if differences in force and BI estimates might reflect subtle adjustments in synergist muscle activity to compensate for imbalances during unilateral force production. Electromyographic activity was measured bilaterally in the primary agonist and antagonist muscles, in addition to scapular stabilizing muscle groups. For each muscle, EMG activity was compared during contractions used for BI calculations in addition to controls that emphasized active and inactive muscle states during unilateral and bilateral contractions.

6.2 Methods

Research Design and Subjects

Eleven healthy participants (6 women, 25.6±3.7 years; 171.81±11.44 cm; 74.4±21.2 kg) volunteered to participate in the counterbalanced repeated measures study. Participants were included if they were between the ages of 18 and 35, with normal or corrected vision, right hand dominant, and active a minimum of 120 minutes per week. Subjects were excluded if (1) suspected

or knowingly pregnant, (2) with current upper extremity musculoskeletal injury, (3) history of upper extremity orthopedic surgery within the past two years, (4) discomfort or unwillingness to complete elbow MVICs, (5) diagnosed with a neurological disorder, epilepsy, cardiovascular, or other major disorders, (6) current use of central nervous system active drugs or anabolic hormonal substance or growth hormone, or (7) alcohol consumption more than 3 drinks/day or 18/week. A 24 hour diet recall log and sleep quality and quantity questionnaire were assessed each test session to determine any mechanism which may affect ability to produce maximal effort. All procedures were approved by the University of Pittsburgh Institutional Review Board.

Experimental Design

Participants took part in a familiarization and five test sessions, separated by 24-72 hr (48.5±16.8 hrs). Prior to all experimental tasks, participants completed a 24-hour diet recall log and sleep quality and quantity questionnaire to ensure similar sleep and dietary patterns were similar each visit. A familiarization session was used to place EMG sensors and familiarize participants with the protocol. Each training session, participants performed 25 maximal voluntary isometric contractions (MVIC) of the elbow muscles, with five trials of bilateral flexion (BH), non-dominant extension (NE), dominant flexion (DF), non-dominant flexion (NF), and dominant flexion with non-dominant extension (BNH).

Electromyography

Electromyography (Delsys Inc, Natick, MA, US) was used to measure skeletal muscle activity. SENIAM recommendations were used for placement, when applicable. A certified and trained clinician used manual muscle tests and palpated the muscle belly to determine optimal

sensor placement if SENIAM guidelines were absent [116]. Prior to placement, hair was removed, skin was abraded and excess oil was removed.

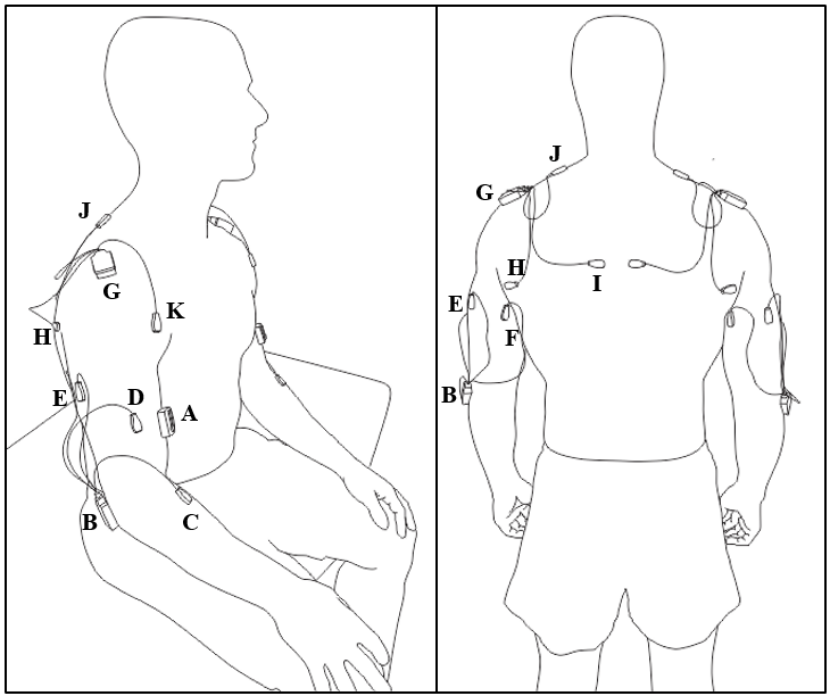


Figure 19. EMG Sensor Placement

A – Bicep Brachii (BB), **B** – Quattro reference sensor 1, **C -** Brachioradialis (BrRa), **D** – Brachialis (BR), **E** – Tricep Lateral Head (TrLa), **F** – Tricep Long Head (TrLo), **G** – Quattro reference sensor 2, **H** – Infraspinatus (IN), **I** – Middle Trapezius (MTr), **J** – Upper Trapezius (UTr), **K** – Anterior Deltoid (AnDe)

Wireless sensors (Delsys, Natick, MA, US; interelectrode distance: 10mm, Noise: 750nV) were placed on bilateral biceps brachii (BB), triceps long head (TLo), triceps lateral (TLat), brachialis (BR), and brachioradialis (BrRa), middle trapezius (MTr), upper trapezius (UTr), infraspinatus (IN) and anterior deltoid (AnDe)(Figure 19). Reference sensors were placed bilaterally on the lateral epicondyle and acromion. Indelible ink was used to place EMG sensors in identical positions across test days. EMG signals were digitized at 2000Hz and captured using commercially-available software (Labchart V8, ADInstruments, Colorado Springs, CO, US; EMGWorks V4, Delsys Inc., Natick, MA, US). EMG signals were bandwidth filtered at 20-450 Hz and transformed to root mean square (RMS) values 1000ms prior to force onset (baseline) and

±500ms around the point of maximal force. Baseline noise was assessed prior to data collection to assure signal quality for all sensors.

Testing Apparatus

MVICs were performed in a commercially-available device (System 4 Pro, Biodex Medical Systems Inc.; Shirley, NY, US). The customized apparatus was designed to test isometric elbow flexion and extension, with shoulders at 90^{o} glenohumeral forward flexion. Elbows were bent at 90^{o}, and cuffs aligned directly beneath the radius and ulna styloid processes. Designed with 80/20 parts (Grainger Inc.; Miami, FL, US) and a 91 x 122 x 2.5cm metal platform, the device was attached to the Biodex chair through two legs in the lateral receiving tubes, and a third leg connected to the floor from the front of the platform. A secondary platform was placed between the vertical posts, which allowed elbows to rest without upper arm contact to the main platform. This reduced potential counterbalances during MVIC testing. The device was adjustable at platform (1) height and (2) depth, (3) elbows at shoulder width apart on secondary platform, (4) secondary platform depth, and (5) forearm height. The cuffs were also adjustable to allow quick transition between elbow flexion and extension. Participants were secured in the Biodex chair at the chest and waist to reduce excessive movement (Figure 20). Device placement was recorded at all joints (mm) to assure accuracy across test days.

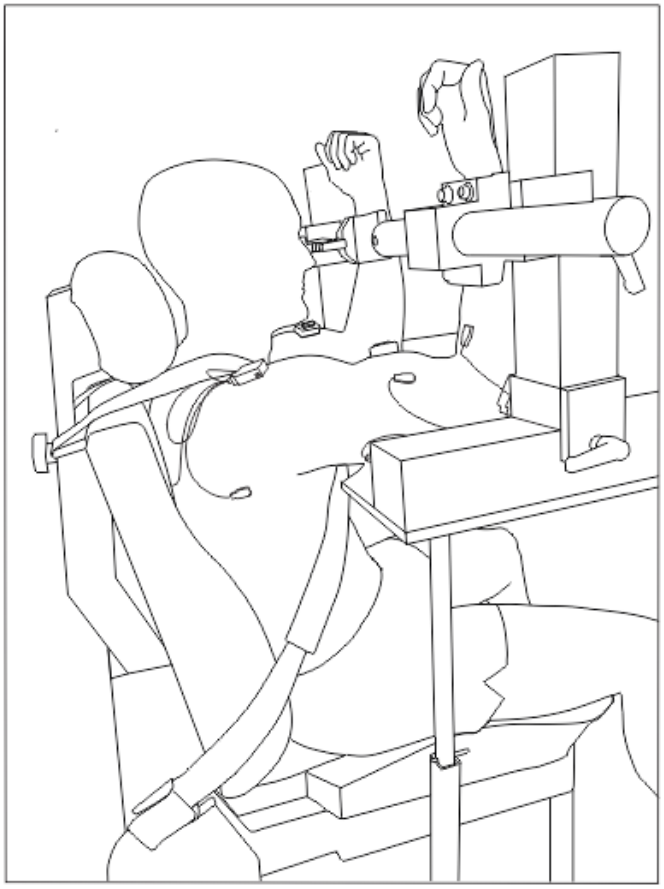


Figure 20. MVIC Test Chair with EMG

EMG Sensors were placed on primary agonist, synergist, and stabilizing muscles to quantify muscle activity during each contraction

Force Transducers

SM-250 load cells (Interface, Scottsdale, AZ, US) connected 3D printed cuffs to the customized device. Load cells were wired with a 3-pin Lemo circular style connector to mate with Trigno Load Cell Adapters (Delsys, Natick, MA, US). Data were digitized at 2000Hz and a gain of x1000, low-pass filtered (butterworth, 40dB/dec), and averaged every 20 data points (10ms). Dominant and non-dominant limb force data were collected using Labchart analysis software (Colorado Springs, CO, US), and summed to determine bilateral MVIC force.

Maximal Voluntary Isometric Contractions

Prior to each MVIC, subjects were instructed to keep the jaw open and relaxed to reduce excess muscle activation superior to the glenohumeral joint. Subjects were allowed to see force produced on a screen in front of them to maintain internal motivation, and verbally encouraged through the full four second contraction. Task MVICs were completed in the following, or reversed order with allocation counterbalanced: BH, NE, DF, NF, and BNH. This allowed rest of muscle groups between tasks. An additional 90-120s of rest was given between each MVIC to avoid fatigue.

Data Analysis

Due to lack of normality between test sessions, EMG measures were analyzed with Friedman ANOVAs. As no differences in EMG activity were found across all five test sessions, for all tasks, data were combined to assess muscle activation patterns at maximal force during (1) unilateral versus bilateral maximal force, (2) unilateral task inactive limb baseline versus maximal force, (3) unilateral active versus inactive limb at maximal force, and (4) dominant limb BH versus BNH at point of maximal force.

Bilateral homologous and BNH tasks were broken into dominant (BH-D, BNH-D) and non-dominant (BH-N, BNH-N) analyses, so to compare with the unilateral tasks. If EMG of one signal was lost due to equipment malfunction or insufficient contact with the skin, paired data was removed from analysis. All EMG data were non-normal as determined by Shaprio Wilk's test and comparisons were therefore made using Wilcoxon Signed-Rank tests with non-parametric effect size estimates (absolute $Z/\sqrt{(\text{number of cases})}$) [145, 146]. Data are presented as mean (SD), t-score or Z-score, p-value and non-parametric effect size (r). Effect sizes were defined as small 0.1

$\leq$ r < 0.3, moderate 0.3 $\leq$ r < 0.5, or large r $\geq$ 0.5. Significance was set *a priori* at $p<0.05$, and all data analysis was performed using commercially-available software (SPSS version 26, IBM Corporation, Armonk, NY, US).

To assess BLD, peak force was averaged each session for BH, NE, DF, NF, and BNH MVICs. BH and BNH BLD were calculated as an index (Equation 1) for each test session. To categorize BLD, grand averaged BH and BNH BLD estimates assessed with paired t-tests or Wilcoxon Signed-Rank tests if non-parametric.

$$BI\% = \left(100 \times \frac{\text{Bilateral Force}}{\text{Right Unilateral Force} + \text{Left Unilateral Force}}\right) - 100 \quad (1)$$

6.3 Results

Force and BLD measures were grand averaged for comparison to grand averaged EMG data. When dominant and non-dominant limb were averaged, separately, greater force was present for DF (272.8±64.2) compared to BH-D (247.8±73.5; Z=-2.128, p=0.016, r=0.203) and for BNH-D (261.7±77.3) compared to BH-D (Z=-3.242, p=0.001, r=0.309; Figure 21). Estimated BLDs for BH (-6.38±3.6) and BNH (0.72±6.2) differed ($t_{(10)=}$-3.238, p=0.009), as BH produced a BLD ($t_{(10)=}$-6.997, p<0.001), which was absent for BNH($t_{(10)=}$0.139, p=0.892) (Appendix C Figure 26).

