NEURAL MECHANISMS OF BILATERAL DEFICIT IN MAXIMAL FORCE PRODUCTION IN SPECIFIC GROUPS OF ATHLETES

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Master's thesis in Biomechanics
Spring 2016
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ABSTRACT

Škarabot, Jakob 2016. Neural mechanisms of bilateral deficit in maximal force production in specific groups of athletes. University of Jyväskylä, Department of Biology of Physical Activity, Master's Thesis in Biomechanics. 128 pp.

The mechanisms of bilateral deficit (BLD) have been studied extensively, but remain obscure. Neural mechanisms have been proposed, including interhemispheric inhibition (IHI). In this study specific groups of athletes who were more likely to exhibit BLD or bilateral facilitation (BLF) were compared with controls. If IHI is truly the underlying cause of BLD it is of interest whether the nature of IHI is reflected in the magnitude of BLD. 20 male subjects (ALL) were split into three groups according to the nature of their activity: bilateral, unilateral and control. Additionally, they were split into two groups whether they exhibited BLD or BLF. Maximal unilateral (UL) and bilateral (BL) isometric knee extensions were performed while receiving electrical stimulation of the femoral nerve and both contralateral and ipsilateral transcranial magnetic stimulation. Main variables of interest included bilateral index in force and EMG activity, voluntary activation level, motor evoked potentials of target and ipsilateral muscles (MEPs), and cortical and ipsilateral silent periods. Significant BLD was observed for ALL (BI = -8.76 ± 13.43, $p = 0.009$), but not for any of the separate groups. No BLD was noted in EMG activity and no parallelisms between force and EMG was found. Voluntary activation level was significantly higher during BL compared to UL contractions (~ 97% vs. 93%, $p = 0.045$), with no differences between groups. MEPs during BL were significantly bigger ($p = 0.042$, and $p = 0.005$, respectively) than during UL contractions with no differences between groups. No differences in silent periods were noted regardless of grouping. Variability of BLD observed was likely due to poor testing specificity. Based on unaltered silent periods, BLD may not be related to inhibition at the cortical level. Conversely, higher values of voluntary activation level and motor evoked potentials during BL when compared to UL contractions may indicate involvement of cortical facilitation.

Key words: Bilateral deficit, force, TMS, interhemispheric inhibition

ABBREVIATIONS

AG	Athlete groups
ALL	The whole population of subjects
ANOVA	Analysis of variance
BF	Biceps femoris
BF EMG	Root-mean-squared EMG activity of biceps femoris
BG	Bilateral group
BI	Bilateral index
aBI_E	Average bilateral index in EMG activity
BI_E	Bilateral index in electromyographic activity
aBI_F	Average bilateral index in force
BI_F	Bilateral index in force
BIG	Groups according to the result of the bilateral index
BL	Bilateral
BLD	Bilateral deficit
CC	Corpus callosum
CG	Control group
CI	Confidence interval
CMEP	Cervicomedullary motor evoked potential
CV	Coefficient of variation
MEP	Motor evoked potential of the target muscle
CMJ	Countermovement jump
CSP	Cortical silent period
D-wave	Direct wave
EMG	Electromyography
F-V	Force-velocity
H-reflex	Hoffman reflex
ICC	Intraclass correlation coefficient
IHI	Interhemispheric inhibition
iMEP	Ipsilateral motor evoked potential
ISI	Inter-stimulus interval
iSP	Ipsilateral silent period

I-wave	Indirect wave
M1	Primary motor cortex
M_{max}	Maximal compound action potential
MRCP	Movement-related cortical potential
MU	Motor unit
MVC	Maximal voluntary contraction
rMT	Resting motor threshold
RFD	Rate of force development
R ratio	Ratio of ipsilateral MEP and MEP of target muscle
SD	Standard deviation
SP	Silent period
TMS	Transcranial magnetic stimulation
UG	Unilateral group
UL	Unilateral
VAL	Voluntary activation level
VL	Vastus lateralis
VL EMG	Root-mean-squared EMG activity of vastus lateralis

CONTENTS

1 INTRODUCTION

As early as in 1961, Henry & Smith observed that the sum of forces produced by left and right limb separately is greater than the force produced during simultaneous contraction of both limbs (Figure 1) (Henry and Smith 1961). Since the 1960s, this phenomenon, termed the bilateral deficit (BLD), has been shown to be present in various movement tasks, contraction-types, and different populations (see Table 1, 2 and 4). In most studies the BLD has been determined through the calculation of bilateral index (BI) as presented by Howard & Enoka (1991):

BI (%) = [100 x (bilateral / (right unilateral + left unilateral))] – 100 (equation 1),

where 'bilateral' is the sum of forces produced by each leg separately during the bilateral action. The positive BI is indicative of bilateral facilitation (BLF), while the negative value indicates BLD.

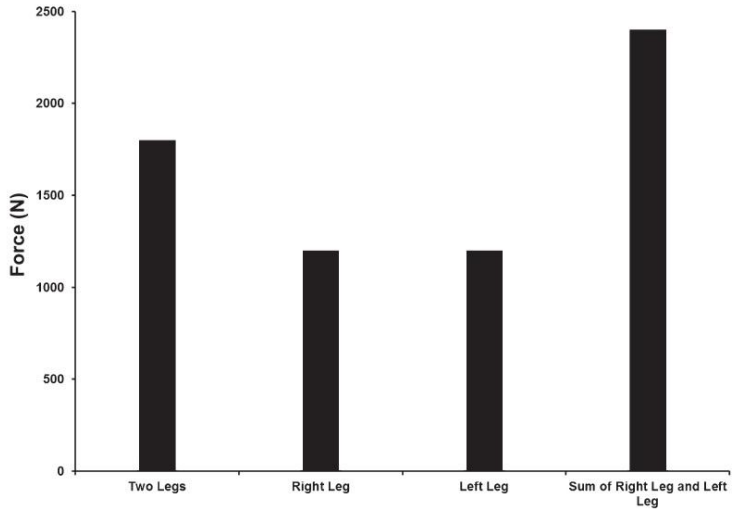

FIGURE 1. Theoretical representation of the bilateral deficit (Nijem and Galpin 2014).

The BLD phenomenon appears to be restricted to twin synchronous movements (Ohtsuki 1983) and contraction of homonymous limbs (Schantz et al. 1989; Howard and Enoka 1991; Herbert and Gandevia 1996). There are some inconsistencies in the literature in regards to the existence of BLD as some studies have observed this phenomenon, while others have not (see Table 1, 2 and 4). In fact some studies have shown the existence of BLF (Secher 1975; Schantz et al. 1989; Howard and Enoka

1991), a phenomenon where maximal bilateral force production is greater than the sum of unilateral forces.

There are many reasons why BLD is worth exploring. Firstly, determining the existence of BLD is important as it may represent a control limitation of the neuromuscular system (Jakobi and Chilibeck 2001). This may have applications to both athletic performance and neural pathological states. Secondly, knowledge of the mechanisms behind this phenomenon may provide us with a better understanding of the complex motor control or biomechanical constraints that concern everyday activities or specific populations (Jakobi and Chilibeck 2001). The latter includes athletes in sports where bilateral (BL) contractions are performed exclusively (e.g. rowers, powerlifters, weightlifters) and potentially athletes in sports where performance is ultimately limited by unilateral (UL) force production (e.g. high and long jumpers, throwing events in track and field etc.). Furthermore, the existence of BLD in the elderly could have an effect on the performance of daily bilateral activities (e.g. rising from a chair), and could potentially predispose them to injury in certain cases (Hernandez et al. 2003). Thirdly, the effect of BLD on athletic performance is largely unknown. The vast majority of sports include locomotion, a "reciprocal" movement pattern (Archontides and Fazey 1993), where forces are produced mostly unilaterally. Therefore, the question remains whether bilateral jumping and resistance exercises in training should better be replaced with their unilateral variations.

The literature review part of the thesis explores some of the important issues of BLD and consists of four larger parts including contraction- and/or movement-type dependency of BLD, the underlying mechanisms of BLD, the effect of training on BLD, and the relationship between BLD and athletic performance.

2 CONTRACTION- AND/OR MOVEMENT-TYPE DEPENDENCY OF BILATERAL DEFICIT

The literature on BLD lacks consistency. While BLD is frequently reported in studies using a dynamic contraction model, the results of isometric contractions are more variable. Despite the variability of BLD phenomenon in the literature, results of Botton et al. (2013), who showed similar magnitude of BLD between isometric and concentric knee extensions, suggest that the existence of BLD is not contraction-type dependent. Furthermore, in a recent paper by the same research group BLD was only observed in isometric, but not dynamic contractions (Botton et al. 2015). In an effort to establish consistency, the discussion is separated into three parts based on the type of contraction.

2. 1 Dynamic contractions

In dynamic contractions, i.e. either concentric, eccentric and/or isokinetic, BLD is reported consistently. BLD has been shown to be present during isokinetic knee extension (Owings and Grabiner 1998a; Cresswell and Overdal 2002; Dickin and Too 2006) and arm extension, i.e. bench press (Taniguchi 1997, 1998), concentric (Janzen et al. 2006; Magnus and Farthing 2008) and isokinetic (Taniguchi 1997, 1998) hip and knee extensions; arm flexion, i.e. concentric lat pulldown (Janzen et al. 2006); isokinetic knee extension and flexion (Brown et al. 1994; Kuruganti et al. 2005; Kuruganti and Seaman 2006), and concentric (Weir et al. 1997; Botton et al. 2013; Costa et al. 2015) and eccentric knee extensions (Weir et al. 1995). The magnitude of BLD during concentric and/or eccentric contractions is about 10% on average, while it has a bigger range during isokinetic contractions and can be as high as 49% (Vandervoort et al. 1984) depending on the speed of contraction, usually increasing with increases in contraction velocity.

TABLE 1. Summary of BLD literature using dynamic contractions. BLD = bilateral deficit in force, BLD (%) = magnitude of bilateral deficit, BLD EMG = bilateral deficit in electromyography, R = randomization, LD = limb dominance.

Reference	Movement	Contraction mode	BLD	BLD (%)	EMG BLD	Subjects	R	LD
(Botton et al. 2013)	Knee extension	Concentric	Yes	9.6 %	/	Physically active (n = 8)	UL and BL on separate days, but randomized	/
(Botton et al. 2015)	Knee extension	Concentric	No	/	/	Young women (n = 43)	BL followed by UL (randomized)	/
(Brown et al. 1994)	Knee extension	Isokinetic	Yes (60-240°/s); No (360 °/s)	1-12 %	/	Females (n = 12)	Yes	/
	Knee flexion	Isokinetic	Yes (60-240°/s); No (360 °/s)	1-16 %	/			
(Costa et al. 2015)	Knee extension	Concentric	Yes	11 %	/	Healthy - 12 M - 24 ± 3.7 yrs	n/m	/
(Cresswell and Overdal 2002)	Knee extension	Isokinetic - 60°/s	Yes	17 %	Yes	Recreationally active young females (n = 13) and males (n = 15)	Yes	/
(Dickin and Too 2006)	Knee extension	Isokinetic - 30 – 180 °/s	Yes	18 - 25 %	/	University-aged females (n = 18	Yes	/
(Häkkinen et al. 1996b)	Knee extension	Concentric	No	/	/	50 year-old males (n = 12) and females (n = 12)	No	/

						70-year old males (n = 12) and females (n = 12)		
(Häkkinen et al. 1997)	Knee extension	Concentric	No (BLF)	/	No (BLF)	Young men (n = 10), middle-aged men (n = 12) and women (n = 12), elderly men (n = 12) and women (n = 12)		No
(Janzen et al. 2006)	Hip and knee extension	Concentric	Yes	12.7 %	/	Postmenopausal women (n = 57)	Yes	/
	Arm flexion		Yes	8.8 %				
	Knee extension		No	/				
(Kuruganti et al. 2005)	Knee extension	Isokinetic	Yes	26.7 %	/	Older men (n = 10) and women (n = 7), younger men (n = 5) and women (n = 11)	BL followed by UL (randomized)	/
	Knee flexion		Yes	32.5 %				
(Kuruganti and Seaman 2006)	Knee extension	Isokinetic	Yes	25.4 %	No	Females – adolescent (n = 8), adult (n = 8), older (n = 7)	BL followed by UL (randomized)	/
	Knee flexion		Yes	27.8 %	No			
(Magnus and Farthing 2008)	Hip and knee extension	Concentric	Yes	12.1 %	No	Male (n = 3) and female (n = 5) students	Yes	/
(Owings & Grabiner 1998a)	Knee extension	Isokinetic (30 and 150 °/s)	Yes	13.7 – 14.0 %	/	Healthy men (n = 20)	UL(R or L), BL, UL (L or R)	/
(Roy et al. 1990)	Knee extension	Isokinetic	Yes	Not reported	/	Physically active male undergraduate students (n =	Yes	/

						42)		
(Taniguchi 1997)	Hip and knee extension	Isokinetic (80 °/s)	Yes	6.5 – 18.6 %	/	Male (n = 17) and females (n = 4) students	Yes	/
	Arm extension		Yes	7.2 – 9.6 %	/	Male (n = 9) and females (n = 9) students	Yes	/
(Taniguchi 1998)	Hip and knee extension	Isokinetic (80 °/s)	Yes	0.5 – 15.3 %	/	Male (n = 32) and female (n = 7) students	Yes	/
	Arm extension		Yes	3.7 – 11.8 %	/			
(Vandervoort et al. 1984)	Hip and knee extension	Isokinetic	Yes	9 - 48.8 %		Male students (n = 9)	No	/
(Vandervoort et al. 1987)	Bench press	Isokinetic	No	/	/	Students (n = 9)	Yes	/
(Weir et al. 1995)	Knee extension	Dynamic (eccentric)	Yes	Not reported	/	Physically active young males (n = 17)	UL (randomized), BL	No
(Weir et al. 1997)	Knee extension	Dynamic (concentric)	Yes	Not reported	/	Physically active young males (n = 16)	UL (randomized), BL	Yes

Studies that were not able to show BLD during dynamic contractions are in minority and mainly include concentric knee extension (Häkkinen et al. 1996b, 1997; Janzen et al. 2006; Botton et al. 2015) and isokinetic bench press (Vandervoort et al. 1984). It is difficult to deduce the cause of such findings as there are many confounding factors that can affect force production during dynamic contractions. There have been some suggestions that the existence and magnitude of BLD may be caused by differences in postural stabilization requirements in different movements (Herbert and Gandevia 1996). Janzen et al. (2006) showed that BLD is present only in multi-joint exercises such as lat pulldown and leg press, but not in single-joint task such as knee extension. Magnus & Farthing (2008) investigated the relationship between the magnitude of BLD and postural stability requirements. They showed BLD for leg press, a task with greater postural stability requirements, while they could not observe any BLD for handgrip exercise. They also measured electromyographic (EMG) activity of the core muscles and showed that although it was not different between UL and BL contractions in both exercises, it did differ between exercises insofar as it was higher during the leg press. It is important to note however, than the handgrip is an isometric task, while the leg press is dynamic and this could have been responsible for differences in the results. Based on the aforementioned findings, it seems plausible that the expression of BLD in knee extension is limited by low postural stability requirements. Future studies should try to control postural stabilization requirements and/or report the exact subject positioning during testing as this appears to affect the expression of BLD.

Jakobi & Chilibeck (2001) suggested that a great amount of studies reporting the existence of BLD during dynamic actions could possibly be due to publication bias (Cleophas and Cleophas 1999), variability of the population, and whether the conditions were randomized or not. In regard to the latter, not all studies have randomized the conditions (see Table 1) and therefore it is possible that fatigue/and or potentiation have affected the results (Jakobi and Chilibeck 2001). Furthermore it has been suggested that great variability between subjects is due to inadequate reproducibility of the dynamic tests as there were only a few studies that have reported it (Vandervoort et al. 1984, 1987; Taniguchi 1997).

It is difficult to interpret the underlying mechanisms during dynamic actions as many factors can affect the ability to produce force including, but not limited to, interaction between actin and myosin filaments, whether the movement is single- or multi-joint,

activation and length of the muscles involved, as well as the velocity of contraction (Jakobi and Chilibeck 2001).

2. 2 Isometric contractions

Studies that have investigated differences in UL and BL contractions during isometric conditions are the most numerous (Table 2). This contraction model is the most suitable for investigation for the possible underlying mechanisms, as mechanics of the movement are somewhat restricted (Jakobi and Chilibeck 2001).

TABLE 2. Summary of BLD literature using isometric contractions. BLD = bilateral deficit in force (BI significantly different than 0), BI (%) = bilateral index denoting the magnitude of bilateral deficit, BLD EMG = bilateral deficit in electromyography, R = randomization, LD = limb dominance.

Reference	Movement	BLD	BI (%)	EMG BLD	Subjects	R	LD
(Aune et al. 2013)	Shoulder flexion Index finger flexion	Yes Yes	- 20.4 - 5.1	/ /	Untrained males (n = 5) and females (n = 5)	Yes	/
(Behm et al. 2003)	Knee extension	No	/	Yes	Resistance trained (n = 10) and untrained (n = 6) males	n/m	Yes (untrained)
(Beurskens et al. 2015)	Hip and knee extension	Yes	- 3.9 – 19.3	/	Old male adults (n = 53) and young male adults (n = 14)	BL followed by UL (randomized)	/
(Botton et al. 2013)	Knee extension	Yes	- 9.7	/	Healthy untrained males (n = 11)	UL and BL on separate days, but randomized	/
(Botton et al. 2015)	Knee extension	Yes	- 10.5 – 13.8	Yes	Young women (n = 43)	BL followed by UL (randomized)	/
(Buckthorpe et al. 2013)	Knee extension	No	/	No	Physically active males (n = 12) kg)	UL – BL – UL	/
(Cengiz 2015)	Hand flexion	Yes	- 9	Yes	Physically active males (n = 10)	Yes	Yes

(Cornwell et al. 2012)	Hand flexion	Yes (left-handed only)	- 1.3	No	Untrained males (n = 31) and females (n = 49)	Yes	Yes (left handed)
(Donath et al. 2014)	Hip and knee extension	Yes	- 5.6 – 7.2	/	Male athletes (n = 20)	Yes	/
(Drury et al. 2004)	Elbow flexion	Yes (45 and 90°); no (135°)	- 11.4 – 20.1	/	Active females (n = 20)	Yes	/
(Häkkinen et al. 1995)	Knee extension	No	/	No	Males: 3 age groups – 30 (n = 11), 50 (n = 12) and 70 (n = 10)	No	No
(Häkkinen et al. 1996a)	Knee extension	No	/	No	Middle-aged (50 year-old) males (n = 12) and females (n = 12) Elderly (70-year-old) males (n = 12) and females (n = 12)	No	No
(Häkkinen et al. 1997)	Knee extension	No (BLF)	/	No (BLF)	Young (n = 10) and older (n = 10) men	No	No
(Henry and Smith 1961)	Hand flexion	Yes	- 3	/	College-aged men (n = 30)		Yes
(Herbert and Gandevia 1996)	Thumb adduction	No	/	No	Males (n = 5) and females (n = 6)	Yes	No
(Hernandez et al. 2003)	Elbow flexion	Yes	- 11.1 – 11.9	Yes	Older men (n = 5) and women (n = 12), and younger men (n = 5) and women (n = 16)	Yes	/
(Howard and Enoka	Knee extension	Yes (untrained	- 9.5	No	Untrained (n = 6)	No	/

1991)		only); No (cyclists, facilitation – weightlifters)	(untrained); - 6.6 (cyclists); + 6.2 (weightlifters)		Cyclists (n = 6) Weightlifters (n = 6)		
(Jakobi and Cafarelli 1998)	Knee extension	No	/	No	Recreationally active males (n = 20)	Yes	No
(Kawakami et al. 1998)	Plantarflexion	Yes	- 6.6 – 13.9	Yes (0° only)	Young males (n = 6)	Yes	/
(Khodiguian et al. 2003)	Knee extension	No	/	No	Untrained young males (n = 17)	Yes	No
(Koh et al. 1993)	Knee extension	Yes	- 17.0 – 24.6	Yes	Recreationally active males (n = 12)	Yes	No
(Kuruganti et al. 2011)	Knee extension	Yes (45°), No (0°, 90°)	- 23.4 (45°)	No	Young, recreationally active males (n = 10)	BL followed by UL (randomized)	/
(Kuruganti and Murphy 2008)	Knee extension	Yes	- 18.5	Yes	Young, athletic males (n = 6)	BL followed by UL (randomized)	

(MacDonald et al. 2014)	Hip and knee extension Hand flexion	Yes No	- 18.6 – 20.2 /	No No	Female swimmers (n = 9) and untrained females (n = 9)	Yes	/
(Magnus and Farthing 2008)	Hand flexion	No	/	No	Males (n = 3) and female (n = 5) students	Yes	/
(Matkowski et al. 2011)	Knee extension	Yes	- 7.8	No	Physically active males (n = 13)	Yes	/
(Oda and Moritani 1994)	Elbow flexion	Yes	- 3.4 – 7.9	Yes	Males (n = 11)	Yes	Yes
(Oda & Moritani 1995a)	Elbow flexion	Yes	- 6 - 10	Yes	College oarsmen (n = 25)	Yes	Yes
(Oda and Moritani 1995b)	Hand flexion	Yes	- 4.5 – 5.2	Yes	Untrained (n = 8)	Yes	Yes
(Oda and Moritani 1996)	Hand flexion	Yes	- 3.9 – 4.9	Yes	Untrained (n = 11)	No	Yes
(Ohtsuki 1981a)	Handgrip	Yes		Yes	Young women (n = 10)		Yes
(Ohtsuki 1981b)	Finger flexion	Yes	- 15 – 30	/	Young males (n = 20) and females (n = 2)		/
(Ohtsuki 1983)	Elbow flexion Elbow extension	Yes Yes	- 6.3 – 7.6 - 18.8 – 24.6	Yes Yes	University students (n = 10)	Yes	No

(Owings & Grabiner 1998b)	Knee extension	Yes	- 6.5 – 12.9	/	Older males (n = 12) and females (n = 23)	Yes	No
(Post et al. 2007)	Finger abduction	Yes	- 1.8 – 2.6	Yes	Healthy males (n = 10) and females (n = 12)	Yes	No
(Schantz et al. 1989)	Knee extension Hip and knee extension	No Yes	/ - 10	/ No	Male (n = 20) and female (n = 13) physical education students; Untrained females (n = 9) and males (n = 5) Professional female (n = 5) and male (n = 5) ballet dancers; Volleyball male players (n = 5) Resistance-trained males (n = 5)	Yes	/
(Secher 1975)	Arm flexion	No (BLF)	/	/	Oarsmen (n = 40)		/
(Secher et al. 1978)	Hip and knee extension	Yes	- 25	/	Males (n = 16)		/
(Secher et al. 1988)	Hip and knee extension Arm extension	Yes No	- 18 /	/ /	Untrained females (n = 90) and males (n = 18); Male weightlifters (n = 38); Male cyclists (n = 8); Female polio patient (n = 1)		No
(Taniguchi 1997)	Hand flexion	No	/	/	Male students (n = 23)	Yes	/
(Teixeira et al. 2013)	Knee extension	Yes	- 8.4	/	Resistance trained males (n =	Yes	No

					27)		
(Vandervoort et al. 1984)	Hip and knee extension	Yes	- 9	Yes	Male students (n = 9)	No	/
(Vandervoort et al. 1987)	Arm extension	No	/	/	Male students (n = 9)	Yes	/
(Van Dieën et al. 2003)	Finger flexion	Yes	- 20 – 26.9	Yes	Untrained males (n = 5) and females (n = 5)	Yes	No
	Knee extension	Yes	- 3.5 – 9.7	Yes	Untrained males (n = 6) and females (n = 6)	No	No
(Vint and McLean 1999)	Elbow flexion	Yes	- 11.4	No	College students (n = 20)	No	Yes
(Zijdewind and Kernell 2001)	Finger abduction	Yes	- 5.1		Young males (n = 2) and females (n = 3)	No	No

With regards to isometric knee extension the literature seems to be the most equivocal (Table 3) as some studies have shown the presence of BLD (Howard & Enoka 1991; Koh et al. 1993; Kuruganti et al. 2011; Kuruganti & Murphy 2008; Matkowski et al. 2011; Owings & Grabiner 1998b; Dieen et al. 2003), while others have not (Schantz et al. 1989; Häkkinen et al. 1996a, 1997; Jakobi and Cafarelli 1998; Behm et al. 2003; Khodiguian et al. 2003; Kuruganti et al. 2011; Buckthorpe et al. 2013). It is possible that the use of different populations have caused the discrepancy in the results as Howard & Enoka (1991) showed BLD only for the untrained group, but not for cyclists, and even facilitation in weightlifters. However, Häkkinen and colleagues (Häkkinen et al. 1996a, 1997) and Owings & Grabiner (1998b) both used older population and only the latter showed BLD. The ambiguity of the literature on isometric knee extension could also be explained by differences in knee joint angles that were employed in different experiments. Kuruganti et al. (2011) were able to show BLD only for 45 degrees, but not for 0 or 90 degrees, respectively, possibly because maximal tension can be produced at intermediate muscle length, while it decreases towards the extremes of muscle lengths (Lieber et al. 1994). However, their results contradict the findings of Owings & Grabiner (1998b) who showed BLD during both 45 and 90 degrees, respectively. Matkowski et al. (2011), who found BLD during isometric knee extension did so at 70 degrees of knee flexion, a joint-angle that had been chosen because it is reportedly close to optimal muscle length for maximal force production (Becker and Awiszus 2001; Kubo et al. 2004). On a related note, an investigation of BLD at different joint angles during elbow flexion also showed that BLD is present only at 45 and 90 degrees, respectively, but not at 135 degrees (Drury et al. 2004). From the reviewed literature there seems to be a trend for a greater prevalence of BLD in knee extension at intermediate muscle lengths (Table 3). As mentioned above it is also possible that postural stabilization requirements in knee extension are in some cases too low to result in BLD. For example, Schantz et al. (1989) observed BLD only for isometric combined hip and knee extension, but not for knee extension.