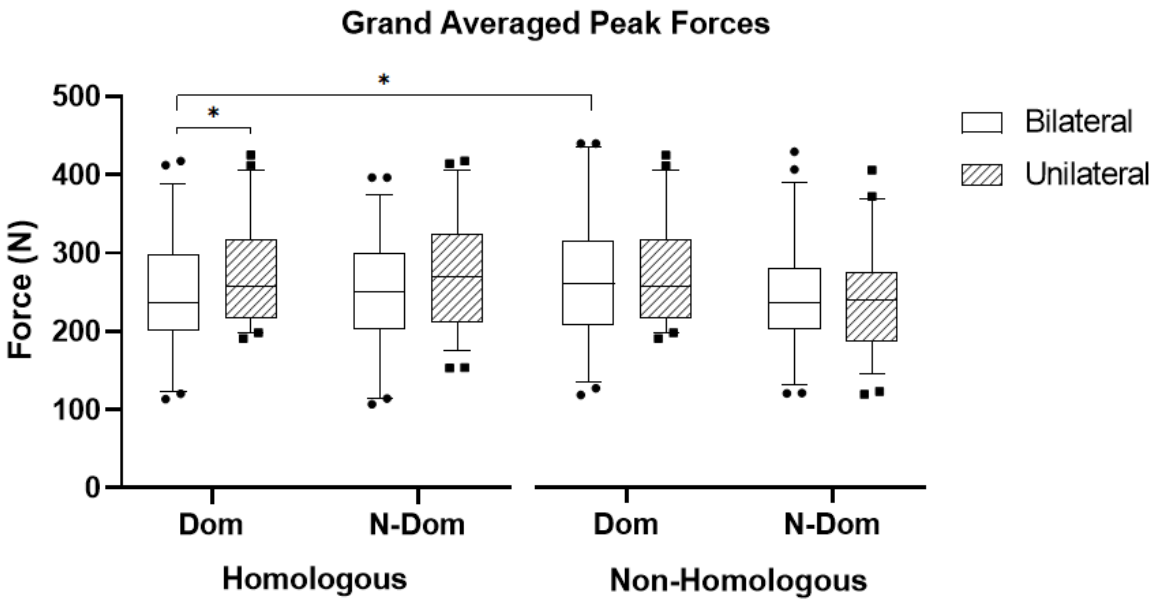


Figure 21. Grand Averaged Peak Forces

All measures of force are displayed as median with bars denoting 95% confidence interval. Bilateral tasks were broken down into dominant (Dom) and non-dominant (N-Dom) measures of force for homologous (bilateral flexion) and non-homologous (dominant flexion and non-dominant extension) tasks. Using paired t-test, bilateral forces were compared with the corresponding unilateral task (ex. BH-D with DF, BNH-N with NE) and dominant homologous was compared with non-homologous, due to the similar task (elbow flexion) where non-dominant tasks were altered by task (*denotes significance set at $p \leq 0.05$).

Differences in EMG activity between bilateral and unilateral tasks indicated that different contractile strategies were used to achieve maximal force (Figure 22 and Appendix D Tables 8 & 9). BH-D had greater activity in BR (Z=-2.245, p=0.024, r=0.214), BrRa (Z=-2.007, p=0.044, r=0.191), and IN (Z=-4.382, p<0.0001, r=0.418) compared to DF, which had greater activity in BB (Z=-2.622, p=0.005, r=0.226), MTr (Z=-2.325, p=0.016, r=0.193), and AnDe (Z=-5.052, p<0.001, r=0.482).

The BH-N task used more BrRa (Z=-2.396, p=0.016, r=0.228) and IN (Z=-5.135, p<0.001, r=0.499) activity compared to NF, which had greater activity in the MTr (Z=-1.988, p=0.047, r=0.193) and AnDe (Z=-5.236, p<0.001, r=0.509). BNH-D had more AnDe (Z=-2.338, p=0.019, r=0.225) activation compared to DF, which produced greater activity in TLat (Z=-2.154, p=0.031, r=0.205), BR (Z=-2.002, p=0.045, r=0.191), and IN (Z=-3.846, p<0.001, r=0.367). BNH-N had

greater BB (Z=-2.229, p=0.025, r=0.213), BrRa (Z=-2.288, p=0.021, r=0.218), and MTr (Z=-2.204, p=0.027, r=0.214), and IN (Z=-2.151, p=0.031, r=0.209) compared to NE.

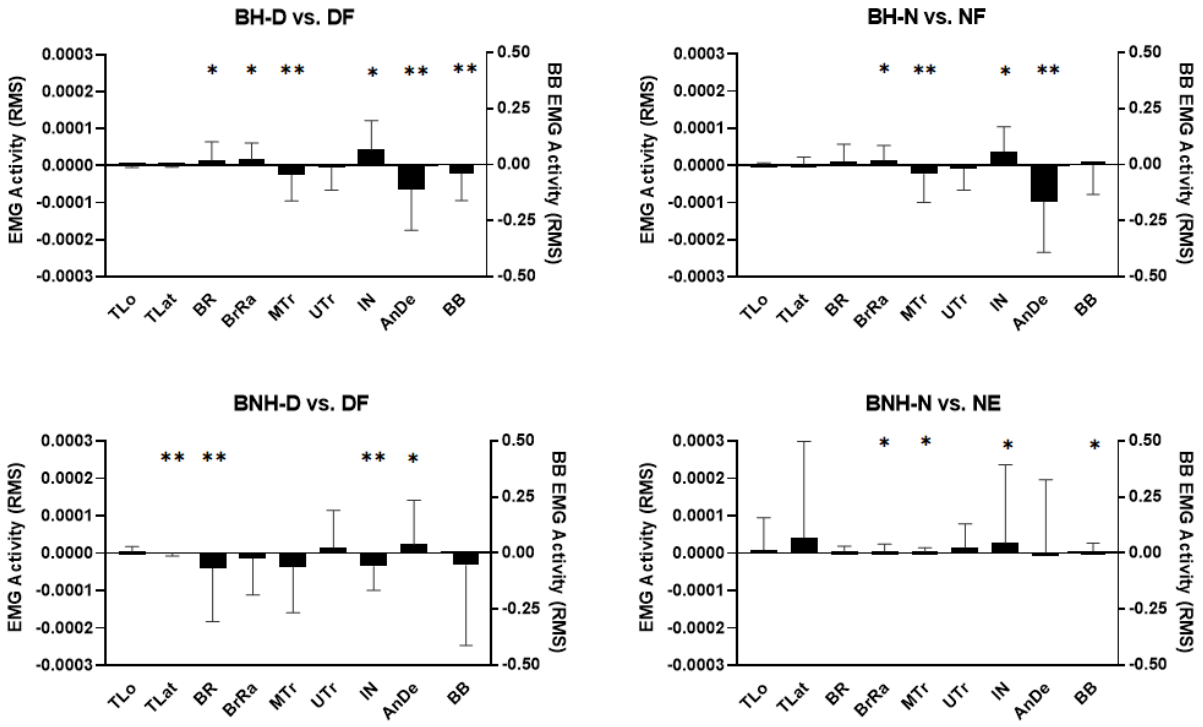


Figure 22. Comparison between Bilateral and Unilateral EMG Sensor at Maximal Force

To demonstrate altered activation patterns between bilateral and unilateral tasks, unilateral measures were subtracted from bilateral, and graphed for each EMG signal **A.** BH-D Flexion Compared with Dominant Flexion **B.** BH-N Flexion with NF **C.** BNH-D Flexion with DF and **D.** BNH-N Extension with NE. Positive values indicates greater bilateral task activation where negative indicates greater unilateral task activation. All EMG measures, between like-tasks were assessed using paired t-tests, where * indicates bilateral EMG RMS is statistically greater ($p \leq 0.05$) than unilateral maximal force and ** indicates unilateral EMG RMS is greater ($p \leq 0.05$) than bilateral maximal force

When inactive limb EMG RMS at maximal force was compared to baseline, all muscles were considered "on" ($p<0.001$), with moderate to large effect sizes (Figure 23A-C; Appendix D Table 10). When inactive limb EMG RMS at maximal force was compared to active limb maximal force, inactive NE MTr was greater than active (Z=-6.001, $p<0.001$, r=0.554) while UTr (Z=-4.661, p=0.130, r=0.147) and AnDe (Z=-5.714, p=0.371, r=0.088) were similar. All other active muscles were greater than their inactive counterparts (Figure 23D-F, Appendix D Table 11).

Comparison of dominant limb muscle activation during BH and BNH contractions revealed (Figure 24, Appendix D Table 12) greater EMG activity in the BR ($Z=-3.335$, $p<0.001$, $r=0.318$), BrRa ($Z=-2.312$, $p=0.02$, $r=0.220$), and IN ($Z=-5.153$, $p<0.001$, $r=0.491$) during BH-D, whereas BNH-D produced greater activity in the AnDe ($Z=-5.084$, $p<0.001$, $r=0.489$).

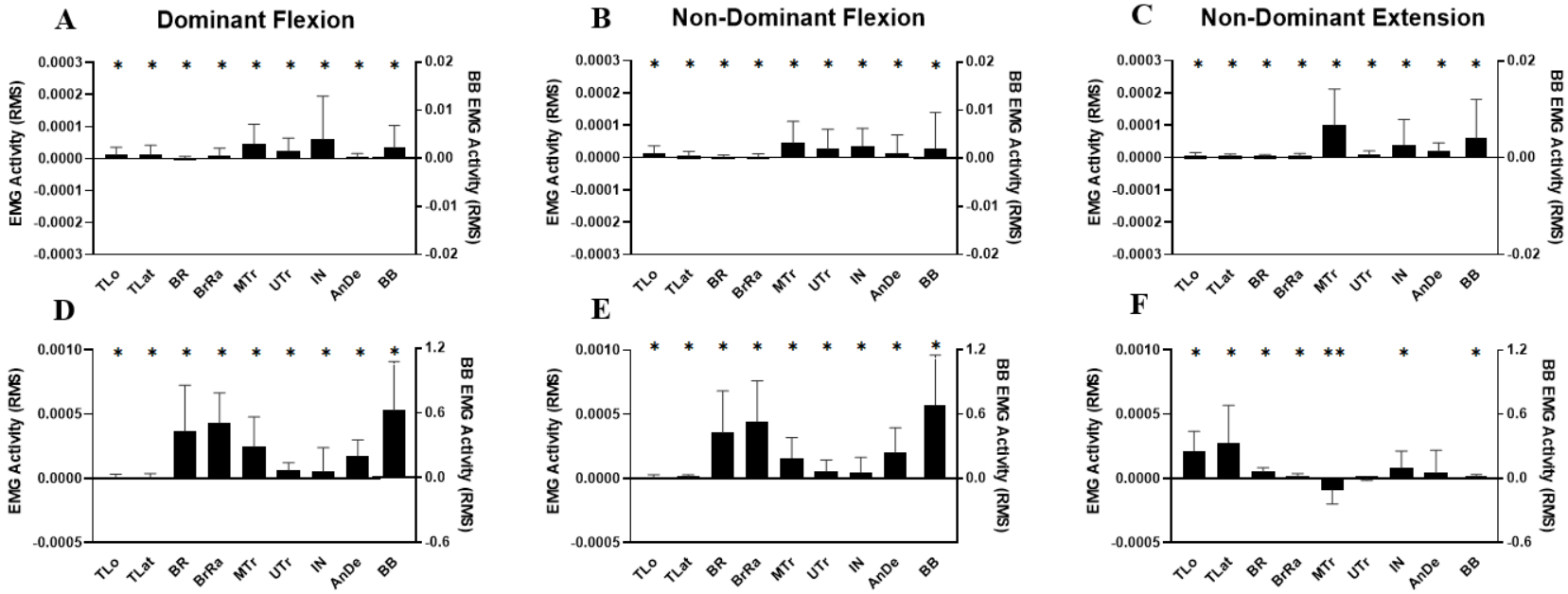


Figure 23. Activity in Resting/Opposing Limb During Unilateral Tasks

Unilateral task inactive limbs (non-dominant limb during DF and dominant limb during NF and NE) and activated limb EMG RMS were analyzed where **A-C** demonstrates all inactive limbs muscles were active at point of maximal force, as compared to baseline, denoted by *, and **D-F** demonstrates all active limb muscles were greater than inactive, denoted by *. With the exception of NE, MTr inactive limb presents with greater activation than the active (as denoted by **), and AnDe and UTr demonstrate similar EMG RMS activity between inactive and active limbs.

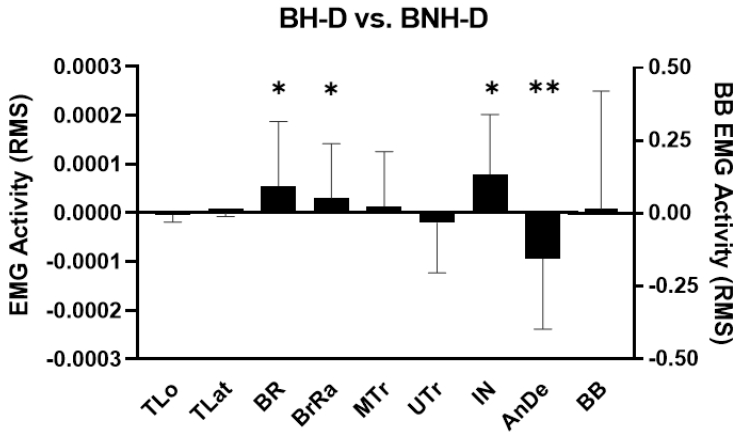


Figure 24. Dominant BH vs. BNH Muscle Activity

The dominant limb for both BH and BNH tasks were analyzed, at point of maximal force. BH-D (*) was achieved with greater BR, BrRa, and IN muscle activation, where the BNH-D(**) task necessitated greater use of AnDe to achieve maximal force. Different muscle activation patterns demonstrate altered lines of action between BH and BNH tasks.