TABLE 3. Summary of BLD literature using isometric knee extension with respective joint angles.

Reference	Joint angle (°)	BLD	BI (%)
(Behm et al. 2003)	90	No	/
(Botton et al. 2013)	60	Yes	- 9.7
(Botton et al. 2015)	60	Yes	- 10.5 – 13.8
(Häkkinen et al. 1995)	73	No	/
(Häkkinen et al. 1996a)	73	No	/
(Häkkinen et al. 1997)	73	No	/
(Howard and Enoka 1991)	71	Yes/No*	- 9.5*
(Jakobi and Cafarelli 1998)	90	No	/
(Khodiguian et al. 2003)	90	No	/
(Koh et al. 1993)		Yes	- 17.0 – 24.6
(Kuruganti et al. 2011)	0	No	0
	45	Yes	- 23.4
	90	No	0
(Kuruganti and Murphy 2008)	45	Yes	- 18.5
(Matkowski et al. 2011)	70	Yes	- 7.8
(Owings and Grabiner 1998b)	45	Yes	- 11.1 – 12.9
	90	Yes	- 6.5 – 8.9
(Schantz et al. 1989)	90	No	0
(Teixeira et al. 2013)	60	Yes	- 8.4
(Van Dieën et al. 2003)	90	Yes	- 3.5 – 9.7

Joint angle - 0° = full extension (all data has been transformed accordingly); BLD = bilateral deficit in force, BI = bilateral index, *population-dependent – BLD was only observed for untrained group, but not for weightlifters and cyclists

Studies of isometric combined hip and knee extension show BLD consistently. All the studies were able to show the BLD phenomenon (Vandervoort et al. 1984; Schantz et al. 1989; Donath et al. 2014; MacDonald et al. 2014; Beurskens et al. 2015) with its magnitude ranging from 3.9% (Beurskens et al. 2015) to 20.2% (MacDonald et al. 2014). More consistent results compared to the knee extension cannot be explained by different populations used, as BLD has been studied both in young and old individuals

for both movement types (Table 2). As suggested by Jakobi & Chilibeck (2001) the differences may possibly be explained by different neural activation of the quadriceps between the two movements. It has been shown that a greater neural activation may be required during multi-joint, compared to single-joint movement (Chilibeck et al. 1998). It is also possible that greater consistency in terms of observing BLD is due to greater postural stability requirements. Furthermore, differences in synergist contribution in combined hip and knee extension between unilateral and bilateral contractions could have been responsible for consistency of the results. For example, a recent study showed that modified single-leg squat had a higher EMG activity of the gluteus medius and hamstrings compared with two-leg squat (McCurdy et al. 2010). Therefore, some synergists may have a greater contribution to the net single-leg force production during UL compared to BL contractions.

In the upper body, BLD of 20.4% has been shown in shoulder flexion (Aune et al. 2013), 1.7% in thumb adduction (Herbert and Gandevia 1996), roughly 3% in finger abduction (Post et al. 2007) and 18.8-24.6% in elbow extension (Ohtsuki 1983). In elbow flexion (Drury et al. 2004; Hernandez et al. 2003; Oda & Moritani 1994; Oda & Moritani 1995a; Vint & McLean 1999) BLD ranges from 3.4% (Oda and Moritani 1994) to as high as 20.12% (Drury et al. 2004). Some ambiguity in the literature exists in regard to BLD in isometric hand flexion, i.e. handgrip. While the majority of studies have reported BLD in hand flexion (Ohtsuki 1981a; b; Oda and Moritani 1995b, 1996; Van Dieën et al. 2003; Cornwell et al. 2012; MacDonald et al. 2014; Cengiz 2015), some have not (Seki and Ohtsuki 1990; Taniguchi 1997; Magnus and Farthing 2008). In those who have, BLD ranges from 1.3% (Cornwell et al. 2012) to as high as 20% (Van Dieën et al. 2003). It is possible that high variability between the results stems from different subject positioning during strength testing between the studies, thereby causing differences in muscle length of hand flexors.

2. 3 Explosive/ballistic contractions

It has also been shown in ballistic actions, such as human jumping, that the sum of one-legged jumping height is higher than the height of a bilateral jump. This is the case for the countermovement jump (CMJ) (van Soest et al. 1985; Bračič et al. 2010), drop jumps (Pain 2014) as well as the squat jump (Challis 1998; Bobbert et al. 2006).

However, it is important to note that jumping height may not be the best quantifying method of performance to determine BLD as it depends on whether it is normalized to the height in upright standing (van Soest et al. 1985) or to the height at takeoff (Bobbert et al. 1996). Despite these considerations, Hay et al. (2006) were still able to observe BLD of 13% during leg press jumps by measuring the resultant ground reaction impulses. Pain (2014) was also able to observe BLD during drop jumps by measuring peak concentric force and peak power.

On the other hand, Ebben et al. (2009) observed bilateral facilitation in jumping when testing athletes from different track and field disciplines. The authors attributed the results to the fact that most of the subjects were participating in throwing events. However, their explanation is difficult to accept, as throwing events are not strictly bilateral in nature such as weightlifting or rowing where bilateral facilitation in isometric force production has been shown (Secher 1975; Howard and Enoka 1991).

Veligekas & Bogdanis (2013) were not able to show the existence of BLD during CMJ in prepubertal boys regardless of their training history, while it was still present in equal-aged girls. Since the boys in the study were less biologically developed based on maturity offset, the authors attributed the observed gender differences to the reduced ability of the boys to activate motor units and/or superior motor skill abilities of girls, such as the ability to keep balance on one leg.

TABLE 4. Summary of BLD literature using explosive contractions. BLD = bilateral deficit in force (BI significantly different than 0), BI (%) = bilateral index denoting the magnitude of bilateral deficit, *If '/' = BI in force not reported; BLD EMG = bilateral deficit in electromyography, R = randomization, LD = limb dominance.

Reference	Movement	BLD	BI (%)*	EMG BLD	Subjects	R	LD
(Bobbert et al. 2006)	Squat jump	Yes	/	Yes	Physically active males (n = 8)	Alternating one- and two-leg jumps	Yes
(Buckthorpe et al. 2013)	Explosive knee extension	Yes (explosive F, RFD); No (MVC)	- 11.2 (explosive F) – 14.9 (RFD)	No	Physically active males (n = 12)	UL-BL-UL	
(Bračič et al. 2010)	Countermovement jump	Yes	- 19.1	/	Elite male sprinters (n = 12)	Yes	Yes
(Challis 1998)	Squat jump	Yes	/	/	College female basketball players (n = 7)	No	/
(Dickin et al. 2011)	Hip and knee extension	Yes	/	/	University-aged males (n = 12)	Yes	Yes
(Ebben et al. 2009)	Countermovement jump	No (BLF)	/		Male (n = 13) and female (n = 10) athletes	Yes	No
(Hay et al. 2006)	Leg press jumps	Yes	- 16.6	Yes	Healthy males (n = 5)	Yes	No

(Pain 2014)	Drop jumps	Yes	- 16.8 – 35.5	/	Elite endurance (n = 7) and power athletes (n = 7)	Yes	//
(Rejc et al. 2010)	Hip and knee extension	Yes	- 30.5	Yes	Young males (n = 10)	Yes	/
(Rejc et al. 2015)	Hip and knee extension	Yes	- 18.1	Yes	Young males (n = 10)	No	/
(Samozino et al. 2014)	Hip and knee extension	Yes	- 36.7	/	Male athletes (n = 14)	No	/
(van Soest et al. 1985)	Countermovement jump	Yes	/	Yes	Male volleyball players (n = 10)	n/m	/
(Veligekas and Bogdanis 2013)	Countermovement jump	Yes (girls); No (boys)	/	/	10-year-olds (59 males, 55 females) and 12-year-olds (24 males, 34 females)	No	/

BLD is also present during explosive dynamic contractions of the leg muscles and can be as high as 35% (Rejc et al. 2010, 2015; Samozino et al. 2014). Furthermore, BLD has been shown to exist in RFD during explosive isometric contractions (Van Dieën et al. 2003; Buckthorpe et al. 2013).

The mechanism of the BLD during explosive and ballistic movements appears to be different from other contraction types as it can be explained, at least to a certain degree, by changes in force-velocity (F-V) relationship (Bobbert et al. 2006; Samozino et al. 2014) or by differences in muscle coordination (Rejc et al. 2010).

3 UNDERLYING MECHANISMS OF BILATERAL DEFICIT

The underlying mechanisms of BLD have been a subject of debate among researchers since the discovery of the phenomenon. The mechanisms appear to be largely unknown due to their complexity. It is likely that more than one mechanism is at play under a given set of circumstances. Many mechanisms have been proposed over the years including, but not limited to, differences in fiber-type recruitment pattern between unilateral and bilateral contractions, limb dominance, differences in perceived exertion, neural, including cortical, mechanisms, and differences in force-velocity curve between unilateral and bilateral contractions. These mechanisms will be discussed below. For better representation, the possible mechanisms have been split into four factors namely psychological, task related, physiological and neurophysiological, as seen before (Aune et al. 2013). Additionally, some methodological considerations have been taken into account.

3. 1 Psychological factors

3. 1. 1 Perceived exertion

Jakobi & Chilibeck (2001) suggested that BLD may simply be caused by differences in perceived exertion between unilateral and bilateral movements, especially during contractions of the lower limb muscles. Seki & Ohtsuki (1990) measured forces during submaximal UL and BL contractions of the upper body muscles. When subjects were told to exert 25%, 50% and 75% of perceived MVC, BLD was noted, suggesting the notion that BLD may simply be due to the inability to exert oneself to the fullest capacity during BL contractions. Vint & McLean (1999) observed that BLD is larger in perceived submaximal contractions, possibly due to greater perceived exertion of BL actions during submaximal efforts. Their results were later also replicated by Hernandez et al. (2003).

3. 1. 2 Subject naïveté

Some authors have suggested that BLD may simply be a result of awareness of BLD

phenomenon, or lack of it. Secher et al. (1988) have shown a reduction of BLD when subjects were given incorrect pre-information (the subjects were told that the BL force should be greater than the sum of UL forces). However, Koh et al. (1993) found no influence of the correct information on the existence of BLD. In the experiment of Donath et al. (2014), a population of athletes performed UL and BL contractions on an isometric leg press on three separate days. On the first day they were not given any information about the existence of BLD, while on the remaining days they were given the standardized false and standardized correct information, respectively. They did not found any influence of information on BLD, as it was clearly present regardless of the instruction given to the subjects.

3. 1. 3 Division of attention

The theory of division of attention suggests a reduction of force will have occurred when two remote parts of the body are generating force simultaneously and is based on the dual task theory in the field of cognitive psychology, which suggests that attention is a limited resource and may put constraints on performance (Takebayashi et al. 2009). Vandervoort et al. (1984) speculated that there is a diffusion of concentration between the two legs during BL effort, which would result in a reduced excitation of the MN pool. However, since BLD has been shown to be restricted to twin synchronous movements (Ohtsuki 1983) and contraction of homonymous limbs (Schantz et al. 1989; Howard and Enoka 1991; Herbert and Gandevia 1996), the attention demands of the task are an unlikely contributor to the existence of BLD.

3. 2 Task related factors

3. 2. 1 Familiarity with the task

Vandervoort et al. (1987) stated that everyday activity (e.g. gait) is usually reciprocal. Since the performance of a maximal strength task improves with learning (Rutherford & Jones 1986) it is possible that BLD may be simply due to the fact that individuals are unaccustomed to performing maximal bilateral tasks. Secher et al. (1988) also noted that magnitude of BLD significantly decreased after familiarization. For that reason, studies

should include some sort of practice or familiarization of maximal contraction in the testing apparatus as suggested by Gandevia (2001). Familiarity of the task may also be responsible for the results of Howard & Enoka (1991) and Secher (1975) as participants in their studies had been used to performing bilateral actions.

3. 2. 2 Postural stability

It was first suggested by Herbert & Gandevia (1996) that the ability to contract the muscles bilaterally may be limited by the ability to make appropriate postural adjustments, and that this may be especially the case for large muscle groups. Janzen et al. (2006) showed BLD to be present only in multi-joint exercises, which should have greater postural stability requirements, but not in single-joint exercise. Magnus & Farthing (2008) tested the contribution of the postural stability requirements to BLD by comparing the magnitude of BLD in the leg press, an exercise with greater postural stability, and hand flexion, i.e. handgrip, an exercise with small postural stability requirements. They found the presence of BLD only in the leg press, but not the handgrip, thereby supporting the hypothesis that postural stability influences the existence and/or magnitude of bilateral deficit. Therefore, if the goal is to study mechanisms of BLD, experimenters should try to control postural stability requirements.