6.4 Discussion

The purpose of this study was to assess BH and BNH MVICs and the corresponding unilateral contractions to evaluate if the BLD phenomenon may reflect differences in muscle activation patterns. Electromyographic activity was captured in a large array of muscles including the TLo, TLat, BR, BrRa, MTr, UTr, IN, AnDe, and BB at baseline and maximal force production, with the results indicative of different activation patterns between all bilateral and unilateral tasks. Unilateral tasks were accompanied by increased activity in the inactive limb at point of maximal force from baseline, while activity in all active limb muscles was greater compared to the inactive counterparts, with the exception of the inactive MTr, UTr, and AnDE, which produced greater (MTr) or similar (UTr, AnDE) activity during NE. Altered dominant limb activation patterns between BH and BNH tasks exhibited adjusted strategies to achieve maximal force and resultant BI.

Each of the aforementioned muscles were examined as primary agonists, antagonists, or stabilizers of elbow flexion and extension. When the shoulders are positioned at 90^{o} forward flexion, elbow flexion force is predominantly generated by BB, BR, and BrRa, where TLo, TLat are considered antagonists and scapula stabilizers, and AnDe, MTr, UTr, and IN serve to stabilize the scapular and glenohumeral joints [147, 148]. Elbow extension force primarily originates from the TLo and TLat, where BB, BR, BrRa and AnDe serve as antagonists, and IN, MTr and UTr stabilize the scapular and glenohumeral joints [147, 148]. Although EMG activity is not directly equated to force [149], the current study demonstrates altered muscle activity patterns during otherwise identical conditions, which likely explains greater force production during DF and BNH-D compared to BH-D. Moreover, all other force values were similar.

As present in the current study, diminished BH dominant limb force as compared to the unilateral was the initial theory [1], but has since presented with mixed results and greater prevalence in the upper extremities since its initial inception [3, 5]. As lower extremities do not share similar neural regulation, BLD was later theorized to be due to lateralized neural control [96]. With greater lower extremity BLD magnitude across studies [5], neural control as the predominant BLD underlying mechanism is weakened.

Magnitude of BLD was assessed across multiple studies to observe common patterns, reporting multi-articular and lower extremity tasks consistently presented with greater BLD over uni-articular and upper extremity tasks [5]. This signifies the necessity of surrounding muscle activation to stabilize and maximize force in *unilateral* multi-articular and lower extremity tasks [5, 6, 23, 66, 85, 94]. Further illustrated with ankle plantar flexion in closed and opened kinetic chain devices, increased contralateral hip torque of the unilateral task in the former directly created BLD [6, 74]. Specifically, the open chain task allowed an uncoupling of the body from the ankle

plantar flexion device, and therefore lack of BI in the closed chain was due to lack of leverage from the contralateral hip [6, 74]. As neural regulation and BLD patterns between upper and lower limbs alter, it is therefore necessary to understand upper extremity muscle activation patterns in relation to BLD.

Shoulder and elbow activation is supported through scapular and glenohumeral stabilization [97] which involves complex coordination of muscles in multiple planes of motion, individually altered by training and discrete kinematics [98-100]. Therefore, an upper extremity closed kinetic device may adequately capture the full extent of typical synergist muscle contributions, necessitating the use of a task which isolates individual upper extremity muscles. Yet, patterns of muscle activity which maximize BH, BNH, and corresponding unilateral forces can be observed through comparison within limb unilateral and bilateral tasks.

In the current study, muscles were chosen in relation to their contributions to the kinetic chain sequence [150]. While all muscles coordinate to achieve the desired performance, they may not all contribute to maximal force. Rather, differences in activity between tasks, as well as effect sizes, exhibit *lines of action,* the geometric vector through which the sum of forces is applied. During NE, as evidenced by increased inactive limb MTr activity as well as bilateral relaxation of the active superior muscles (UTr and AnDe), the upper torso was stabilized by horizontal plane rotation. Coordination of these muscles permitted TLo and TLat to push the non-dominant elbow into the test device and leverage the wrist away from the body, as mimicked in prior horizontal plane stabilization patterns established through leverage of the contralateral hip, causing BLD during isometric ankle plantarflexion [6].

In the current study, however, active limb DF and NF presented with greater muscle activity than the inactive limb, demonstrating rotation is not apparent but BH BLD still is. We

theorize this is likely due to rotation variation between push and pull tasks, and corresponding stabilization techniques. Unlike the push motion seen in ankle plantarflexion and elbow extension, the pull task is stabilized through rotation at the sagittal plane, pulling the upper torso posteriorly.

This is further considered as BH maximal force required greater IN, BrRa, and BR (BH-D only) activation, where NF and DF were completed with greater MTr and AnDe than bilateral tasks. All these pull tasks demonstrated a posterior stabilization with subsequent upward isometric pull. Yet, high effect sizes, only evident in bilateral IN and AnDe (Appendix D, Table 8) reflect different strategies to stabilize the scapular and glenohumeral joints. While BH activation patterns exhibited lateralized stabilization leveraged through the opposing side, NF and DF demanded leverage through increased superior flexion of the humerus and coordinated scapular stabilization [147, 148].

Conversely, BNH produced no BI, but horizontal plane rotation stabilization patterns were similar to the unilateral counterparts. For DF, increased TLat, IN, and BR activation underscored the necessity for scapulohumeral and elbow stability to achieve the task. In contrast, given amplified AnDe activation, BNH-D produced force through leverage of the non-dominant limb. Interestingly, this activation pattern mimics DF when compared with BH-D. We additionally suggest greater BNH-N MTr and IN activation, as compared to NE, were used to stabilize the joint and leverage BNH-D in the horizontal plane, resulting in increased force. This resulted in comparable BNH-D and DF forces, and diminished resultant BNH BI.

Additional evidence of altered stabilization techniques is recognized in comparison of BNH-D and BH-D activation patterns. Due to mimicked dominant tasks, researchers theorized similar muscle activation patterns would be produced. Yet, modified performance demonstrates altered foundation stability due to non-dominant task performance. As previously discussed,

prevalent AnDe implicates rise of the humeral flexion, as stabilized through the horizontal rotational plane, whereas increased BR, BrRa, and IN BH-D activity suggests greater posterior stabilization. Therefore, inconsistencies between BNH and BH muscle activation patterns illustrates altered stabilization tactics, with BNH and unilateral tasks supported through horizontal rotation and BH in the sagittal plane. Although speculated, altered strategies influence resultant BI, and therefore diminishes the ability to distinguish from any other potential BLD underlying mechanism.

7.0 Conclusion

7.1 Summary and Conclusions

The primary purpose of this study was to assess the neural mechanisms contributing to discrepancies in BH and BNH BI, with a secondary purpose to evaluate BI as influenced by methodological concerns, including changes from task familiarity, influence of maximal force calculation techniques, and contributions of stabilizing musculature. To address, TMS was used to assess TCI and VA pre and post task-specific training over five sessions. Every session, 25 MVIC were completed, consisting of five of each BH, NE, DF, NF, and BNH tasks. BH and BNH BI were captured each test session using measures of absolute and averaged peak and plateau force. Bilaterally placed EMG sensors captured levels of muscle activity at baseline and maximal force to assess differences in muscle activation patterns between tasks.

The initial aim of this study was to assess the neurophysiological factors that may contribute to BLD. It was theorized (1) TCI will increase (decrease) during BH (BNH) as compared to DF, (2) VA will decrease during BH as compared to BNH and DF, (3) TCI and VA will strongly relate to BH and BNH BI, and (4) VA will increase and TCI will decrease, across BH, BNH, and DF MVIC, from pre to post testing.

BI was similar to prior research, demonstrating BH BI altered from no BI to BLD (sessions 2-7) while BNH BI presented with no BI across tasks. No differences in TCI and VA between BH, BNH, and DF tasks were observed, with unreal decreases in BH VA post task-specific training, as change in VA did not exceed the MDC. Correlation of BI and peak force to VA and TCI revealed

association of session one BH BI with DF and BH VA, session seven BH TCI area normalized with BH peak force, and BNH TCI area normalized with BNH peak force.

Correlation of BH BI and VA posed a high negative correlation with BH BI session one, but not seven, as did DF VA. Logical interpretation suggests error of BI measures, specifically due to additional outside muscle activation, as BH BI increases with decreased BH force and/or increased DF force, but both cannot be inversely correlated. Relationship of TCI and maximal force is nevertheless still apparent in BH and BNH session seven, and cannot be ruled out as an influence in BH, BNH, and unilatearl maximal force production. We theorized production of maximal force necessitated altered muscle activation patterns between tasks, consequently generating excess noise within TCI and VA measures, thereby influencing resultant BI, or lack thereof.

The secondary aim of this study was to examine changes in optimal maximal force strategy with increased movement task familiarity. It was theorized that (1) CV will decrease with progressed task familiarity and (2) RFD will increase with task familiarity. Data reduction, analysis, and results presented in Appendix E, demonstrate some increases in RFD from session 1 to 2. Only NE and BNH tasks decreased plateau variability, measured by CV, with increased task familiarity.

Due to lack of differences across sessions 2-7, RFD was combined, similar to measures of EMG, and compared between like-movements (Appendix E, tables 13 and 14). When compared to BH, unilateral tasks were faster across all measures of RFD, but BNH presented with similar slopes as the unilateral at 0-plateau (left BNH and NE only) and 0-max. Right BNH was also faster than BH 75-150ms and 0-plateau, where DF was faster than NF in comparable measures. Although

not directly proven, results present increased force production speed with dominant over non-dominant, unilateral over bilateral, and non-homologous over homologous maximal tasks.

To assess ability to achieve and maintain maximal force, plateau CV was calculated and averaged for all tasks within each test session. Task familiarity improved BNH and NE (Appendix E Figure 27), yet differences in CV and RFD did not directly explain changes in BH and BNH BI. Acute training may, therefore, not alter resultant BI and is subsequently not considered the predominant underlying mechanism. Despite force consistency between test sessions, BI variability was high (BH: Chapter 4 Figure 10; BNH: Appendix G Figure 30), and therefore prompted assessment of BH (Chapter 4) and BNH (Appendix G) BI reliability.

Previous studies have defined maximal force using absolute and averaged peak and plateau forces to calculate BI. Each of these measures were realized significantly reliable within (ICC(2,1) $\geq$ 0.925) and between session (ICC(2,1) $\geq$ 0.524). Sessions 2-3 and 4-5 consistently produced ICC > 0.900 across all MVIC tasks and force measures, and logically considered the most reliable input for BI calculations (BH BI: Chapter 4 Figure 9; BNH BI: Appendix G Figure 30). When analyzed, unreliability was apparent across BH BI (Sessions 2-3 ICC(2,1)=-0.041-0.296; Sessions 4-5 ICC(2,1)=0.038-0.319), with none to moderate BNH BI reliability apparent (Sessions 2-3: ICC(2,1)=0.073-0.449, Sessions 4-5: ICC(2,1)=0.466-0.692). Bilateral index was, therefore, assessed in a forward (eg. trials 1-2, 1-3, etc), reversed (eg. trials 5-4, 5-3, etc), and combined forward and reverse order (eg. 2-3, 4-3) to establish number of familiarization and testing sessions necessary to achieve optimally reliable BH and BNH BI (Appendix G, Figure 31).

BH BI was most reliable sessions 3-5 for average peak, absolute plateau, and average plateau and sessions 5-6 for absolute peak, and least reliable between sessions 3-4 and 5-6 for peak forces and plateau forces, respectively. Calculated with absolute and averaged peak force, BI was

never statistically reliable across all session combinations (Chapter 4 Table 2). BNH BI was the most reliable sessions 5-6 and least reliable sessions 2-4, across all measures of maximal force (Appendix G Table 16).

These finding challenge the stability of the BI measure within prior literature. Where one or two test sessions is common practice, our findings suggest inherent methodological error. To overcome the risk of incorrect BI classification, currently based on statistical differences from zero, studies should rather be structured to emphasize meaningful magnitudes changes within BI. Measures of MDC should, therefore, be considered when estimating true BI change based upon the boundaries set by the least and most reliable values (BH: Table 2, BNH: Table 16).

We additionally noticed differences in variability between BH and BNH BI measures across test days (Chapter 5, Figure 18). The standard deviation (SD) of all test days were therefore analyzed, demonstrating BNH BI variability (mean SD = 8.74) was greater than BH BI (mean SD = 5.81) across test days ($Z = -2.197$, $p = 0.016$). This further supports differences in BH and BNH BI may not be from altered TCI or VA, but from increased variability in the BNH measure, resulting in a BI not statistically different from zero.

The tertiary aim of this study was to examine the relationship between BLD and co-activation of non-primary agonist musculature. It was theorized bilateral and unilateral MVIC will produce similar muscle activation patterns.

No differences in muscle activity were found across test sessions two through six. All EMG data were, therefore, combined to assess muscle activation patterns between (1) unilateral and bilateral tasks at point of maximal force (±500ms), (2) unilateral task inactive limb baseline and maximal force, (3) unilateral active and inactive limb at maximal force, and (4) dominant limb BH and BNH at point of maximal force. Force and BI measures were grand averaged across the

practice sessions to assess in accordance with grand averaged EMG data (averaged BI measures across test sessions were previously determine reliable, found in Appendix H).

When broken down into individual tasks within dominant and non-dominant limb, diminished force was present in BH-D (247.8±73.5) as compared to DF (272.8±64.2; Z=-2.128, p=0.016, r=0.203) and BNH-D (261.7±77.3; Z=-3.242, p=0.001, r=0.309; Chapter 6 Figure 21). BH (-6.38±3.6) and BNH BI (0.72±6.2) were statistically different, and presented with BLD ($t_{(10)=}$-6.997, p<0.001) and no BI when compared to zero, respectively (Appendix C Figure 26).