3. 2. 3 Limb dominance

In the pioneering study of Henry & Smith (1961) it was proposed that BLD is due to the force reduction in the dominant limb. The effect of limb dominance on BLD has been shown in several studies examining UL and BL contractions, yet not in others (Table 1, 2 and 4). However, it seems to be more prevalent in the upper- than the lower body. This may be due to differences in the physical activity level between the upper and lower limbs in the activities of daily living as lifetime assessments of physical activity have shown the difference in activity level between dominant and non-dominant limbs in the upper-, but not the lower body (Jakobi and Chilibeck 2001). Since left-handed individuals show less discrepancy between the strength of the dominant and non-dominant limb (Crosby et al. 1994; Armstrong and Oldham 1999) it is also possible that

the limb dominance effect on BLD is limited to right-handed individuals. However, this is not supported by Cornwell et al. (2012) who performed the only direct investigation of the effect of limb dominance on BLD. The subjects performed UL and BL hand grip contractions and were separated into left-handed or right-handed group. BLD was evident only in the left-handed group, and only the left hand of the left-handed group showed a significant reduction in force during BL contractions, despite the fact that the discrepancy between the hand strength was smaller than in the right-handed group. Since some of the participants were stronger in their non-dominant hand they later decided to rearrange the groups based on the strength-dominance. A greater significance of force reduction of the left hand was observed for the left-hand-strength-dominant group, but only a trend for the same reduction was observed for the right-hand group. These results suggest that limb dominance effect on BLD may be restricted to left-handed individuals. However, the results may have been different had the right-handed subjects exhibited BLD. Furthermore, the degree of BLD was relatively small, only 1.3 percent, compared to other studies investigating unilateral and bilateral handgrip contractions where deficits between 5 and 22 percent have been shown (Ohtsuki 1981a; Oda and Moritani 1995b; Van Dieën et al. 2003; Post et al. 2007).

In this light it is interesting to note that Oda & Moritani (1995b) observed a greater deficit in cortical activity in the non-dominant arm, while a greater deficit in force and EMG was observed for the dominant arm during BL handgrip contractions.

3. 3 Physiological factors

3. 3. 1 Contribution of synergists, core muscles, and antagonists

Antagonist co-activation has been shown not to be different during BL and UL contractions, thus it appears not to have an effect on the existence of BLD (Howard and Enoka 1991; Koh et al. 1993; Jakobi and Cafarelli 1998; Cresswell and Overdal 2002; Behm et al. 2003; Van Dieën et al. 2003; Kuruganti et al. 2011; Buckthorpe et al. 2013). If BLD was to be affected by antagonist co-activation, it would be expected to be greater during BL compared to UL contraction, as it would result in reduced net force produced by agonist muscles. However, Koh et al. (1993) were able to show greater

antagonist co-activation during UL compared to BL contractions, thus supporting the hypothesis of antagonist activation having no effect on BLD.

An interesting observation regarding the co-activation came from the study of Cresswell & Overdal (2002) who investigated BLD during knee extension. During the UL performance subjects were not given specific instructions in regards to the non-active leg and that limb was also not specifically attached. They noticed a burst of hamstring EMG activity in the contralateral leg, which had also previously been shown by Howard & Enoka (1991). Furthermore, the subjects who activated the hamstrings in the contralateral leg during UL actions exhibited greater BLD compared to the subjects who did not (BLD of 21 vs. 14%, respectively). They suggested that "afferent feedback produced by the contralateral hamstrings activation may interact in a facilitatory manner with the descending command to the quadriceps muscle performing the UL extension", thereby increasing the force production of the agonist (Cresswell and Overdal 2002). However, it has to be kept in mind that such kind of crossed facilitation would usually be expected to result from the original action, i.e. extensors in this case and not flexors. Another possibility is that the contralateral hamstring co-activation contributed to increased stability, thereby increasing the torque of the UL actions as previously suggested by Howard & Enoka (1991).

Magnus & Farthing (2008) were the only investigators who assessed the contribution of core muscles to BLD. They showed that the activity of core musculature was greater in leg press than in hand grip exercises, which corresponded to BLD in the leg press, but not the handgrip exercise. Differences in the activation of core muscles between unilateral and bilateral contractions were not noted between the exercises. However, Magnus & Farthing (2008) speculated that similar core activation may have created a disadvantage for bilateral conditions by providing smaller input to the postural stability since the ground reaction forces were likely higher in bilateral conditions. Exploring the potential lateral difference in the activity of the core muscles may also be worth considering in future research as it may have an effect on net force production of the kinetic chain.

Co-activation of synergist muscles has not been taken often into consideration as a possible underlying mechanism of BLD. A study by McCurdy et al. (2010) showed that activation of gluteus medius was greater in modified single-leg squat compared to

bilateral squat exercise. Since greater synergist contribution leads to greater net torque about a joint it may explain the deficit observed during bilateral conditions. Further research in this area is warranted and researchers should try to include recordings of the synergist muscles.

3. 3. 2 Biomechanical mechanisms

Based on the available evidence it seems possible that during ballistic actions such as human jumping or during explosive dynamic contractions, BLD may be simply explained by differences in the force-velocity (F-V) curve between UL and BL actions. This has been suggested to be the case despite a tendency for EMG activity to be coupled with BLD in force (Bobbert et al. 2006).

Comparison of one-legged and two-legged CMJs performed by van Soest et al. (1985) showed the presence of BLD during human jumping. They noted many differences in performance of one-legged and two-legged jumps. The main one was that the work production per one leg in a two-legged jump was less than in one-legged jump. This finding led authors to believe that F-V relationship may contribute to the existence of BLD. However, after observing that differences in length and contraction velocities were relatively small, they discarded this hypothesis.

Bobbert et al. (2006) found that during squat jumps there is a large BLD in peak joint moments (20-30%) and suggested that differences in the contractile conditions of the muscles could explain their results. Since the velocity of the center of mass was greater in two-leg- compared to one-leg jumps, the extensor muscles will have shortened at higher velocities in the two-leg jump and therefore produce less force and consequently less work. Also, it is important to consider that the body weight is equally distributed between two legs during the two-legged jump, which results in the muscles of individual legs having a reduced active state in the initial equilibrium position. Therefore, it seems plausible that in the initial part of range-of-motion the muscles in the two-legged jump are in submaximal active state (Bobbert et al. 2006). As stated by Bobbert et al. (2006) this consideration is especially important in squat jumps, since they do not involve a preparatory countermovement that allows for a development of the active state of the extensor muscles (Bobbert and Casius 2005). Furthermore, Bobbert et al. (2006) performed musculoskeletal model simulation, and showed that as

much as 75% of the BLD can be explained by higher shortening velocities in the two-legged jump, which suggests that differences in the F-V relationship may be a possible underlying mechanism of the BLD.

It has to be noted that the body position differs between one- and two-legged jumps, especially that of a musculoskeletal model (Figure 2), which could have had an effect on the differences reported by Bobbert et al. (2006). Furthermore, the average push-off time appears to be longer in UL compared to BL jumps (Bobbert et al. 2006).

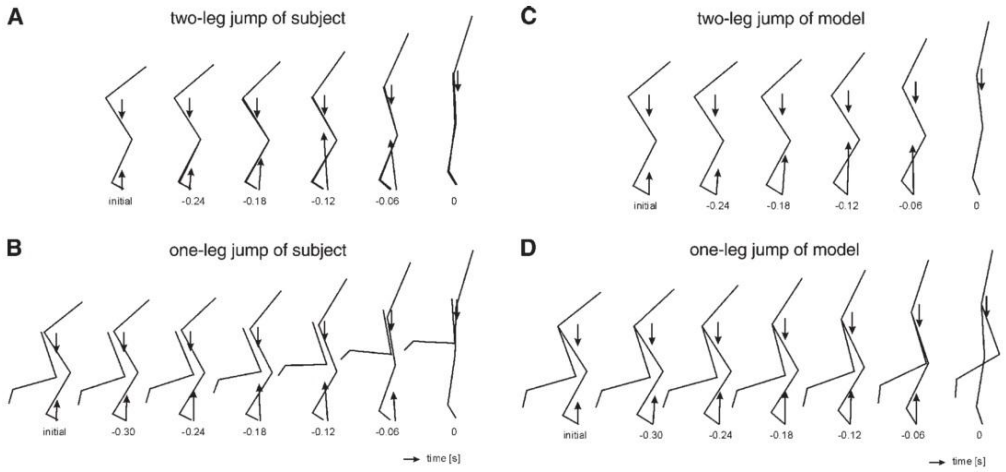

FIGURE 2. Average body positions of subjects and musculoskeletal model for the push-off in one- and two-legged jumps. Upward pointing arrows – ground reaction force vector; downward pointing arrows – force of gravity; time expressed relative to the instant of take-off (Bobbert et al. 2006).

Rejc et al. (2010) investigated explosive combined hip and knee extensions against different loads and showed that BL actions are characterized by a displacement of the F-V curve, rather than a shift, to a lower level compared to UL actions (Figure 3). It is also important to note that mean pushing times and shortening velocities did not differ between UL and BL contractions, suggesting that BLD is due to different force outputs in the two- versus one-limb conditions. Subsequent work performed by the same research group included modeling the external dynamic mechanical capabilities of the lower limb via F-V relationship during UL and BL explosive combined hip and knee extension (Samozino et al. 2014). They showed that about 43% of the BLD in ballistic actions could be explained by a shift F-V relationship due to a change in movement velocity, with the remaining part being a shift in F-V relationship due to neural factors. Furthermore, the non-neural mechanism of BLD appears to be highly individual, as

lower BLDs were observed in subjects with F-V relations oriented towards velocity capabilities.

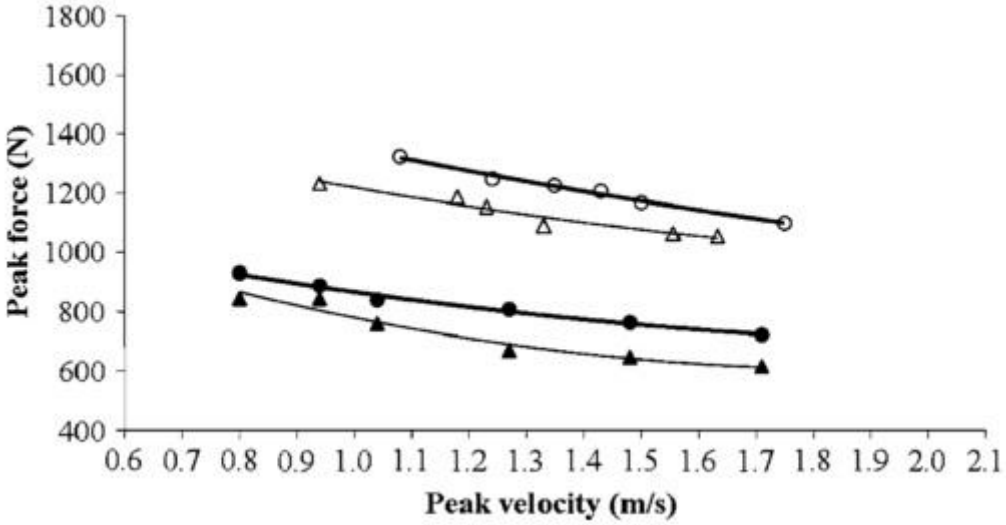

FIGURE 3. F-V relationships for UL and BL contractions during explosive hip and knee extension. Thick curves – right limb, thin curves – left limb, filled circles and triangles – right and left BL actions, respectively; open circles and triangles – right and left UL actions, respectively (Rejc et al. 2010).

3. 3. 3 Recruitment pattern of motor units / inhibition of types of muscle fibers

One of the objectives of older research of BLD mechanisms was investigation of inhibition of motor units (MUs) during BL actions (Archontides and Fazey 1993). First investigations have suggested that the BLD may be caused by selective inhibition of slow-twitch muscle fibers. This conclusion was based on the studies using pharmacological agents in order to block a certain muscle fiber type. Since a larger deficit was observed when type II muscle cells were blocked (when a greater amount of type I fibers were contributing to force production), the researchers suggested that type I fiber inhibition may be the underlying mechanism of BLD (Secher 1976; Secher et al. 1978). The problem with this conclusion is that it violates Henneman's principle of orderly recruitment of MUs (Henneman 1957). Furthermore, as suggested by Archontides & Fazey (1993), when Secher and colleagues (Secher 1976; Secher et al. 1978) blocked type I fibers, BLD was still present, albeit to a lesser extent.

Many studies have found that BLD increases in magnitude with increasing speed of contraction (Vandervoort et al. 1984; Koh et al. 1993; Dickin and Too 2006;

Buckthorpe et al. 2013). Since it has been shown that fast-twitch fibers contribute more to force production at high velocities (Thorstensson et al. 1976; Coyle et al. 1979; Tihanyi et al. 1982; Moritani et al. 1991) it has been suggested by many researchers that BLD may be due to the inhibition of the fast-twitch muscle fibers during BL contractions. Koh et al. (1993) investigated the differences in BLD during step and ramp contractions. They found that BLD was greater when force was produced rapidly compared to when the force was increased linearly. They were also able to show that EMG amplitude decreased with increasing torque. Therefore, they suggested that BLD could be explained by fast-twitch muscle fiber inhibition (Koh et al. 1993). Interestingly, Buckthorpe et al. (2013) investigated BLD using explosive force, rate of force development (RFD) and maximal voluntary contraction (MVC). The existence of BLD was limited to explosive force (force in the first 100 ms) and RFD. However, they did not observe any changes in the EMG activity. On the other hand, Owings & Grabiner (1998a) showed that the magnitude of BLD was the same when isokinetic knee extensions were performed at 30 and 150 degrees per second, respectively. Similarly, Dickin et al. (2011) did not observe any differences in the magnitude of BLD with increasing speed of combined hip and knee extensions. Furthermore, Brown et al. (1994) showed that the magnitude of BLD decreased with increasing speed of isokinetic contractions from 60 to 240 degrees per second, and was actually absent at 360 degrees per second thereby contradicting the findings of other studies (Vandervoort et al. 1984; Koh et al. 1993; Dickin and Too 2006; Buckthorpe et al. 2013).

Another possible way to assess the contribution of fast-twitch fibers is to study the effect of fatigue on BLD since fast-twitch fibers are more fatigable (Burke et al. 1973). Vandervoort et al. (1984) showed that there was a smaller decline in the BL force over the duration of concentric combined hip and knee extension fatigue test, suggesting that there was a reduction in recruitment of high-threshold MUs. However, during the bench press exercise fatigue test, the BL actions were more susceptible to fatigue (Vandervoort et al. 1987). Vandervoort et al. (1987) tried to explain these results by differences in the training level of the muscles, familiarity of the movement patterns used in both investigations and/or differences in the fiber type distribution between different muscles, respectively. Owings & Grabiner (1998a) only showed an increase in the magnitude of BLD after a fatiguing leg extension protocol performed at 30°/s, but not at 150°/s. Their results suggest speed-dependent influence on BLD following

fatigue, but contradict the hypothesis that BLD may be caused by inhibition of fast-twitch MUs.

Kawakami et al. (1998) tested the hypothesis that the magnitude of BLD would be greater in muscles consisting of predominantly fast-twitch MUs by investigating BLD during plantarflexion. By manipulating knee joint angle (Sale et al. 1982), they were able to distinguish between the contribution of gastrocnemius, a mixed-muscle in terms of fiber-type composition, and soleus, a predominantly slow-twitch muscle (Johnson et al. 1973). They found that BLD was greater when the knee was extended, i.e. at the point of greater gastrocnemius contribution to the movement, supporting the hypothesis of fast-twitch MU inhibition.

An indirect way to assess the relative contribution of the MU-type is to perform EMG power spectrum analysis. It has been shown that fiber-type composition may influence the mean power frequency of the EMG (Gerdle et al. 1988; Beck et al. 2007b). Oda & Moritani (1994) showed a shift to lower values of median power frequency during BL compared to UL contractions, albeit only in the dominant arm, and therefore suggested that BLD in neural activation may be due to decreased activation of fast-twitch MUs. Khodiguian et al. (2003) measured force output during reflexively evoked contraction, i.e. after induction of patellar myotatic reflex with a patellar tendon strike, as well as during the MVC. They were also able to show a decrease in peak power frequency of the EMG signal during reflexively evoked BL compared to UL contractions, which suggests inhibition of the fast-twitch MUs. They further supported this hypothesis by showing that during reflexively evoked contractions the premotor time was longer in the BL condition. However, they were not able to replicate this during MVC, thereby making their findings difficult to interpret. Other studies that have analyzed EMG power spectrum (Schantz et al. 1989; Koh et al. 1993) have not been able to show any differences between UL and BL actions, thus contradicting the theory of fast-twitch fiber inhibition as a cause of BLD. Koh et al. (1993) suggested that median frequency may not be sensitive enough to indicate differences in the relative contribution of slow and fast-twitch MUs between UL and BL conditions.

The aging process has been shown to be accompanied by a decrease in the size of the fast-twitch muscle fibers (Essén-Gustavsson and Borges 1986; Lexell et al. 1988; Evans and Lexell 1995). Therefore, it could provide an indirect model to study the mechanism

of fast-twitch fiber inhibition during BL contractions. Based on the changes that occur with aging, if fast-twitch fiber inhibition contributes to the existence of BLD, older individuals should have reduced or absent BLD. While the research done by Häkkinen and colleagues (Häkkinen et al. 1995, 1996a; b, 1997) did not find the presence of BLD in older individuals, Owings & Grabiner (1998b) clearly showed that BLD can be present in the elderly. However, their main limitation was the lack of a control group consisting of young individuals. Later work, such as that of Hernandez et al. (2003) compared older and younger individuals during UL and BL actions and found similar BLD during isometric elbow flexion. Their finding is further supported by Kuruganti et al. (2005) who showed that BLD was present in both young and older individuals during knee flexion and extension, respectively. This data was later also compared against adolescent subjects (Kuruganti and Seaman 2006) and again no differences in the magnitude of BLD were found between different age groups. Recently, Beurskens et al. (2015) showed that BLD can be even higher in older compared to younger individuals. Based on the BLD literature in the elderly, there is not much support for the hypothesis that the BLD is influenced by inhibition of fast-twitch fibers during BL contractions, at least not in this particular population.

Since fiber type composition has been shown to change with disuse and is usually characterized by a shift from type I to type II fibers (Häggmark et al. 1986) it is possible that immobilization or disuse resulting in a greater percentage of fast-twitch fibers would result in a greater magnitude of BLD if fiber type has any effect on the existence of this phenomenon. However, Rejc et al. (2015) showed that the magnitude of BLD remains unaltered after 35-day bed rest. Despite not measuring the change in fiber-type composition after a period of disuse, their findings suggest that BLD may be independent of the percentage of fast-twitch muscle fibers.

3. 4 Neurophysiological factors

3. 4. 1 Muscle activity (EMG)

Surface EMG has been applied concurrently with force recordings in many investigations concerning the differences between UL and BL contractions. There is some ambiguity in the literature in regards to the parallelism between force and EMG,

as some studies have shown that BLD in force follows the same trend in the EMG activity, while there have also been others who did not show such coupling (see Table 1, 2 and 4). If BLD in EMG activity is present it may be contributed to changes within muscles fibers, changes in the motoneuron excitability and/or cortical excitability, respectively (Post et al. 2007).

The equivocal nature of this particular line of research is debatable. Howard & Enoka (1991) suggested that since the magnitude of force change is relatively small between BL and UL contractions, it is less likely to be detected with surface EMG. Lawrence & Luca (1983) showed that when forces are greater the force-EMG relationship seems clearer; however it may still depend on the muscle being investigated. It has also been suggested that different contribution of antagonists and/or synergists could have affected the EMG activity of the agonist, thereby causing this discrepancy (Herbert and Gandevia 1996; Post et al. 2007).

Solomonow and colleagues warned against using EMG to predict force since different muscles use different recruitment strategies to produce force (Solomonow et al. 1990). Therefore, it could be argued that investigating different muscles could be responsible for the discrepancy in the literature. However, Howard & Enoka (1991) did not show coupling between force and EMG during knee extension, while Van Dieën et al. (2003) did, despite the fact that they both investigated the vastus lateralis muscle. Howard & Enoka (1991) also showed that the EMG-force relationship varies greatly between subjects and between UL and BL contractions, respectively. For example, they showed that the parallelism between EMG and force was observed only for highly-trained weightlifters, but no such trend was observed for cyclists or untrained. Therefore, differences in the studies could be explained by variability of the EMG and force recordings. Jakobi & Chilibeck (2001) suggested that differences observed in the literature may be due to data analysis, particularly due to the time period of integration window. Additionally, EMG amplitude cancellation can vary and therefore underestimate the amount of MU activity (Keenan et al. 2005). Siegler et al. (1985) also indicated that different signal processing may lead to slight variation in EMG-force relationship. It is also noteworthy to mention that small fluctuations in MU activity are not detectable with EMG (Farina et al. 2014). It is possible that differences between UL and BL contractions in terms of MU activity were too small in some studies to detect any significant difference.

It is important to note that the amplitude of the EMG signal is not a direct indicator of muscle activation (Farina et al. 2010). Therefore, if the parallelism between force and EMG recordings in regard to BLD is not observed, the possible effect of neural factors should not be discounted. This is especially the case with dynamic contractions, where changes in muscle length occur (Farina 2006), which may be the reason for a greater consistency of force-EMG coupling in terms of BLD in isometric compared to dynamic contractions (see Table 1 and 2).

Koh et al. (1993) were one of those that were able to show evidence for BLD in EMG activity of the agonist. An interesting finding was that during the BL contractions the antagonist activity decreased thrice as much as agonist activity. Despite these changes not reaching statistical significance Jakobi & Cafarelli (1998) suggested the explanation of these results insofar as decreased agonist activation during BL contraction may have simply been due to less antagonist co-activation.

The only study that investigated the discharge rate of MUs during UL and BL contractions was that of Jakobi & Cafarelli (1998). A difference in the MU recruitment and its firing rate between UL and BL contractions would indicate that the motoneuron pool modulates UL and BL contractions differently. They showed that average MU firing rates did not differ between the contractions performed with one limb or two limbs concurrently, irrespective of the intensity of the contraction. However, they did not observe BLD in force. Therefore, it remains unclear if discharge rate would have differed between UL and BL actions, had BLD been observed.

Rejc et al. (2010) also investigated muscle coordination with the use of integrated EMG during explosive BL and UL contractions of combined hip and knee extension against different loads, which were based on percentage of body mass. They calculated the dispersion index and plotted its values at different time windows, thereby obtaining an index of the time course of muscle coordination (Figure 4). They showed that the muscles investigated (rectus femoris, vastus lateralis, biceps femoris, gastrocnemius) follow a different time course in BL and UL contractions, showing a contribution of muscle coordination to the BLD. Whether the same principle applies to one-joint, non-explosive and/or isometric contractions, respectively, remains unclear.

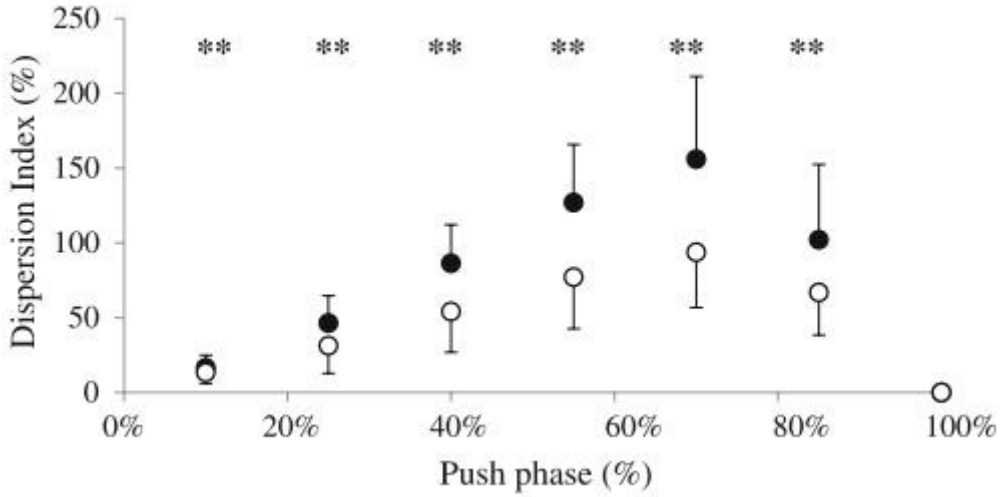

FIGURE 4. Differences in dispersion index between BL (filled circle) and UL (open circle) contractions at different time points during the concentric (push) phase of the explosive hip and knee extension (Rejc et al. 2010). Dispersion index refers to the algebraic sum of iEMG values of each pair of muscles, and their plotting at different time windows, thereby representing an index of the time course of muscle coordination.

3. 4. 2 Spinal mechanisms

It has been proposed that inhibition of spinal mechanisms may contribute to the existence of BLD (Ohtsuki 1983). During BL actions the afferent sensory input in one limb may induce an inhibition of the motoneurons of the contralateral limb at the spinal cord level. Delwaide et al. (1988) showed that activation of the contralateral arm movement increases the degree of reciprocal inhibition, suggesting the effect of Ia afferents on the contralateral limb. Kawakami et al. (1998) showed that H-reflex was reduced in the contralateral leg during the UL performance, which would indicate that BLD is due to decreased motoneuron excitability. However, Howard & Enoka (1991) contradicted the theory of spinal reflexes as electrical stimulation of one limb caused facilitation in the contralateral limb. As suggested by Kawakami et al. (1998) the stimulation may have also resulted in the withdrawal reflex, thereby facilitating the crossed-extensor reflex in the contralateral limb.