Muscle activation patterns between BH and BNH tasks were additionally altered, presenting with sagittal plane stabilization in the former and horizontal rotation stabilization strategies in the latter. Unilateral tasks shared similar stabilization patterns with BNH, suggesting lack of BNH BI may be due to these similarities where BH BLD may be due to ability to produce greater unilateral force using horizontal stabilization strategies. When all results are considered, *the BLD phenomenon may no longer be considered real, but a result of unreliable measures and altered muscle activation patterns which contribute to BH, BNH and unilateral task maximal forces, influencing the resultant BI.*

7.2 Limitations

The present study reported BI as an unstable measure, in which true change is not dictated by classification of BI (BLD, BLF, and no BI). If significant reliability was reached, it did not achieve high absolute ICC values, and was not consistent and continuous across sessions. This was specifically demonstrated by BH BI reliability sessions 3-5 (ICC(2,1) = 0.392(0.014,0.752), p = 0.022), which lost significant reliability when session 6 was added. Additionally, BNH BI was

determined reliable sessions 5-6, but it is unknown if that reliability would have been maintained with an additional test session. To overcome, when corticospinal and muscle activity analyses were assessed in relation to BI, it was evaluated by MDC or averaged across test days, respectively.

Production of maximal force inherently requires augmented muscle activation through coordination of numerous muscle groups, co-activating to achieve desired task performance. Although muscle activation was assessed for elbow flexion and extension agonist, antagonist, and synergist muscles at maximal force, the contribution of force added from each muscle is unknown. Moreover, activation of these surrounding muscles was theorized to have altered measures of TCI and VA, and their relation to BI.

This was further investigated by comparing dominant and non-dominant MEP amplitude, force, and TMS stimulation error in trials presenting with and without TCI (Chapter 5 Table 6). MEP amplitude, force, and TMS error did not present with consistent differences between days or tasks. If differences were realized, trials without TCI consistently reported with diminshed MEP, increased force, and reduced TMS error. As prior studies have found diminished TMS error and increased force are likely to increase MEP amplitude, these patterns suggest trials without TCI were likley due to outside muscle activation [121, 135]. This is enforced as prior studies have demonstrated excessive excitability diminishes identification of MEP responses [137]. Maximal contraction, therefore, may provide difficult in identifying TCI influences within maximal BH, BNH, and unilateral tasks.

Due to noise and error in identifying VA using TMS, we used maximal VA from each trial for data analysis. When maximal VA trials were compared with non-maximal trails, it was found that 50% and 100% MVIC MEP, SIT, target force, and TMS error were statistically different. Although use of maximal VA was scientifically sound, it may have introduced a ceiling effect

within the analysis. This effect may have introduced error and ignored true findings in the present study.

Lack of statistical finding in neurophysiological measures, between test days one and seven, may have also been due to statistically equal forces between sessions. Although all absolute peak maximal force values were statistically equal across all seven sessions, all tasks steadily increased peak force over sessions one through six. Session seven, maximal force dropped back down to baseline values. Researchers theorize this may have been due to a psychological need to store energy in the final test session. Although rest was provided, subjects were asked to repeat elbow flexion and extension MVICs over the course of three to four hours. This may have introduced a psychological necessity to reduce measures of maximal force. Session seven values were therefore removed from reliability and EMG analyses. Yet, as these force values were used as a target in the TCI and VA methodology, the diminished force may have had some effect upon the assessment of neurophysiological outcomes post-training.

Throughout MVIC testing, unwarranted movements were limited to space between the chair and platform device, as subjects were strapped in using three belts (one at the waist and two strapped across the chest from the shoulders to the waist). Subjects were also instructed to relax the jaw each MVIC, which was monitored for adherence, to reduce contributions from outside muscles including upper trapezius and sternocleidomastoid. Yet, the magnitude of NE MTr EMG values suggest there may have been movement outside the elbow flexion and extension. As discussed in chapter six, inactive (dominant) limb NE MTr muscle activation was statistically greater than the active limb, indicating necessity of rotational stabilization to achieve MVIC. Yet, due to this rotation, the MTr EMG sensor may have been pushed into the back of the chair, creating excess noise. This could not be monitored, as the subjects' back was always in contact with the

back of the chair, and any difference in pressure could not be seen. Nevertheless, if noise was present, the outcome is still the same. The necessity to rotate in a push task, unilateral or bilateral, alters the muscle activity patterns from that of a pull task, and therefore changes the resultant BI

7.3 Future Directions

The BLD phenomenon is considered the inability to produce maximal force, bilaterally, as compared to the summed unilateral contractions, classified as BLF, BLD, or no BI based upon the statistical difference from zero. The implications of this phenomenon upon performance optimization is unknown. Yet, a multitude of underlying mechanisms have been considered, rooted in psychological, neurophysiological, task-specific, and physiological theories. Common BLD research practice has assessed these mechanisms based upon a single test session, rarely with a reported familiarization, or has tested BI prior to and after a training protocol. Having established this unreliability in the present study, future research should assess BI across multiple test sessions, with use of MDC or multi-session averaged BI analyses to establish effects of theorized underlying mechanisms.

The present study was also the first to assess muscle activation patterns in BH, BNH, and corresponding unilateral tasks, suggesting differences in BI may be due to altered stabilization techniques. To minimize this effect, and breach further into BLD underlying mechanisms, future research should test BLD using more precise movements, such as finger or hand grip tasks, or be able to assess force produced from outside muscles. This would reduce excess noise from outside muscle activity, and resultant error, and further reduce BLD methodological errors.

The present study was also the first to assess differences in BI, as calculated by measures of absolute and averaged peak and plateau forces, as each have been used in prior BLD research. Although each measure of force is equally reliable, or unreliable when assessing BI, each measure accounts for distinct measures of the MVIC. Therefore, future researcher should consider the underlying mechanism tested, and choose the measure of maximal force accordingly.

Finally, elbow BH flexion and BNH flexion/extension, with corresponding unilateral MVIC, were the only tasks tested in the present study. Prior research has demonstrated greater BLD in lower extremity and multi-articular tasks. These tasks should be explored to set boundaries for true change in BI. If sufficiently larger populations and tasks are used to assess these boundaries, investigations may begin to refine scientific methods to approach the true BLD underlying mechanism.

Appendix A

Study Questionnaires

Screening Questionnaire for rTMS Candidates

Please answer each question by checking the yes or no box. Provide any additional details where requested.

Question	Yes	No	Details
1. Have you ever received TMS?	□	□	If yes, were there any problems?
2. Do you have a cochlear implant?	□	□	
3. Do you have a neurostimulator implanted in your body?	□	□	If yes, of what type?
4. Do you have an implanted device for drug delivery?	□	□	
5. Do you have a cardiac pacemaker?	□	□	
6. Do you have any metal particles in the brain or skull (such as shrapnel, surgical clips, or fragments from metal work)?	□	□	If yes, what type?
7. Have you ever had a seizure?	□	□	If yes, can you describe the occasion?
8. Does anyone in your family have a history of epilepsy?	□	□	
9. Have you ever had syncope?	□	□	If yes, can you describe the occasion?
10. Do you have hearing problems?	□	□	If yes, what type?
11. Do you suffer from frequent or severe headaches?	□	□	
12. Have you ever had a stroke?	□	□	
13. Have you undergone MRI examination in the past?	□	□	If yes, were there any problems?
14. Have you ever had a severe head injury, where you lost consciousness?	□	□	
15. Are you pregnant or could you be pregnant?	□	□	
16. Do you take medications?	□	□	If yes, please list them

Edinburgh Handedness Inventory

Please mark the box that best describes which hand you use for the activity in question

	Always Left	Usually Left	No Preference	Always Right	Usually Right
Writing					
Throwing					
Scissors					
Toothbrush					
Knife (without fork)					
Spoon					
Match (when striking)					
Computer mouse					

Waterloo Footedness Questionnaire

Answer each of the following question as best you can. Please do not simply check one box for all questions, but imagine yourself performing each activity in turn, and then mark the appropriate answer. If necessary, stop and simulate the activity.

	Always Left	Usually Left	Equal	Always Right	Usually Right
1. Which foot would you use to kick a stationary ball at a target straight in front of you?					
2. If you had to stand on one foot, which foot would it be?					
3. Which foot would you use to smooth sand at the beach?					
4. If you had to step up onto a chair, which foot would you place on the chair first?					
5. Which foot would you use to stomp on a fast-moving bug?					
6. If you were to balance on one foot on a railway track, which foot would you use?					
7. If you wanted to pick up a marble with your toes, which foot would you use?					
8. If you had to hop on one foot, which foot would you use?					
9. Which foot would you use to help push a shovel into the ground?					
10. During relaxed standing, people usually put most of their weight on one foot, leaving the other leg slightly bent. Which foot do you put most of your weight on first?					
11. Is there any reason (i.e. injury) why you have changed your foot preference for any of the above activities?	YES	NO	(circle one)		
12. Have you ever been given special training or encouragement to use a particular foot for certain activities?	YES	NO	(circle one)		
13. If you answered YES for question 11 or 12, please explain:					

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → *Skip to question 4*

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → *Skip to question 6*

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

24 Hour Diet Log

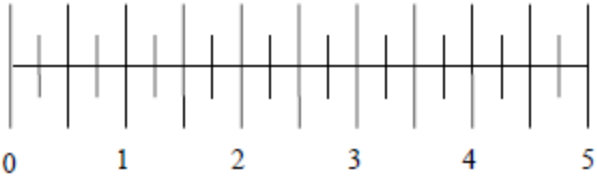
Date:_____ SUBJECT #: _____

Time	FOOD/BEVERAGE DESCRIPTION *(Type, descriptors, & method of preparation)*	AMOUNT	Total kcal *(from label)*

Comments:

Subject Number: _____ **Date:** _____

Sleep Quality



No sleep Best sleep

1- Very light sleep
2- Poor sleep quality
3- Moderate quality sleep
4- Very good sleep quality

Hours of sleep last night: _____

Where did you sleep? _____

What Kind of Surface did you sleep on?

CIRCLE:

BED

SOFA

OUTDOORS

CARPET

HARDWOOD

WATERBED

Appendix B

Voluntary Activation TMS Error

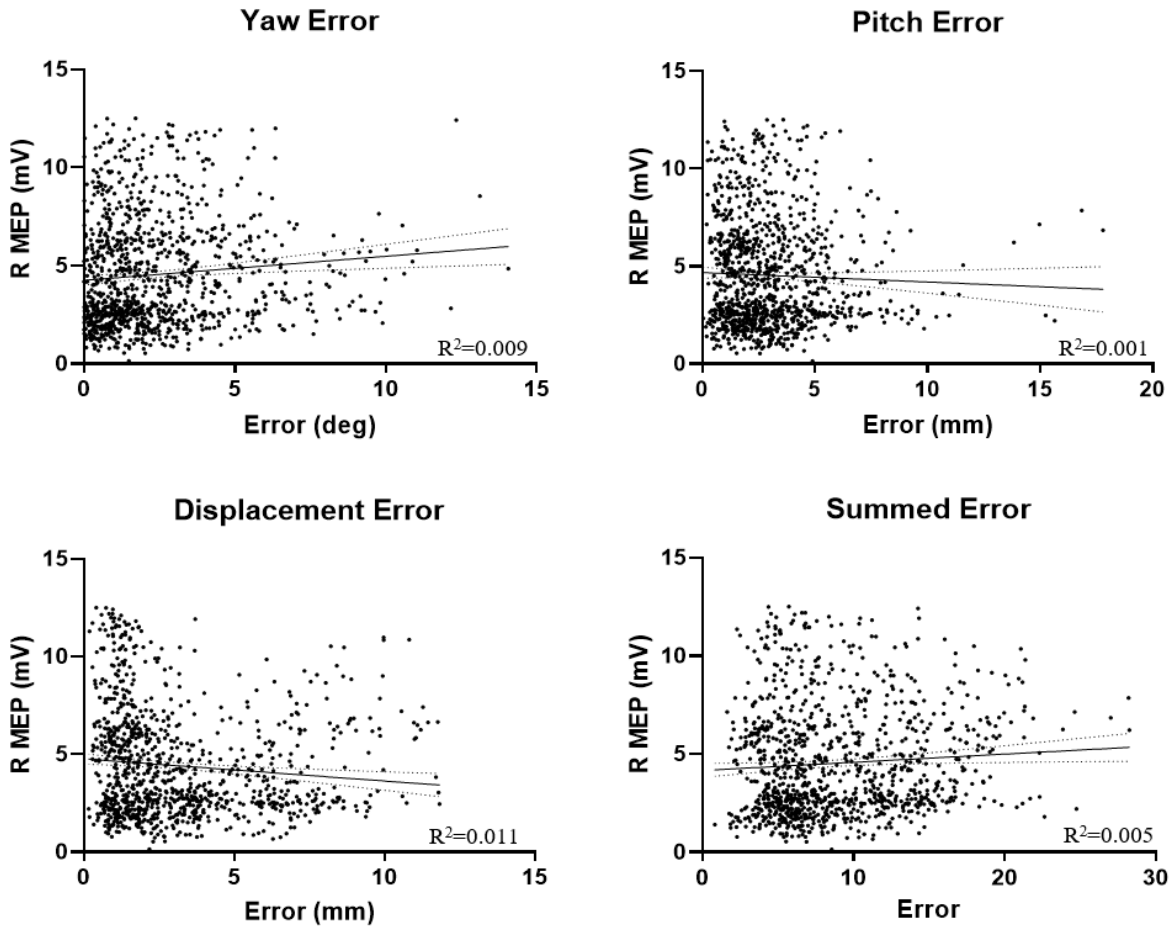


Figure 25. Voluntary Activation TMS Coil Error from Hotspot

Peak-to-peak amplitude of the MEP (mV) of the dominant bicep (R MEP), during VA experimental tasks, were mapped to assess if TMS coil placement altered VA. MEP amplitude and coil error, in relation to the hotspot, presented with minimal relationship for **A** – Yaw error (deg), considered angular deviation from the target **B-** Pitch error (mm), considered anterior-posterior and medial-lateral tilt deviation from hotspot, **C** – Displacement error (mm), considered distance from the hotspot, and **D-** All error summed to determine if cumulative targeting error affected motor evoked responses. Linear regression, with 95% CI lines, are demonstrated for all graphs.