Khodiguian et al. (2003) set out to test the hypothesis that spinal reflexes may contribute to BLD. They measured force and EMG after patellar myotatic reflex initiation, i.e. reflexively evoked contractions, during UL and BL contractions. They found BLD in force and EMG activity for reflexively evoked contractions (Figure 5).

However, they could not replicate the existence of BLD during the condition of MVC, which makes the contribution of spinal reflexes to BLD difficult to interpret. Khodiguian et al. (2003) observed that subjects who exhibited the strongest reflex were also the one who showed the greatest withdrawal of the contralateral leg. Furthermore, they suggested that during BL actions it is possible that two opposing inputs were at play, namely an excitatory input of ipsilateral Ia afferents and indirect inhibitory input from the contralateral Ia afferents, which would mean that BLD may be caused by mutual contralateral inhibitory inputs.

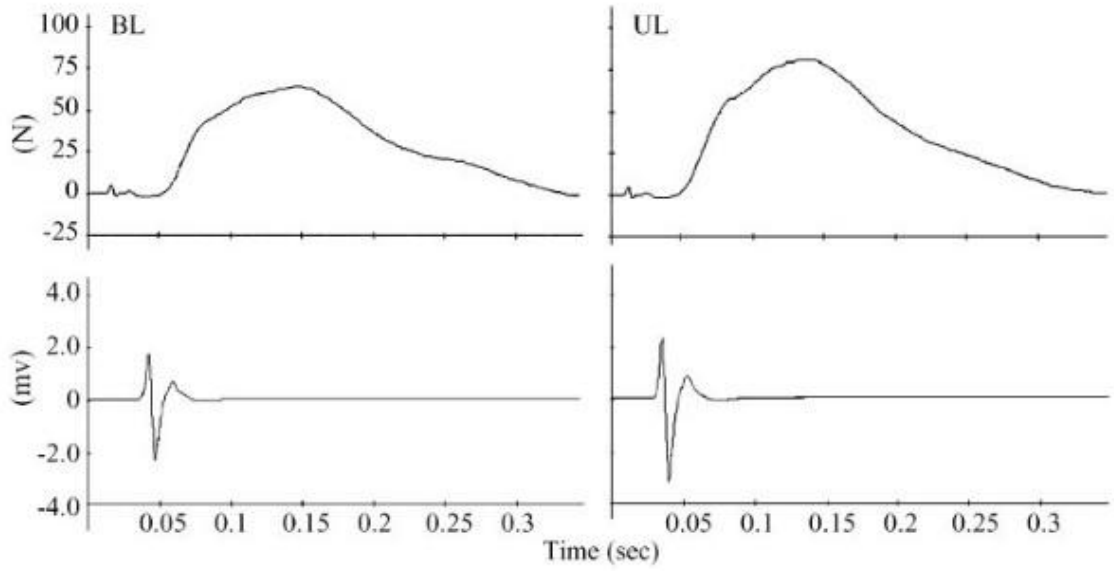

FIGURE 5. Force and EMG response during reflexively evoked BL and UL contractions (Khodiguian et al. 2003).

Perez et al. (2014) performed transcranial magnetic stimulation during unilateral and bilateral contractions, concurrently with cervicomedullary stimulation, a stimulation of the descending tracts at the cervicomedullary junction, which evokes a short-latency response termed cervicomedullary motor evoked potential (CMEP) (Taylor 2006). CMEPs are not affected by changes in cortical excitability and presynaptic inhibition and can therefore be used to measure the changes in motor neuronal excitability (Taylor 2006). Perez et al. (2014) showed that CMEPs remained unchanged during BL compared to UL actions, suggesting that the spinal mechanisms are not different during UL and BL contractions. It is important to note, however, that they performed the measurements during low-force actions (10-30% of MVC).

3. 4. 3 Voluntary activation level

Quantitative assessment of the voluntary activation level (VAL) has been used extensively to evaluate muscle function (Bampouras et al. 2006). The assessment of VAL is usually performed by applying supramaximal electrical stimulus either to the nerve trunk or intramuscular nerve branches during an active voluntary contraction. Those MUs that have not been recruited and/or fire at submaximal rates respond with a twitch-like force increment (Figure 6), suggesting that the agonist was not activated to its fullest capacity (Belanger and McComas 1981). The first application of twitch interpolation method was done by Merton (1954) who concluded that the human muscle can be activated completely during voluntary actions. However, not all subsequent studies have been able to show the complete level of VAL (Hales and Gandevia 1988; McKenzie 1992; Dowling et al. 1994; Allen et al. 1995, 1998; Herbert and Gandevia 1996; Jakobi and Cafarelli 1998; Roos and Rice 1999; Babault et al. 2002; Behm et al. 2002b). They also showed great variability between the subjects, contraction types, and muscles investigated, respectively.

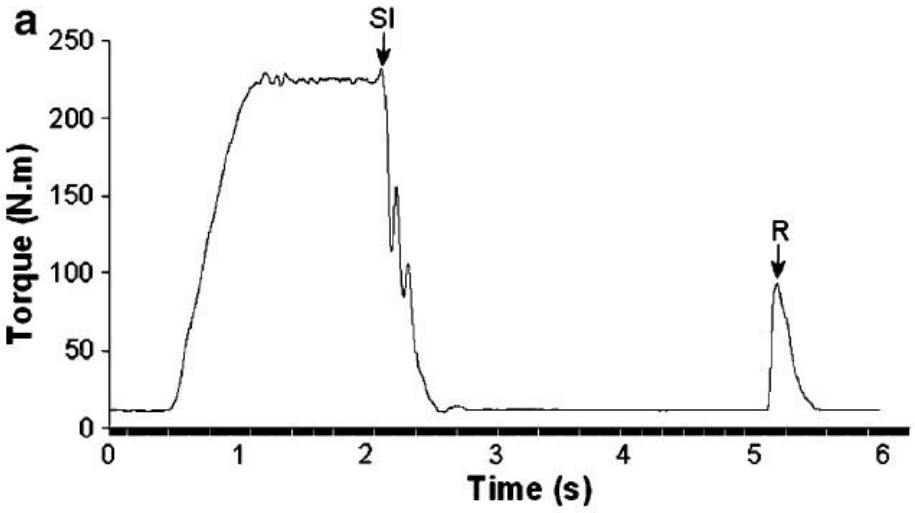

FIGURE 6. An example of interpolated twitch technique. SI = superimposed stimulation, R = control twitch during rest (O'Brien et al. 2008).

The most common method to assess the level of VAL is the twitch interpolation technique introduced by Merton (1954), which is based on the linear relationship between twitch and voluntary force. Therefore, VAL can be assessed with a linear equation, the most common being that of Allen et al. (1995):

Voluntary activation (%) = [1 – (superimposed twitch/control twitch)] x 100 (equation 2),

with the superimposed twitch being the force increment observed during the contraction at the point of stimulation and the control twitch being the twitch evoked in the relaxed muscle.

There are some considerations that need to be taken into account when trying to determine the VAL by using electrical stimulation. Firstly, the timing of the stimulation should be such that the post-contraction potentiated twitches are used as a control twitch since superimposed twitch during MVC appears to be potentiated (Folland and Williams 2007). Secondly, multiple stimuli appear to be less variable (Suter and Herzog 2001; Oskouei 2003). If double stimuli are to be used the inter-stimulus interval (ISI) should be either 5 or 10 ms (Karimpour 2013). Thirdly, supramaximal stimulation intensity should be employed. Increasing the magnitude of the supramaximal stimulus does not appear to make a difference (Behm et al. 1996; Folland and Williams 2007). Lastly, the stimulus duration of 0.5-1 ms should normally be utilized. Stimuli longer than 1 milisecond appear to increase the discomfort without increasing the amplitude (Panizza et al. 1989).

Studies that investigated the extent of VAL during UL and BL actions show somewhat conflicting results. Although they all show near-complete muscle activation during both BL and UL contractions not all of them have shown differences between the contractions performed with one- or two limbs concurrently. Herbert & Gandevia (1996) showed that the VAL is greater during UL than BL thumb contractions (90.3% vs. 88.6%, respectively). Van Dieën et al. (2003) reported significantly greater VAL during UL compared to BL contractions (94% vs. 89%, respectively; VAL deficit of 3.5%) and a strong relationship between BLD and the level of VAL ($r = 0.80$), suggesting that reduced neural drive may underline the BLD phenomenon. Conversely, Behm et al. (2003) reported significantly smaller activation levels measured with ITT during UL compared to BL knee extensions in both resistance-trained and untrained individuals. In contrast, Jakobi & Cafarelli (1998) were not able to show a difference in VAL between UL and BL contractions. However, despite not reaching statistical significance the relative level of VAL during UL and BL contractions was similar to other studies investigating VAL (93.6% vs. 90.1% for UL and BL contractions,

respectively). Matkowski et al. (2011) was also not able to find any differences in VAL between UL and BL contraction (roughly 91% for both). Their methodology was unique compared to other studies insofar as they applied interpolated twitch technique in both legs simultaneously during BL actions. It is important to note that the majority of the abovementioned studies reported great variability between subjects. As suggested by Jakobi & Chilibeck (2001) it is possible that this great variability between subjects may account for general differences between studies in regards to the existence of BLD. Furthermore, small differences in VAL between UL and BL contractions indicate reproducibility and validity of MVCs during one- or two-limb actions (Jakobi and Chilibeck 2001).

3. 4. 4 Higher-order neural inhibition

A possible method for the assessment of cortical activity is transcranial magnetic stimulation (TMS). In 1985, Barked et al. showed that the corticospinal pathway can be activated painlessly by applying magnetic field to the human motor cortex (Barker et al. 1985) (Figure 7). TMS is not only painless, but also relatively safe (Wassermann et al. 1996; Hallett 2000).

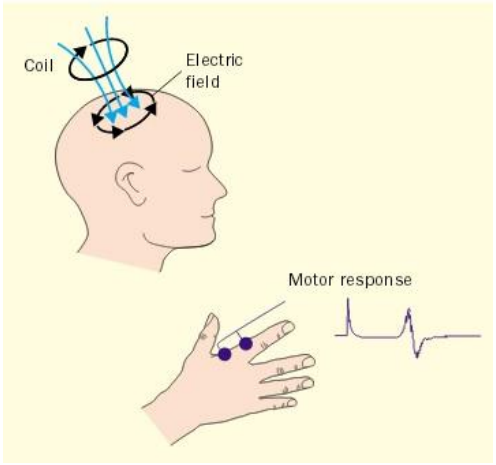

FIGURE 7. Transcranial magnetic stimulation (Kobayashi & Pascual-Leone 2003).

TMS activates corticospinal cells transsynaptically (Abbruzzese G and Trompetto 2002). This is evidenced by specificity of multiple descending volleys that are evoked by TMS. At low intensities indirect waves (I waves) are evoked with different latencies (I1, I2, I3, I4 according to their latency), while direct wave (D wave) is evoked only if stimulation is performed at a high enough intensity (Nakamura et al. 1996; Di Lazzaro

et al. 1998; Ziemann and Rothwell 2000). Motor cortex activation by TMS can be investigated indirectly by assessing the EMG activity. TMS of the motor cortex evokes EMG responses in the contralateral muscles with a brief latency, called motor evoked potentials (MEPs) (Abbruzzese G and Trompetto 2002). Voluntary muscle contraction facilitates MEPs by increasing their amplitude and shortening their latency by several milliseconds (Abbruzzese G and Trompetto 2002). The standardization of TMS output intensity is done by defining the resting motor threshold (rMT) in the relaxed target muscle, representing the global excitability of the corticospinal pathway (Avela and Gruber 2011). Suprathreshold stimulation (> rMT) is usually employed during the experiments. The curve depicting the rise of MEP size (recruitment of MUs) with increasing TMS intensities is called the input-output curve and is also known as the recruitment curve or the stimulus-response curve (Abbruzzese G and Trompetto 2002; Avela and Gruber 2011). The shape of the input-output curve is sigmoidal and is characterized by threshold, steepness, and plateau (Devanne et al. 1997; Ridding and Rothwell 1997; Cacchio et al. 2009). The plateau value as well as the slope of the curve have been considered as a general measure of corticospinal excitability (Carroll et al. 2001), and thus appear to be steeper in muscles with large representation at the cortical level, e.g. hand muscles (Chen et al. 1998; Abbruzzese et al. 1999). Following MEP there is a pause in the ongoing EMG activity called the silent period (SP) (Figure 8). Silent period is both spinal and cortical in nature (Wassermann et al. 1991b; Cantello et al. 1992; Ziemann et al. 1993; Chen et al. 1999) and is thought to be generated in the primary motor cortex (Giesen et al. 1994). Silent period has been shown to have variable duration depending on the muscle stimulated (Abbruzzese G and Trompetto 2002), increases in duration with increased stimulus intensity (Holmgren et al. 1990; Wilson et al. 1993), but appears not to be dependent on the background muscle activity (Haug et al. 1992; Inghilleri and Berardelli 1993; Roick et al. 1993). Silent period duration can be regarded as an indicator of motor cortical excitability (Abbruzzese G and Trompetto 2002; Avela and Gruber 2011) and intracortical inhibition (Säisänen et al. 2008).