Appendix C

Grand Averaged BI

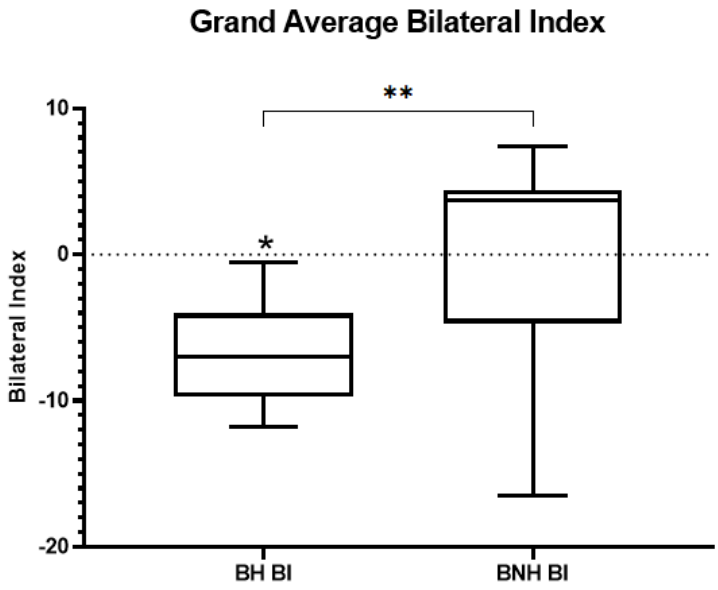


Figure 26. Grand Averaged Bilateral Index

Averaging all BI across subjects and sessions, BH BI is statistically less than zero (BLD*), where BNH presents with no BI. BI between BH and BNH tasks are statistically different (**).

Appendix D

Muscle Activation Patterns Between Task

Table 9. EMG RMS Mean(SD) Between Unilateral and BH Tasks

	N	BH-D	DF	p-value	Effect Size
Bicep	55	0.588157 (0.44212)	0.628394 (0.45239)	0.008*	0.250‡
Tricep Long	55	0.000028 (0.00001)	0.000029 (0.00001)	0.086	0.164‡
Tricep Lateralis	55	0.000028 (0.00001)	0.000029 (0.00001)	0.067	0.174‡
Brachialis	55	0.000394 (0.00036)	0.000380 (0.00036)	0.024*	0.214‡
Brachioradialis	55	0.000464 (0.00025)	0.000449 (0.00024)	0.044*	0.191‡
Middle Trapezius	55	0.000268 (0.00024)	0.000294 (0.00024)	0.019*	0.222‡
Upper Trapezius	55	0.000097 (0.00009)	0.000103 (0.00008)	0.291	0.101‡
Infraspinatus	55	0.000167 (0.00018)	0.000124 (0.00013)	< 0.001*	0.418↓
Anterior Deltoid	55	0.000120 (0.00009)	0.000185 (0.00012)	< 0.001*	0.482↓
		BH-N	**NF**		
Bicep	55	0.686369 (0.47225)	0.689860 (0.46656)	0.280	0.104‡
Tricep Long	55	0.000028 (0.00001)	0.000027 (0.00001)	0.467	0.070
Tricep Lateralis	55	0.000030 (0.00002)	0.000028 (0.00001)	0.988	0.002
Brachialis	55	0.000372 (0.00033)	0.000361 (0.00033)	0.141	0.141‡
Brachioradialis	55	0.000463 (0.00032)	0.000449 (0.00032)	0.016*	0.228‡
Middle Trapezius	53	0.000196 (0.00020)	0.000220 (0.00019)	0.047*	0.193‡
Upper Trapezius	53	0.000089 (0.00008)	0.000097 (0.00008)	0.161	0.137‡
Infraspinatus	53	0.000138 (0.00017)	0.000101 (0.00012)	<0.001*	0.499↓
Anterior Deltoid	53	0.000126 (0.00013)	0.000225 (0.00017)	<0.001*	0.509§

*indicates significance at $p \leq 0.05$
‡indicates small effect size ($0.1 > r \geq 0.3$); ↓ indicates moderate effect size ($0.5 \geq r > 0.3$);
§ indicates high effect size ($r > 0.5$)

Table 10. EMG RMS Mean(SD) Between Unilateral and BNH Tasks

	N	BNH-D	DF	p-value	Effect Size
Bicep	55	0.572636 (0.40179)	0.628394 (0.45239)	0.530	0.061
Tricep Long	55	0.000033 (0.00002)	0.000029 (0.00001)	0.551	0.057
Tricep Lateralis	55	0.000028 (0.00001)	0.000029 (0.00001)	0.031*	0.205‡
Brachialis	55	0.000339 (0.00028)	0.000380 (0.00036)	0.045*	0.191‡
Brachioradialis	55	0.000434 (0.00024)	0.000449 (0.00024)	0.159	0.135‡
Middle Trapezius	55	0.000255 (0.00019)	0.000294 (0.00024)	0.065	0.176‡
Upper Trapezius	55	0.000117 (0.00015)	0.000103 (0.00008)	0.969	0.004
Infraspinatus	55	0.000088 (0.00008)	0.000124 (0.00013)	<0.001*	0.367⁺
Anterior Deltoid	54	0.000212 (0.00015)	0.000185 (0.00012)	0.019*	0.225‡
		BNH-N	**NE**		
Bicep	55	0.030431 (0.03465)	0.022739 (0.02002)	0.025*	0.213‡
Tricep Long	55	0.000235 (0.00017)	0.000226 (0.00016)	0.682	0.040
Tricep Lateralis	55	0.000341 (0.00039)	0.000300 (0.00030)	0.643	0.045
Brachialis	55	0.000061 (0.00004)	0.000057 (0.00003)	0.110	0.153‡
Brachioradialis	55	0.000028 (0.00002)	0.000024 (0.00002)	0.021*	0.218‡
Middle Trapezius	53	0.000031 (0.00002)	0.000027 (0.00001)	0.027*	0.214‡
Upper Trapezius	53	0.000038 (0.00006)	0.000023 (0.00001)	0.873	0.016
Infraspinatus	53	0.000162 (0.00023)	0.000135 (0.00013)	0.031*	0.209‡
Anterior Deltoid	53	0.000072 (0.00014)	0.000071 (0.00018)	0.066	0.179‡

*indicates significance at $p \leq 0.05$

‡indicates small effect size ($0.1 > r \geq 0.3$); ⁺ indicates moderate effect size ($0.5 \geq r > 0.3$);

§ indicates high effect size ($r > 0.5$)

Table 11. Inactive Limb EMG RMS Mean(SD) Between Baseline and MVIC Max

	N	DF Inactive Max	DF Inactive Baseline	p-value	Effect Size
Bicep	55	0.004402 (0.00367)	0.002289 (0.002696)	< 0.001*	0.520[§]
Tricep Long	55	0.000021 (0.00002)	0.000010 (0.000003)	< 0.001*	0.583[§]
Tricep Lateralis	55	0.000021 (0.00003)	0.000010 (0.000003)	< 0.001*	0.604[§]
Brachialis	55	0.000013 (0.00001)	0.000011 (0.000003)	< 0.001*	0.573[§]
Brachioradialis	55	0.000016 (0.00002)	0.000008 (0.000002)	< 0.001*	0.550[§]
Middle Trapezius	53	0.000052 (0.00006)	0.000006 (0.000004)	< 0.001*	0.604[§]
Upper Trapezius	53	0.000039 (0.00004)	0.000015 (0.000005)	< 0.001*	0.538[§]
Infraspinatus	53	0.000069 (0.00014)	0.000009 (0.000010)	< 0.001*	0.576[§]
Anterior Deltoid	53	0.000009 (0.00001)	0.000004 (0.000002)	< 0.001*	0.602[§]
		NF Inactive Max	**NF Inactive Baseline**		
Bicep	55	0.004586 (0.00562)	0.002694 (0.004078)	< 0.001*	0.471[ǂ]
Tricep Long	55	0.000018 (0.00002)	0.000005 (0.000001)	< 0.001*	0.574[§]
Tricep Lateralis	55	0.000013 (0.00001)	0.000008 (0.000008)	< 0.001*	0.512[§]
Brachialis	55	0.000006 (0.00001)	0.000004 (0.000003)	< 0.001*	0.531[§]
Brachioradialis	55	0.000007 (0.00001)	0.000004 (0.000001)	< 0.001*	0.538[§]
Middle Trapezius	53	0.000061 (0.00007)	0.000016 (0.000005)	< 0.001*	0.615[§]
Upper Trapezius	53	0.000041 (0.00006)	0.000016 (0.000006)	< 0.001*	0.502[§]
Infraspinatus	53	0.000054 (0.00005)	0.000019 (0.000019)	< 0.001*	0.569[§]
Anterior Deltoid	53	0.000023 (0.00006)	0.000010 (0.000007)	< 0.001*	0.427[ǂ]
		NE Inactive Max	**NE Inactive Baseline**		
Bicep	54	0.006671 (0.00615)	0.002666 (0.004396)	< 0.001*	0.533[§]
Tricep Long	54	0.000010 (0.00001)	0.000005 (0.000001)	< 0.001*	0.598[§]
Tricep Lateralis	54	0.000011 (0.00001)	0.000007 (0.000001)	< 0.001*	0.610[§]
Brachialis	54	0.000006 (0.00001)	0.000002 (0.000001)	< 0.001*	0.610[§]
Brachioradialis	55	0.000009 (0.00001)	0.000004 (0.000001)	< 0.001*	0.578[§]
Middle Trapezius	55	0.000116 (0.00011)	0.000016 (0.000005)	< 0.001*	0.627[§]
Upper Trapezius	55	0.000023 (0.00001)	0.000015 (0.000005)	< 0.001*	0.577[§]
Infraspinatus	55	0.000056 (0.00009)	0.000018 (0.000010)	< 0.001*	0.627[§]
Anterior Deltoid	54	0.000029 (0.00003)	0.000009 (0.000003)	< 0.001*	0.621[§]

*indicates significance at $p \leq 0.05$

[ǂ] indicates moderate effect size ($0.5 \geq r \geq 0.3$); [§] indicates high effect size ($r \geq 0.5$)

Table 12. EMG RMS Mean(SD) Active and Inactive Limb at Maximal Force

	N	DF Inactive	DF Active	p-value	Effect Size
Bicep	55	0.004402 (0.00367)	0.628394 (0.45239)	< 0.0001*	0.615[§]
Tricep Long	55	0.000021 (0.00002)	0.000029 (0.00001)	< 0.0001*	0.425[ɻ]
Tricep Lateralis	55	0.000021 (0.00003)	0.000029 (0.00001)	< 0.0001*	0.444[ɻ]
Brachialis	55	0.000013 (0.00001)	0.000380 (0.00036)	< 0.0001*	0.615[§]
Brachioradialis	55	0.000016 (0.00002)	0.000449 (0.00024)	< 0.0001*	0.615[§]
Middle Trapezius	53	0.000052 (0.00006)	0.000294 (0.00024)	< 0.0001*	0.582[§]
Upper Trapezius	53	0.000039 (0.00004)	0.000103 (0.00008)	< 0.0001*	0.596[§]
Infraspinatus	53	0.000069 (0.00014)	0.000124 (0.00013)	< 0.0001*	0.419[ɻ]
Anterior Deltoid	53	0.000009 (0.00001)	0.000185 (0.00012)	< 0.0001*	0.613[§]
		NF Inactive	**NF Active**		
Bicep	55	0.004586 (0.00562)	0.689860 (0.46656)	< 0.0001*	0.614[§]
Tricep Long	54	0.000018 (0.00002)	0.000027 (0.00001)	< 0.0001*	0.376[ɻ]
Tricep Lateralis	54	0.000013 (0.00001)	0.000028 (0.00001)	< 0.0001*	0.514[§]
Brachialis	54	0.000006 (0.00001)	0.000361 (0.00033)	< 0.0001*	0.621[§]
Brachioradialis	54	0.000007 (0.00001)	0.000449 (0.00032)	< 0.0001*	0.621[§]
Middle Trapezius	53	0.000061 (0.00007)	0.000220 (0.00019)	< 0.0001*	0.583[§]
Upper Trapezius	53	0.000041 (0.00006)	0.000097 (0.00008)	< 0.0001*	0.453[ɻ]
Infraspinatus	53	0.000054 (0.00005)	0.000101 (0.00012)	0.0100*	0.247
Anterior Deltoid	53	0.000023 (0.00006)	0.000225 (0.00017)	< 0.0001*	0.555[§]
		NE Inactive	**NE Active**		
Bicep	55	0.006671 (0.00615)	0.022739 (0.02002)	< 0.0001*	0.582[§]
Tricep Long	55	0.000010 (0.00001)	0.000226 (0.00016)	< 0.0001*	0.610[§]
Tricep Lateralis	55	0.000011 (0.00001)	0.000300 (0.00030)	< 0.0001*	0.610[§]
Brachialis	55	0.000006 (0.00001)	0.000057 (0.00003)	< 0.0001*	0.610[§]
Brachioradialis	55	0.000009 (0.00001)	0.000024 (0.00002)	< 0.0001*	0.519[§]
Middle Trapezius	53	0.000116 (0.00011)	0.000027 (0.00001)	< 0.0001**	0.554[§]
Upper Trapezius	53	0.000023 (0.00001)	0.000023 (0.00001)	0.130	0.147[‡]
Infraspinatus	53	0.000056 (0.00009)	0.000135 (0.00013)	< 0.0001*	0.494[ɻ]
Anterior Deltoid	53	0.000029 (0.00003)	0.000071 (0.00018)	0.371	0.088

*indicates greater active muscle activity, significance set at $p \leq 0.05$, **indicates greater inactive muscle activity, significance set at $p \leq 0.05$.
[‡]indicates small effect size ($0.1 > r \geq 0.3$); [ɻ] indicates moderate effect size ($0.5 \geq r > 0.3$);
[§] indicates high effect size ($r > 0.5$)

Table 13. EMG RMS Mean(SD) at BH-D and BNH-D Maximal Force

	N	BH-D	BNH-D	p-value	Effect Size
Bicep	55	0.588157 (0.44212)	0.572636 (0.40179)	0.296	0.101‡
Tricep Long	55	0.000028 (0.00001)	0.000033 (0.00002)	0.205	0.122‡
Tricep Lateralis	55	0.000028 (0.00001)	0.000028 (0.00001)	0.559	0.056
Brachialis	55	0.000394 (0.00036)	0.000339 (0.00028)	< 0.001*	0.318ǂ
Brachioradialis	55	0.000464 (0.00025)	0.000434 (0.00024)	0.020*	0.220‡
Middle Trapezius	55	0.000268 (0.00024)	0.000255 (0.00019)	0.919	0.010
Upper Trapezius	55	0.000097 (0.00009)	0.000117 (0.00015)	0.460	0.071
Infraspinatus	55	0.000167 (0.00018)	0.000088 (0.00008)	< 0.001*	0.491ǂ
Anterior Deltoid	54	0.000120 (0.00009)	0.000212 (0.00015)	< 0.001*	0.489ǂ

*indicates significance at $p \leq 0.05$

‡indicates small effect size ($0.1 > r \geq 0.3$); ǂ indicates moderate effect size ($0.5 \geq r \geq 0.3$)

Appendix E

Specific Aim 2: Task Familiarity Data Reduction, Analysis, and Results

Data Reduction

Rate of Force Development

Measures of force were defined for each MVIC using Labchart analysis software. A first order derivative of the MVIC force, averaged to every 15 data points (3.75ms), was used to define MVIC onset when the last point of 0 N/s was reached immediately before force incline. RFD was assessed from MVIC onset (0ms) to 75ms, 75-150ms, 0ms-force plateau, and 0ms-peak force. Force plateau was defined as the point when the same derivative reached 0 N/s immediately after force incline. Peak force was defined as the single most maximal point of each MVIC. To calculate RFD, the difference in force was divided by the change in time between the time variables.

Coefficient of Variation

CV was used to define variability of force between each MVIC plateau onset and plateau offset. Plateau onset was defined as described previously, plateau offset was defined as last the last point the first order derivative was at 0 N/s prior to force decline. CV was defined as the standard deviation divided by average force, all multiplied by 100. The average CV of each task within test session was used for analysis.

Data Analysis

All analyses were conducted with SPSS Statistics for Windows (IBM Corp., Armonk, NY). RFD and CV were assessed across days to determine any changes due to training using Friedman ANOVA, due to small sample sizes. If significance was found, Wilcoxon Rank Sum (WRS) tests were used. WRS tests were used to assess differences in RFD between task for the following comparisons: right BH and DF, left BH and NF, right BNH and DF, left BNH and NE, right BH and left BH, right BH and right BNH, and DF and NF.

Results

DF RFD at 75-150ms ($\chi^2 = 15.351$, $p = 0.018$) and NF at 75-150ms ($\chi^2 = 13.481$, $p = 0.036$) and 0-maximal force ($\chi^2 = 17.143$, $p = 0.009$) presented with decreased RFD on day 1 as compared to days 2-7 (Table 13). Day 1 was removed to maintain consistency across all tasks, presenting all measures of RFD as statistically equal and non-parametric, and therefore combined to assess differences between tasks using WRS tests. RFD was statistically faster in DF compared to right BH in all measures, right BNH at 0-75ms, 75-150ms, and 0-plat, and NF at 75-150ms, and 0-plat, NF was greater than left BH in all measures, NE was greater than left BNH at 0-75ms and 75-150ms, right BNH was greater than right BH at 75-150ms, and 0-plat, and DF was greater than NF at 75-150ms, and 0 – plat (Table 14). All other RFD values were statistically the same.

NE and BNH tasks presented with increased CV across test days, where NE day 1 was greater than days 2, 4, 5, and 6 (Figure 27C) and BNH CV day 1 was greater than days 2-7 (Figure 27F). No other task presented with statistical difference.

Table 14. Rate of Force Development Mean(SD) (N=11)

		Right BH	Left BH	Right BNH	Left BNH	DF	NF	NE
0-75ms	Day 1	309.9(111.1)	338.0(602.6)	439.3(657.4)	432.7(637.8)	554.9(917.1)	505.5(753.4)	438.2(658.6)
	Day 2	307.6(299.3)	318.2(296.0)	290.3(376.1)	373.6(427.3)	516.3(498.7)	300.8(265.3)	367.6(460.2)
	Day 3	227.1(386.4)	234.2(360.3)	196.5(208.2)	292.5(336.6)	377.6(279.9)	278.9(236.7)	387.3(432.5)
	Day 4	259.5(354.5)	242.7(253.1)	303.4(362.5)	366.8(393.2)	420.7(341.9)	424.3(558.2)	425.8(354.3)
	Day 5	266.0(357.5)	284.4(268.6)	436.4(685.0)	363.1(553.0)	337.8(322.7)	426.8(491.7)	312.1(310.1)
	Day 6	209.7(278.4)	222.5(237.2)	204.7(247.8)	222.5(299.1)	412.6(384.2)	307.0(266.2)	262.4(242.6)
	Day 7	275.6(227.0)	151.9(177.7)	186.8(179.4)	198.4(170.9)	279.0(226.5)	351.8(229.4)	289.3(281.0)
75-150ms	Day 1	366.4(258.2)	399.4(327.0)	429.5(282.7)	353.7(209.5)	475.3(255.3)*****	355.6(221.2)*****	402.5(227.6)
	Day 2	642.0(481.8)	305.7(221.2)	810.2(521.2)	344.7(203.9)	888.5(493.2)	682.6(339.9)	638.4(350.0)
	Day 3	522.1(537.3)	380.0(240.2)	820.7(698.8)	412.5(288.6)	929.2(595.6)	701.6(449.3)	562.4(299.4)
	Day 4	561.0(346.3)	327.3(229.6)	782.9(565.5)	401.3(260.4)	824.3(473.7)	750.7(333.4)	704.9(357.8)
	Day 5	558.0(446.6)	358.6(257.7)	676.9(419.2)	298.6(143.1)	863.2(572.5)	747.6(430.4)	629.1(444.6)
	Day 6	450.4(297.3)	297.8(209.4)	642.2(417.2)	331.9(199.9)	838.1(408.4)	718.6(475.4)	552.1(361.5)
	Day 7	519.5(385.5)	491.1(343.5)	637.8(472.0)	534.2(346.9)	664.8(424.1)	740.8(466.9)	498.3(332.4)
0-plateau	Day 1	352.9(264.2)	342.8(228.3)	419.1(500.8)	292.3(466.9)	546.5(622.8)	497.7(606.5)	360.2(279.1)
	Day 2	461.2(244.8)	430.2(222.1)	463.0(258.5)	377.1(158.7)	519.1(263.9)	429.2(176.5)	430.3(208.0)
	Day 3	390.9(269.9)	381.9(213.7)	475.6(205.3)	406.1(161.7)	525.1(220.9)	455.3(186.9)	420.8(173.1)
	Day 4	407.2(204.9)	418.9(179.1)	502.9(306.8)	439.6(227.5)	501.8(272.2)	492.1(243.0)	424.1(172.5)
	Day 5	404.9(252.0)	419.6(236.8)	463.9(286.7)	423.8(218.9)	515.2(302.0)	493.3(266.9)	419.7(224.2)
	Day 6	366.8(218.5)	408.4(221.7)	428.8(236.3)	410.1(252.9)	477.2(247.9)	483.8(284.3)	397.9(220.5)
	Day 7	352.0(217.2)	345.6(214.2)	366.8(203.6)	435.1(192.3)	429.2(196.3)	434.8(263.8)	342.6(180.1)
0-maximal force	Day 1	100.9(58.5)	101.1(61.5)	90.5(47.6)	90.9(47.9)	118.2(58.6)	92.5(39.9)*****	89.9(29.4)
	Day 2	120.9(46.4)	121.5(55.2)	138.9(57.8)	117.8(34.9)	146.3(68.5)	147.2(59.8)	104.4(32.6)
	Day 3	108.2(37.5)	114.9(36.0)	148.5(70.0)	138.8(64.3)	150.8(79.9)	159.6(78.7)	107.0(39.0)
	Day 4	123.9(67.9)	136.2(64.7)	140.6(69.4)	134.2(69.8)	164.1(81.9)	145.1(63.8)	135.4(88.0)
	Day 5	127.7(60.6)	125.9(69.3)	125.4(68.4)	111.4(64.3)	160.7(84.1)	162.6(84.1)	115.7(52.0)
	Day 6	146.6(107.7)	154.9(95.0)	127.9(60.9)	125.9(57.9)	153.2(104.9)	169.4(119.5)	106.1(44.5)
	Day 7	117.6(76.7)	118.7(93.2)	121.4(78.7)	120.5(94.8)	131.4(73.3)	133.4(79.8)	108.8(56.5)

Table 15. Averaged Rate of Force Development Across Task, Omit Day 1

	N	BH-D	DF	p-value
0-75ms	66	241.2 (312.4)	400.5 (349.0)	< 0.001*
75-150ms	66	361.5 (290.1)	816.3 (455.9)	< 0.001*
0-plateau	66	395.1 (221.7)	500.34 (247.7)	< 0.001*
0-max	66	125.7 (62.8)	150.1 (74.2)	< 0.001*
		BH-N	**NF**	
0-75ms	66	242.3 (265.8)	344.4 (336.2)	< 0.001*
75-150ms	66	343.4 (254.3)	725.7 (407.0)	< 0.001*
0-plateau	66	400.8 (208.9)	463.56 (222.5)	< 0.001*
0-max	66	128.70 (70.4)	150.5 (72.1)	< 0.001*
		BNH-D	**DF**	
0-75ms	66	275.1 (369.1)	400.5 (349.0)	< 0.001*
75-150ms	66	703.2 (503.5)	816.3 (455.9)	< 0.001*
0-plateau	66	446.6 (235.4)	500.34 (247.7)	< 0.001*
0-max	66	135.0 (64.6)	150.1 (74.2)	0.054
		BNH-N	**NE**	
0-75ms	66	302.8 (373.8)	346.3 (354.2)	0.030*
75-150ms	66	387.8 (252.4)	594.0 (335.6)	< 0.001*
0-plateau	66	391.2 (201.4)	407.3 (185.2)	0.153
0-max	66	124.8 (64.8)	120.3 (59.0)	0.394
		BH-D	**BNH-D**	
0-75ms	66	241.2 (312.4)	275.1 (369.1)	0.666
75-150ms	66	361.5 (290.1)	703.2 (503.5)	< 0.001*
0-plateau	66	395.1 (221.7)	446.6 (235.4)	< 0.001*
0-max	66	125.7 (62.8)	135.0 (64.6)	0.082
		BH-D	**BH-N**	
0-75ms	66	241.2 (312.4)	242.3 (265.8)	0.948
75-150ms	66	361.5 (290.1)	343.4 (254.3)	0.072
0-plateau	66	395.1 (221.7)	400.8 (208.9)	0.948
0-max	66	125.7 (62.8)	128.70 (70.4)	0.603
		DF	**NF**	
0-75ms	66	400.5 (349.0)	344.4 (336.2)	0.071
75-150ms	66	816.3 (455.9)	725.7 (407.0)	0.006*
0-plateau	66	500.34 (247.7)	463.56 (222.5)	0.001*
0-max	66	150.1 (74.2)	150.5 (72.1)	0.274

All data is non-parametric, analyzed with Wilcoxon Rank Sum

* indicates difference between within task ($p \leq 0.05$)