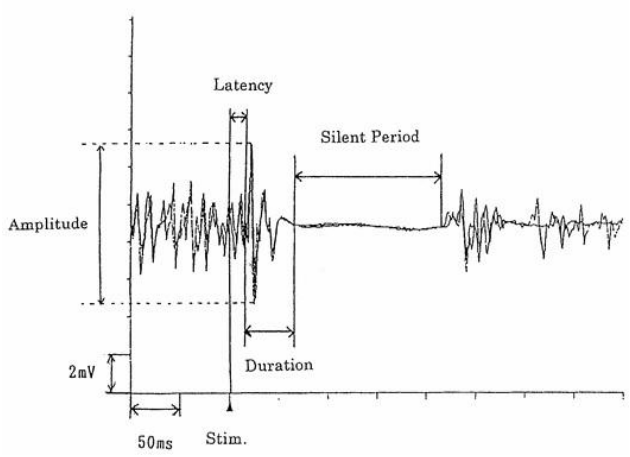

FIGURE 8. Silent period – a pause in the ongoing EMG activity following MEP (Suyama et al. 1996).

Execution of strictly unilateral movement is a result of complex interhemispheric interactions between comprehensive cortical areas (Beaulé et al. 2012). This interhemispheric inhibition (IHI) is mediated by transcallosal fibers passing through corpus callosum (CC) as it has been shown to be absent or it has delayed onset latency in patients with radiographical abnormalities in CC (Meyer et al. 1995, 1998). Corpus callosum is the largest white matter structure in the brain connecting homologous cortical areas of the two hemispheres and has a major role in the sensory, cognitive and motor information transfer (Perez and Cohen 2009). The modulation of unilateral movement through IHI appears to be crucial for restricting the unwanted mirror movement in the contralateral muscles (Beaulé et al. 2012). Studies done on animals have suggested that BL contraction is generated by simultaneous activation of the precentral motor cortex of both hemispheres (Tanji et al. 1988).

In his classic work Ferbert et al. (1992) applied two magnetic stimulators to the motor cortex of the human subjects and studied the effect of suprathreshold conditioning stimulus over one hemisphere on the size of the MEP by stimulation of the opposite hemisphere. When the ISI was 5-6 ms or longer they were able to observe an inhibition of the MEP. They named this phenomenon interhemispheric inhibition due to its short latency. Their findings were later confirmed by Di Lazzaro et al. (1999) who demonstrated IHI of the human motor cortex directly by recording the descending volleys with epidural electrodes implanted in human subjects. They were able to show that later I-waves (I3) were suppressed by application of paired-pulse paradigm.

Another approach to measure IHI is to assess a pause in the ongoing EMG activity in the ipsilateral muscles after the application of TMS, the so-called ipsilateral silent period (iSP) (Wassermann et al. 1991a; Ferbert et al. 1992; Giovannelli et al. 2009). This phenomenon is thought to be modulated via a transcallosal pathway (Wassermann et al. 1991b; Meyer et al. 1995) and has been suggested to help restrict motor output in the contralateral M1 (Beaulé et al. 2012). .

In the study of Ferbert et al. (1992), it was observed that the amount of IHI, recorded by paired-pulse paradigm of transcranial magnetic stimulation, increased in the relaxed right first dorsal interosseous muscle (FDI) when the left FDI was active at the same time, suggesting that there is a difference in voluntary control of BL versus UL contractions. They proposed that transcallosal connections could inhibit activity in one hand and thus secure strictly UL movement. Oda & Moritani (1995b) recorded movement-related cortical potentials (MRCPs) with electroencephalography during unilateral and bilateral maximal handgrip contractions. They showed that during the UL contractions the MRCPs were most prominent in the contralateral hemisphere. However, during BL contractions symmetrical MRCPs of lower amplitude were evident (Figure 9). This was later confirmed in another study done by the same researchers (Oda and Moritani 1996). In that study they also showed that a common drive exists between the motor cortices in the modulation of maximal BL contraction. They suggested that this common drive may be associated with the interhemispheric interactions possibly suppressing potentials of opposite hemispheres insofar that the amplitude of both MRCPs becomes very similar (Oda and Moritani 1996). These results suggest that the underlying mechanism of BLD is inhibition of the activity of the primary motor cortex. As already mentioned, an interesting finding from the study of Oda & Moritani (1995b) was that a greater deficit was shown in cortical activity in the non-dominant (left) arm, whereas a greater deficit in force and EMG was shown for the dominant (right) arm during BL handgrip contractions. As postulated by Oda (1997) this discrepancy indicates that the effect of change in the cortical activity in the right hemisphere is smaller than the effect of change in the left hemisphere. Oda (1997) also stated that possible contribution of decreased neural input to both the motor cortices or inhibitory mechanism in other brain stem pathways should be considered as an underlying mechanism of BLD.

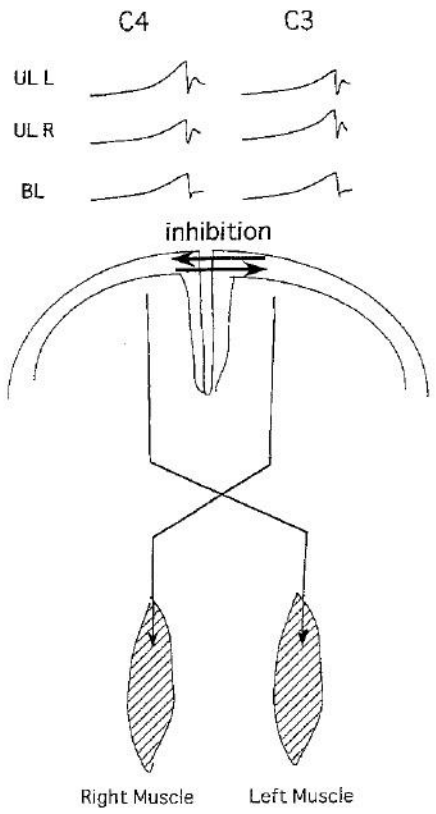

FIGURE 9. Interhemispheric inhibition and corresponding MRCPs during UL and BL handgrip contractions (Oda and Moritani 1995b).

Post et al. (2007) recorded brain activity with functional magnetic resonance imaging along with force and EMG recordings during UL and BL abductions of the index finger. They observed a significant decline in the blood oxygen dependent response in the precentral gyrus during BL actions, thereby decreasing the input to the primary motor cortex. This expands on the observation of Oda & Moritani (1995b) that the underlying mechanism of BLD is supraspinal, but its origin may be upstream of the primary motor cortex.

A recent study by Perez et al. (2014) examined iSP after TMS during UL or BL elbow flexion and extension. They showed than in both movements iSP depth and area, indices of IHI, were increased during BL compared to UL contractions. Their study was also in line with investigations of BL and UL contractions of the finger muscles, which have also shown that IHI is more pronounced during BL compared to UL contractions (Yedimenko and Perez 2010; Soteropoulos and Perez 2011). However, caution needs to be taken when interpreting their findings as the measurements were performed during low-force actions, i.e. 10-30% of MVC (Perez et al. 2014), and may not necessarily reflect motor control during MVC.

It appears that IHI can be altered with training as musicians have been shown to have lower IHI than controls (Ridding et al. 2000). Since BL strength training has been shown to reduce BLD (Häkkinen et al. 1996b; Taniguchi 1997, 1998; Kuruganti et al. 2005; Janzen et al. 2006; Beurskens et al. 2015) and since cross-sectional studies have shown that athletes involved in "bilateral" sports can exhibit BLF (Secher 1975; Howard and Enoka 1991), it is possible that IHI can be overcome with selective prescription of BL strength training exercises.

Archontides & Fazey (1993) also provided cortical explanation as to why BLD is limited to twin synchronous movement of homonymous limbs. They suggested that this is due to the fact that the area controlling flexor on one side of the body is not interconnected with the area that controls the extensor on one side of the body.

The existence of higher order neural inhibition is also supported by different magnitude of BLD in proximal compared to distal muscles (Aune et al. 2013). Aune et al. (2013) tested a theory that different levels of BLD will be observed in muscles with different anatomical and physiological characteristics. Since it has been shown that the amount of corticospinal projections is greater in distal compared to more proximal arm muscles (Kuypers 1978; Brouwer and Ashby 1992; Palmer and Ashby 1992), Aune et al. (2013) speculated that this could potentially result in smaller IHI. They were able to show that BI was greater in shoulder flexion (proximal) compared to index finger flexion (distal), thereby supporting the contribution of higher-order neural inhibition to BLD. Since they restricted the movement during the measurements so that only one degree of freedom could be performed their results suggest that the differences in BLD could not have been due to different postural stability requirements as suggested before (Herbert and Gandevia 1996; Magnus and Farthing 2008). However, they did not perform any direct measures of IHI (e.g. via EEG or TMS). Future studies should try to replicate their hypothesis with the inclusion of IHI measures to confirm the cortical mechanism.

3. 5 Methodological considerations

There are also some non-physiological factors that could contribute, at least to a certain degree, to the existence and/or magnitude of BLD. Buckthorpe et al. (2013) suggested that the methodological issues may play a role in determination of BLD. Since only a small number of UL and BL contractions are usually performed during the experiments

and the comparison is usually performed between the peak values, the results could potentially favor the UL performance (Buckthorpe et al. 2013). Therefore, it is suggested that future research considers calculation of BI by taking the average value of all trials as a representative of bilateral and unilateral forces, respectively.

It has also been suggested that since the BL actions rely on performance of two limbs at the same time it seems unlikely that both limbs operate at their highest force-producing capacity, which could contribute to BLD irrespective of physiology (Buckthorpe et al. 2013). Buckthorpe et al. (2013) tested this hypothesis by recording the unilateral forces during the BL actions and found no differences in force between the limbs. Similarly to Matkowski et al. (2011) they also found only a small onset of force discrepancy between the limbs, suggesting that the neuromuscular system is capable of almost simultaneous activation of both limbs during BL actions.

4 EFFECT OF TRAINING ON BILATERAL DEFICIT

Physiological alterations as a result of strength training have been shown to be very specific (Sale and MacDougall 1981). Therefore it is to be expected that the type of training performed has an effect on BLD. Available literature is consistent that BL training reduces BLD, while UL training increases it (Weir et al. 1995; Häkkinen et al. 1996b; Taniguchi 1997, 1998; Kuruganti et al. 2005; Janzen et al. 2006; Beurskens et al. 2015) . Interestingly, a 35-day bed rest did not affect the existence and magnitude of BLD (Rejc et al. 2015) despite previous findings suggesting that prolonged disuse alters MU recruitment pattern and activation strategy of the muscle (Duchateau 1995; Shinohara et al. 2003; Narici and De Boer 2011).

Cross-sectional studies of specific populations of athletes remain equivocal. Based on the longitudinal studies it should be expected that athletes involved in sports that regularly practice bilateral movements should exhibit reduced BLD. Howard & Enoka (1991) showed even bilateral facilitation in weightlifters. Similar findings were obtained by Secher (1975) who found bilateral facilitation in rowers. However, the existence of bilateral facilitation in their study was limited to the highly-experienced group, which consisted of Olympic medalists. The results of weightlifters in the study of Howard & Enoka (1991) could not be replicated by Secher et al. (1988) who found this specific group of athletes not to be different from untrained individuals. Schantz et al. (1989) was also not able to show any difference in BLD between trained and untrained people. A recent study compared female swimmers with untrained controls and showed that BLD was evident in both groups during the performance of the dynamic leg press exercise with no differences between groups (MacDonald et al. 2014). Since swimmers are involved in a “reciprocal” activity and since everyday activity (e.g. gait) is also reciprocal (Vandervoort et al. 1987) their results should have been expected. Interestingly, Pain (2014) observed BLD during drop jumps from different heights in peak force and peak power in elite endurance and power athletes, but the former exhibited bilateral facilitation in jumping height, while the latter showed BLD. Since endurance athletes are not involved in specific bilateral activities the author speculated that the results may be due to the protocol, in particular due to controlled single leg jumps and the choice of specific drop jumping heights (Pain 2014). The ambiguity of

the cross-sectional studies is possibly due to the specificity of testing. It has been suggested that the adaptations to training may be masked if the movement pattern of testing does not match the movement pattern used in training (Sale and MacDougall 1981). This could explain why Howard & Enoka (1991) showed bilateral facilitation, while Secher et al. (1988) did not, as the subjects comprising the weightlifting group in the former study had been performing maximal bilateral knee extension exercises 1 year prior to the experiment. Secher et al. (1988) did however note the decrease in BLD after familiarization with experimental apparatus, further supporting the need for testing specificity.