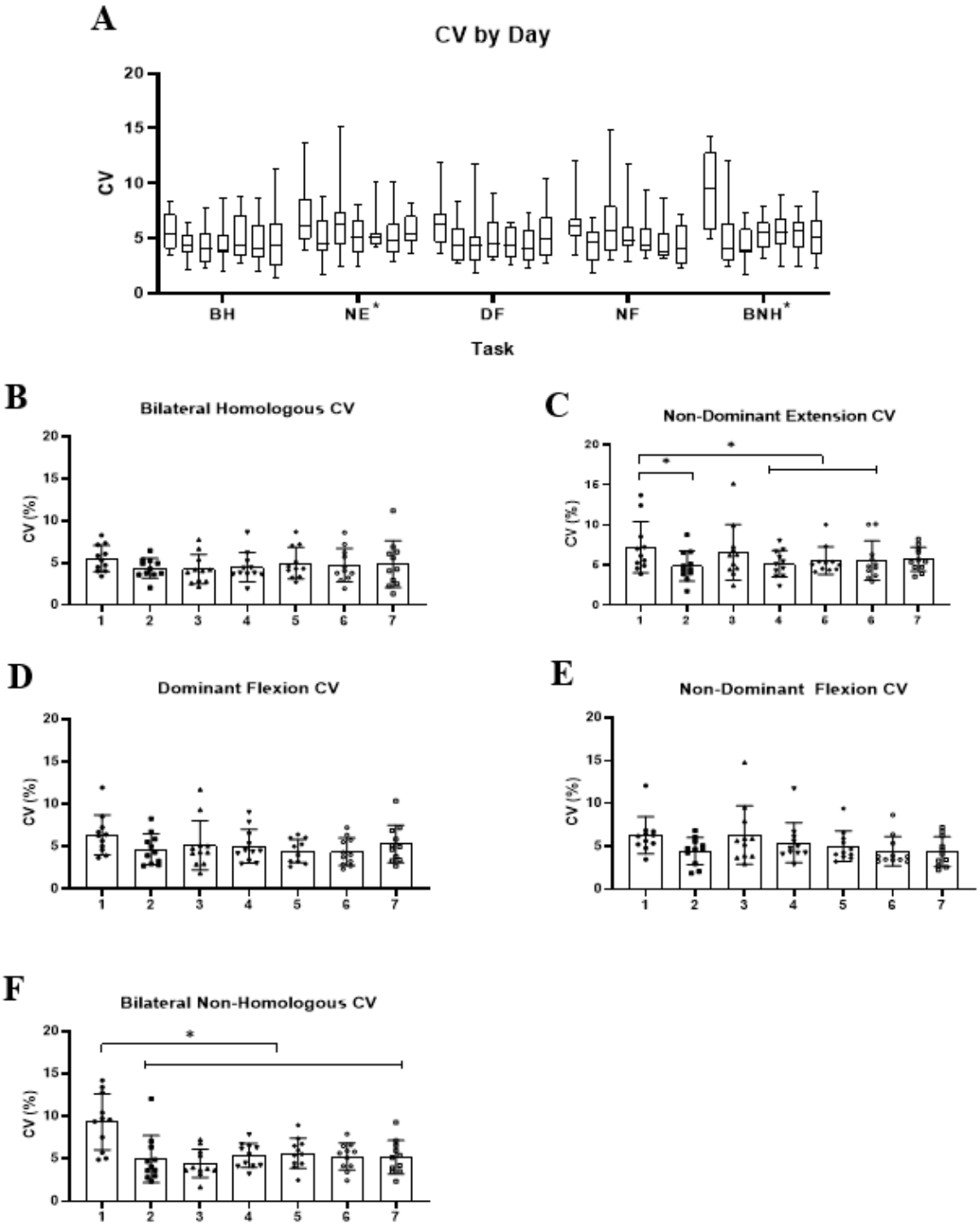


Figure 27. Coefficient of Variation Across Task and Test Session

A – Boxplot of all CV by task across all test sessions, in consecutive order. NE and BNH present with significant differences between test days (significance indicated with *), when analyzed with Friedman's ANOVA, broken into individual task and subjects **B-F**: **B** – BH CV presents with consistency across all test days. **C** – NE CV demonstrates increased CV on day 1 as compared to days 2, 4, 5, and 6. **D** – DF CS presents with consistency across all test days. **E** – NF presents with consistency across all test days. **F** – BNH day 1 CV is greater than all other test days.

Appendix F

Trials Absolute Force Achieved

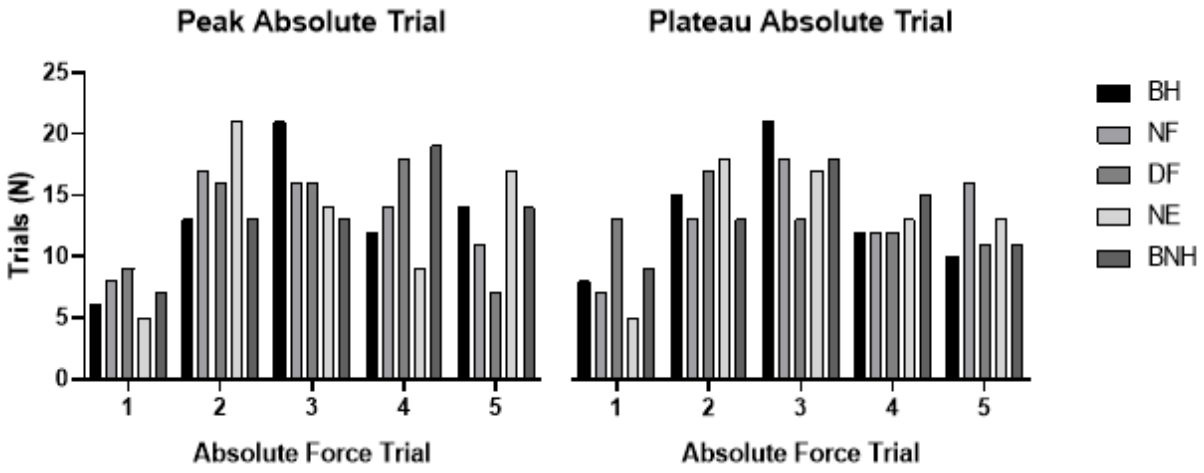


Figure 28. Trial Absolute Peak and Plateau Force Achieved

Absolute force was consistently achieved through all five trials for all tasks within each test session. Therefore, all five trials were used for within session analysis.

Appendix G

Bilateral Non-Homologous Reliability

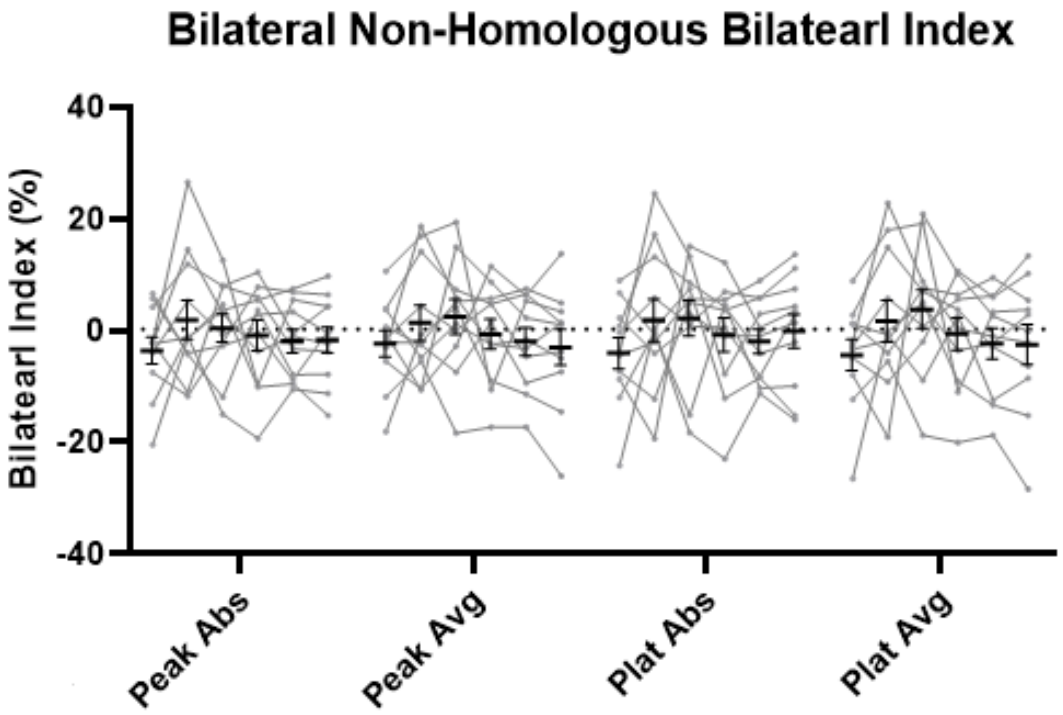


Figure 29. BNH BI Across all Sessions and Measures of Maximal Force

BNH BI were not statistically different from zero and considered as no BI. Individual participant data is tracked across all sessions with the grey line, with mean and SEM marked in black for each test session.

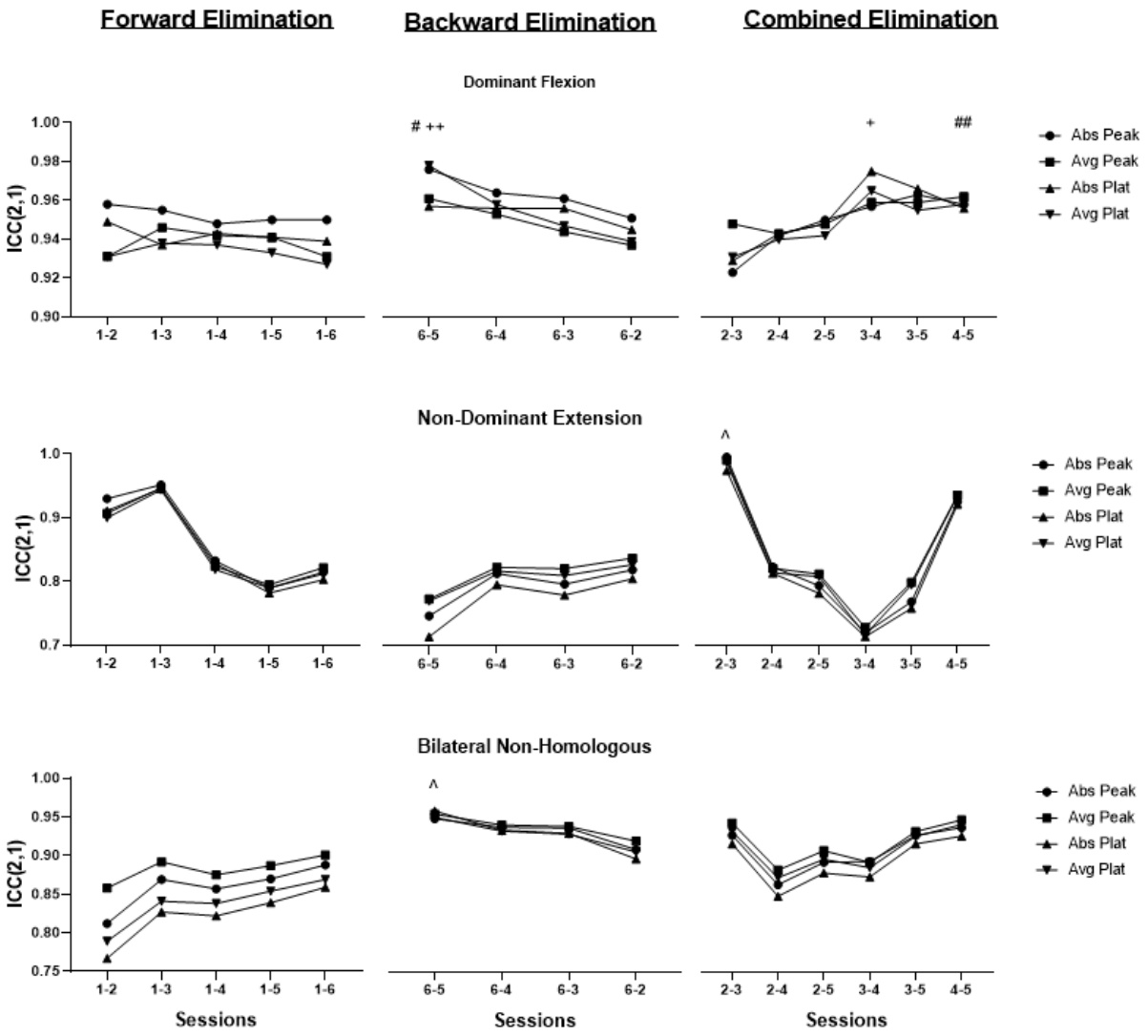


Figure 30. BNH and Unilateral Force Reliability between Sessions

Reliability was assessed in an iterative method to assess when force was most reliable between test days, for all tasks and definitions of maximal force. Maximal ICC(2,1) for NE, and BNH are the same across all definitions of force$^{\wedge}$, but DF maximal ICC differs between abs peak$^{\#}$, avg peak$^{\#\#}$, abs plat^{+}, and avg plat^{++}. Although maximal ICC varies across task, sessions 2-3 and 4-5 consistently presented ICC(2,1) > 0.900 across all tasks and measures of force.

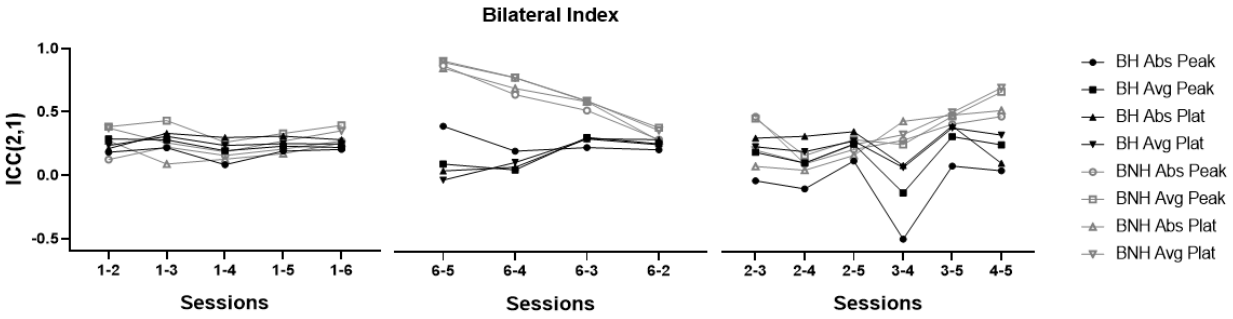


Figure 31. BH and BNH BI Across all Sessions

Similar to Figure 11 in Chapter 4, Reliability was assessed in an iterative method (forward, backward, and combined elimination) to assess when BH (black) and BNH (grey) BI was most reliable. Unlike between session force reliability, BNH BI maximal reliability was achieved test sessions 5-6 for all measures of maximal force.

Table 16. BNH Bilateral Index Most and Least Reliable Test Sessions

	Sessions	CA	ICC(2,1) (95% CI)	p-value	SEM	MDC
Most Reliable						
Peak Abs BI	5-6	0.921	0.864(0.568,0.962)	<0.001*	2.779	7.704
Peak Avg BI	5-6	0.939	0.890(0.654,0.969)	<0.001*	3.209	8.894
Plat Abs BI	5-6	0.920	0.844(0.540,0.955)	<0.001*	3.341	9.261
Plat Avg BI	5-6	0.943	0.901(0.673,0.973)	<0.001*	3.476	9.636
Least Reliable						
Peak Abs BI	2-4	0.223	0.093(-0.237,0.549)	0.302	9.307	25.798
Peak Avg BI	2-4	0.345	0.158(-0.188,0.599)	0.201	9.124	25.290
Plat Abs BI	2-4	0.109	0.042(-0.271,0.504)	0.394	10.870	30.131
Plat Avg BI	2-4	0.241	0.100(-0.224,0.551)	0.286	10.621	29.439

The most and least reliable BI values were pulled to establish the range of SEM and MDC as thresholds for true changes in BI. Significance was set at $p \leq 0.05$ *.

Appendix H

Cumulative Bilateral Index Reliability

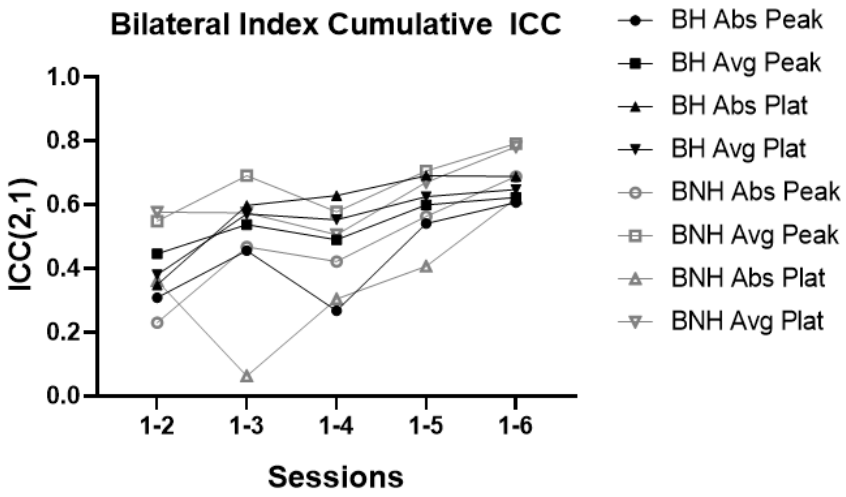


Figure 32. Cumulative BH and BNH BI Reliability

Although not previously discussed in Chapter 4, BH BI only reached statistical reliability when values from test sessions were averaged. With each additional session, the majority of measures increased in reliability. Single and cumulative averaged values are displayed in the following tables.

Table 17. Bilateral Index (%) Single Day and Cumulative Averaged Mean(SD)

	Absolute Peak		Average Peak		Absolute Plateau		Average Plateau	
	Single	**Averaged**	**Single**	**Averaged**	**Single**	**Averaged**	**Single**	**Averaged**
Bilateral Homologous BI								
Day 1	-4.0 (8.3)	-	-2.4 (11.6)	-	-0.7 (8.4)	-	0.1 (11.7)	-
Day 2	-6.2 (2.9)	-5.1 (6.5)	-5.9 (4.4)	-4.2 (9.1)	-4.7 (3.1)	-2.7 (6.8)	-5.3 (4.5)	-2.6 (9.5)
Day 3	-7.1 (6.6)	-5.8 (6.6)	-7.1 (6.7)	-5.1 (8.5)	-5.7 (5.5)	-3.7 (6.6)	-5.2 (6.6)	-3.5 (8.7)
Day 4	-5.5 (5.1)	-5.7 (6.2)	-6.9 (2.7)	-5.6 (7.5)	-5.1 (3.3)	-4.0 (5.9)	-6.1 (2.6)	-4.1 (7.7)
Day 5	-7.3 (5.4)	-6.0 (6.1)	-7.6 (5.5)	-6.0 (7.2)	-6.9 (6.8)	-4.6 (6.2)	-7.3 (7.2)	-4.7 (7.7)
Day 6	-7.5 (4.1)	-6.2 (5.8)	-6.6 (4.7)	-6.1 (6.8)	-6.1 (2.9)	-4.9 (5.8)	-5.4 (3.1)	-4.9 (7.1)
Bilateral Non-Homologous BI								
Day 1	-3.6 (7.7)	-	-2.3 (7.4)	-	-5.0 (9.3)	-	-5.2 (9.4)	-
Day 2	2.1 (11.0)	-0.7 (10.1)	2.0 (10.1)	-0.2 (9.3)	-0.5 (11.4)	-2.7 (10.9)	-0.3 (11.5)	-2.7 (11.4)
Day 3	0.8 (7.6)	-0.2 (9.4)	3.1 (9.9)	0.9 (9.7)	-0.5 (10.0)	-2.0 (10.7)	2.7 (10.1)	-0.9 (11.0)
Day 4	-0.9 (8.7)	-0.4 (9.2)	0.1 (8.7)	0.7 (9.4)	-2.7 (9.6)	-2.2 (10.4)	-2.2 (9.3)	-1.2 (10.6)
Day 5	-1.8 (6.5)	-0.7 (8.7)	-1.4 (7.9)	0.3 (9.2)	-3.9 (6.8)	-2.5 (9.8)	-3.7 (8.7)	-1.7 (10.3)
Day 6	-1.5 (7.3)	-0.8 (8.5)	-2.4 (10.3)	-0.1 (9.4)	-2.6 (8.4)	-2.5 (9.6)	-5.1 (10.9)	-2. 3 (10.5)

Each test day sums into a single BI measure for each measure of force. The cumulative measure is calculated as the average from the assigned day to each day before (ex: Day 4 is the average of days 1-4).

Table 18. BH Bilateral Index Single and Averaged Reliability ICC(2,1)

	N	Single ICC (95% CI)	p-value	Averaged ICC (95% CI)	p-value	SEM	MDC
Absolute Peak							
Days 1-2	11	0.182 (-0.447,0.688)	0.289	0.309 (-1.616,0.815)	0.289	5.90	16.37
Days 1-3	11	0.218 (-0.127,0.639)	0.122	0.456 (-0.512,0.841)	0.122	5.88	16.31
Days 1-4	11	0.084 (-0.137,0.475)	0.251	0.268 (-0.931,0.784)	0.251	6.08	16.85
Days 1-5	11	0.191 (-0.021,0.552)	0.044*	0.541 (-0.113,0.860)	0.044*	5.61	15.55
Days 1-6	11	0.205 (0.015 , 0.547)	0.016*	0.607 (0.084,0.879)	0.016*	5.31	14.73
Averaged Peak							
Days 1-2	11	0.287 (-0.317,0.737)	0.180	0.446 (-0.093,0.848)	0.180	7.72	21.39
Days 1-3	11	0.280 (-0.066,0.677)	0.065	0.538 (-0.227,0.863)	0.065	7.19	19.94
Days 1-4	11	0.194 (-0.052,0.576)	0.073	0.490 (-0.246,0.844)	0.073	6.72	18.63
Days 1-5	11	0.230 (0.014,0.585)	0.018*	0.600 (0.066,0.876)	0.018*	6.29	17.43
Days 1-6	11	0.216 (0.026,0.556)	0.011*	0.623 (0.138,0.882)	0.011*	6.07	16.83
Absolute Plateau							
Days 1-2	11	0.211 (-0.313,0.683)	0.232	0.349 (-0.912,0.811)	0.232	5.83	16.16
Days 1-3	11	0.331 (0.002,0.703)	0.026*	0.598 (0.006,0.876)	0.026*	5.08	14.07
Days 1-4	11	0.298 (0.038,0.656)	0.011*	0.629 (0.138,0.884)	0.011*	4.76	13.20
Days 1-5	11	0.309 (0.080,0.649)	0.002*	0.691 (0.304,0.902)	0.002*	4.95	13.73
Days 1-6	11	0.207 (0.071,0.603)	0.002*	0.689 (0.315,0.901)	0.002*	4.79	13.28
Averaged Plateau							
Days 1-2	11	0.235 (-0.296,0.697)	0.209	0.380 (-0.841,0.821)	0.209	7.98	22.12
Days 1-3	11	0.308 (-0.027,0.690)	0.041*	0.571 (-0.086,0.870)	0.041*	7.02	19.46
Days 1-4	11	0.236 (-0.010,0.606)	0.034*	0.553 (-0.043,0.860)	0.034*	6.52	18.07
Days 1-5	11	0.250 (0.036,0.598)	0.009*	0.625 (0.156,0.881)	0.009*	6.45	17.88
Days 1-6	11	0.234 (0.045,0.569)	0.005*	0.648 (0.220,0.888)	0.005*	6.08	16.85

Table 19. BNH Bilateral Index Single and Averaged Reliability ICC(2,1)

	N	Single ICC (95% CI)	p-value	Averaged ICC (95% CI)	p-value	SEM	MDC
Absolute Peak							
Days 1-2	11	0.130 (-0.402,0.639)	0.331	0.230 (-1.347,0.780)	0.331	8.36	23.17
Days 1-3	11	0.227 (-0.103,0.638)	0.104	0.468 (-0.391,0.841)	0.104	8.86	24.57
Days 1-4	11	0.154 (-0.084,0.542)	0.121	0.422 (-0.446,0.826)	0.121	9.42	26.10
Days 1-5	11	0.206 (-0.007,0.564)	0.032*	0.564 (-0.038,0.866)	0.032*	8.64	23.96
Days 1-6	11	0.270 (0.061,0.609)	0.003*	0.689 (0.280,0.903)	0.003*	8.23	22.81
Averaged Peak							
Days 1-2	11	0.378 (-0.184,0.775)	0.099	0.549 (-0.452,0.874)	0.099	9.63	26.69
Days 1-3	11	0.427 (0.074,0.766)	0.010*	0.691 (0.194,0.908)	0.010*	10.67	29.56
Days 1-4	11	0.255 (-0.012,0.631)	0.034*	0.578 (-0.048,0.872)	0.034*	10.08	27.94
Days 1-5	11	0.325 (0.082,0.687)	0.003*	0.706 (0.307,0.909)	0.003*	9.40	26.06
Days 1-6	11	0.388 (0.155,0.706)	<0.001*	0.792 (0.524,0.935)	<0.001*	8.74	24.23
Absolute Plateau							
Days 1-2	11	0.220 (-0.378,0.702)	0.242	0.361 (-1.216,0.825)	0.242	9.22	25.56
Days 1-3	11	0.022 (-0.268,0.476)	0.430	0.063 (-1.735,0.731)	0.430	8.18	22.66
Days 1-4	11	0.099 (-0.127,0.491)	0.220	0.305 (-0.825,0.794)	0.220	8.54	23.67
Days 1-5	11	0.121 (-0.068,0.478)	0.126	0.407 (-0.464,0.821)	0.126	7.89	21.87
Days 1-6	11	0.214 (0.019,0.558)	0.014*	0.620 (0.103,0.883)	0.014*	7.42	20.57
Averaged Plateau							
Days 1-2	11	0.405 (-0.158,0.788)	0.084	0.577 (-0.376,0.882)	0.084	7.19	19.92
Days 1-3	11	0.311 (-0.022,0.691)	0.038*	0.575 (-0.069,0.871)	0.038*	7.21	19.98
Days 1-4	11	0.204 (-0.042,0.583)	0.062	0.506 (-0.191,0.848)	0.062	8.22	22.79
Days 1-5	11	0.289 (0.058,0.636)	0.005*	0.670 (0.235,0.897)	0.005*	7.63	21.16
Days 1-6	11	0.374 (0.146,0.694)	<0.001*	0.782 (0.506,0.931)	<0.001*	7.46	20.68

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