5 RELATIONSHIP BETWEEN BILATERAL DEFICIT AND ATHLETIC PERFORMANCE

It is currently still unclear what role does the magnitude of BLD of an individual play in his or her respective sport. The only investigation that tried to answer this question was done by Bračič et al. (2010) who investigated the relationship between BLD in the CMJ and sprint-start performance in elite sprinters. They showed that lower BLD values in the CMJ were associated with higher peak force production of the rear leg during the double sprint-start and higher total force impulse on the blocks. More studies are needed in different athlete populations to determine the relationship between BLD and performance. These studies would also help to clear up debate about whether certain athletes should train using BL or UL contractions. It would seem logical that since most sports require reciprocal movements (e.g. swimming, running) (Archontides and Fazey 1993) athletes competing in those sports should include predominantly UL actions into their training regimen.

6 PURPOSE

BLD has been studied extensively, but appears to be a highly variable and inconsistent phenomenon. Moreover, some experiments have even shown the existence of BLF (Secher 1975; Howard and Enoka 1991). The underlying mechanisms of the BLD phenomenon still remain poorly understood due to their complex nature.

Potential neurophysiological mechanisms have gained a lot of attention in the literature, but remain equivocal. While motor unit activation assessed by EMG has been shown to parallel force BLD in some studies, it has not in others (Table 1 and 2). Differences in VAL between UL and BL contractions have also been explored but conflicting evidence has been presented (Herbert and Gandevia 1996; Jakobi and Cafarelli 1998; Behm et al. 2003; Van Dieën et al. 2003; Matkowski et al. 2011). Higher-order neural inhibition may possibly be responsible for the phenomenon, but there is some ambiguity as to whether it is occurring at the cortical level, i.e. through the transcallosal pathway (Oda and Moritani 1995b), or upstream of the primary motor cortex (Post et al. 2007).

Bilateral and unilateral training have been shown to reduce and increase the magnitude of BLD, respectively (Weir et al. 1995; Häkkinen et al. 1996b; Taniguchi 1997, 1998; Kuruganti et al. 2005; Janzen et al. 2006; Beurskens et al. 2015). Thus, athletes in sports where BL contractions are performed exclusively (e.g. rowing, weightlifting) have been shown to exhibit BLF (Secher 1975; Howard and Enoka 1991). Conversely, athletes from sports where performance is ultimately limited by UL force production (e.g. high and long jumpers) may possibly exhibit a greater magnitude of BLD than untrained individuals. Therefore, studying these populations gives us a unique opportunity to study the neural inhibitory mechanisms as a possible underlying cause of BLD. It is of interest whether characteristics of inhibitory pathways are indicative of the magnitude of BLD. That is, if the interhemispheric inhibition is truly the underlying cause of BLD, then the presence or absence of BLD should be reflected in the nature of interhemispheric interaction during UL and BL contractions.

In the primary motor cortex, transcallosal inhibition can be assessed non-invasively with TMS by assessing iSP following ipsilateral stimulation (Ferbert et al. 1992). Interestingly, ipsilateral responses have not been studied extensively in the leg

musculature and evidence suggests that cortical control of lower and upper limb differs (Luft et al. 2002; Volz et al. 2015). Given the important role of lower limb musculature in locomotion, daily activities, and sports performance, the ipsilateral responses are worth considering in the leg musculature. Furthermore, cortical mechanisms have not yet been studied in lower limb musculature in relation to potential differences between UL and BL contractions, and more specifically to the BLD phenomenon.

The purpose of this study was two-fold. Firstly, the purpose was to investigate whether there are differences in corticospinal and transcallosal modulation between UL and BL contractions of lower limbs, and if this modulation differs between the bilaterally- and unilaterally-dominant athletes. Secondly, the purpose was to investigate if the magnitude of BLD, which we hypothesized to be different between groups, is reflected in the nature of corticospinal and transcallosal responses. To further investigate the latter, subjects were grouped post hoc according to whether they exhibited BLF or BLD.

7 METHODS

7. 1 Subjects

Twenty male subjects were recruited for the study (referred to as ALL). Additionally, they were separated into three groups according to the nature of their activity (referred to as athlete groups, AG for short). The bilateral group (BG) consisted of weightlifters (n = 5) and powerlifters (n = 2) who had been competing in their respective sport for at least two years. The unilateral group (UG) consisted of high jumpers (n = 1) and long jumpers (n = 4) who had been competing in their respective sport for at least two years. The control group (CG) included subjects who were physically active but had not been involved in a structured program of physical activity in the past two years. We recognize that splitting the subjects in groups may result in small size per group and thereby affect our statistical power. However, researchers that have studied neuromuscular responses in high-level athletes have used a similar number of subjects before (Howard and Enoka 1991; Maffiuletti et al. 2001; Avela et al. 2006). Additional analysis was performed by splitting subjects post hoc into two groups depending on whether they exhibited BLD (n = 14) or BLF (n = 6) according to the bilateral index (referred to as BI groups, BIG for short). Subject details are listed in Table 5. The exclusion criteria for all groups included suffering from any cardiovascular, neurological or neuromuscular disorders, musculoskeletal injury that may attenuate the ability to produce maximal force, and taking any medications known to affect the nervous system. To ensure their safety subjects were also screened for contraindications for TMS (Rossi et al. 2009). Lateral preference was assessed using a lateral preference inventory (Coren 2013) modified for lower limbs only. Subjects were instructed to refrain from alcohol, caffeine and exhaustive exercise for 24, 12, and 48 hours before the experiment, respectively (O'Leary et al. 2015). Moreover they were naïve to the existence of BLD phenomenon and the purpose of the study. Subjects were informed of all the experimental procedures and risks associated with the measurements and provided written consent prior to participation. All of the procedures of the study were in accordance with Declaration of Helsinki. Republic of Slovenia National Medical Ethics Committee approved the study.

TABLE 5. Subject details.

	n	Age (yrs)	Height (cm)	Body mass (kg)	Activity level (h/week)	Training age (yrs)
All	20	23.6 ± 3.9	180.1 ± 5.6	79.8 ± 13.0	8.7 ± 5.1	/
BG	7	26.0 ± 5.2	178.9 ± 6.8	90.0* ± 14.6	13.3† ± 2.1	5.6* ± 3.4
UG	5	21.4 ± 2.8	181.6 ± 5.2	70.9 ± 5.9	10.4† ± 1.8	10.4 ± 1.7
CG	8	22.9 ± 1.9	180.1 ± 5.2	76.4 ± 9.2	3.5 ± 3.5	/
BLD	14	23.4 ± 4.3	181.1 ± 5.8	81.1 ± 14.2	8.8 ± 5.1	/
BLF	6	24.0 ± 3.0	177.5 ± 4.5	76.8 ± 10.0	8.3 ± 5.7	/

Values as means ± SD. All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, WL = weightlifter, PL = powerlifter, LJ = long jumper, HJ = high jumper, BLD = exhibited bilateral deficit, BLF = exhibited bilateral facilitation, * significantly different than UG, † significantly different than CG

7. 2 Study design

All subjects reported to the laboratory for the familiarization session during which anthropometric measures (height and weight) were assessed and test apparatus was set according to the anthropometry of the individual. Furthermore, TMS and femoral nerve stimulations were performed to familiarize the subjects with the procedure. The subjects proceeded to practice the performance of MVC during UL and BL isometric knee flexion and extension, with and without TMS and electrical stimulation. Familiarization was deemed completed when subjects were able to maintain a torque plateau for approximately 3 seconds and when their performance was not attenuated by stimulation. At least 48 hours after familiarization the subjects returned to the laboratory for the experimental session. The experimental protocol consisted of three randomized parts designed to test corticospinal and transcallosal modulation, and the level of voluntary

activation, during BL and UL isometric knee extensions. Each part was separated by 10-minute rest to avoid fatigue from repeated maximal contractions. The experimental protocol was preceded by a standardized warm-up consisting of four UL (two with the left and two with the right leg) and two BL knee extensions and flexions, respectively, at 50% and 80% of perceived MVC, respectively. Additionally the subjects performed a MVC accommodation trial both unilaterally and bilaterally to eliminate the effect of post-activation potentiation. After the warm-up the subjects performed two to three knee flexion MVCs for biceps femoris (BF) EMG normalization, which was followed by a 10-minute period of rest. During each part of the experimental protocol the subjects were asked to perform UL and BL knee extension MVCs in a randomized order two times while receiving either TMS or electrical stimulation of the femoral nerve. If the torque was greater during the second trial compared to the first one, a third trial was performed. MVCs were separated by a 2-minute rest to avoid fatigue and to ensure maximal force production. A graphic representation of the experimental protocol is depicted in Figure 10. All randomizations in the experiment were performed using a computer-based random number generator.

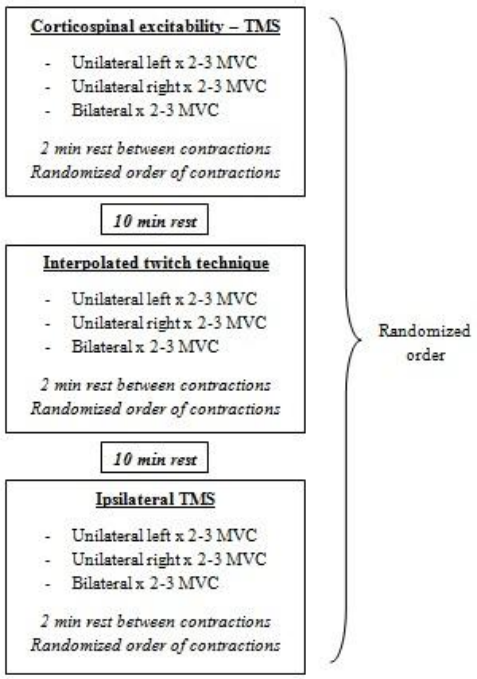

FIGURE 10. Experimental protocol.

7.3 Torque measurements

During the experimental protocol subjects were seated in a custom-made isometric leg extension chair with built-in force transducer (MES, Maribor, Slovenia). The knee and hip joint angles were set at 60 and 110 degrees, respectively. The knee joint angle used is close to the optimal muscle length for maximal force production (Becker and Awiszus 2001). Furthermore, BLD in knee extension has been most consistently shown at intermediate muscle lengths. The subjects were strapped into the chair against the pad, at the pelvis, chest and over the distal part of the thigh to prevent movement of the trunk and pelvis, and had their arms folded across the chest (Figure 11). That way the stability requirements and contribution of synergist muscles were controlled, which has been shown to affect the BLD phenomenon (Magnus and Farthing 2008). The lever axis of the device was aligned with the center of the knee joint and the pad of the lever arm was positioned approximately 2-3 cm above lateral malleolus. Subjects were verbally encouraged during MVCs and had their force level displayed on a computer screen to provide feedback for maximal expression of effort (Gandevia 2001). Subjects were asked to perform the contractions for approximately 3 seconds. During UL contractions the non-active leg remained strapped against the pad, but was kept relaxed, which was monitored by the investigators via corresponding EMG activity. Subjects were further instructed to try not to activate the contralateral leg during UL contractions and try to maintain a constant torque level despite the stimulation. The electrical data from the force transducer were A/D converted at a sampling rate of 1000 Hz (MKII 1401, Cambridge Electronic Design Limited, Cambridge, UK) and recorded on a computer for subsequent analysis (Spike 2 v6.17, Cambridge Electronic Design Limited, Cambridge, UK). Force signals were converted to torque values (Nm) by calibrated conversion factors obtained prior to the experiment.

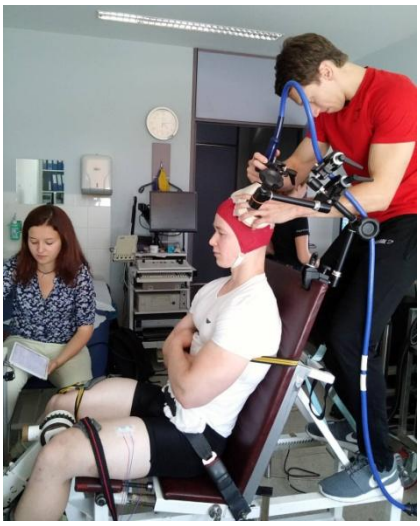

FIGURE 11. Experimental setup.

7. 4 Femoral nerve stimulation

Rectangular electrical stimuli with pulse duration of 1 ms were delivered to the femoral nerve by a constant-current stimulator (Model DS7A, Digimeter Ltd., Hertfordshire, UK). Self-adhesive rectangular neurostimulation electrodes (5x5 cm; Axelgaard Manufacturing Co. Ltd., Fallbrook, CA, USA) were used. Cathode was placed in the femoral triangle, 3-5 cm below the inguinal ligament, and the anode was placed on the greater trochanter. The optimal stimulation intensity was determined in resting muscles by increasing the intensity about every 10 seconds until a torque plateau and maximal compound action potential (M_{max}) were achieved. Once the optimal intensity was found it was further increased by 25%, to ensure that it was supramaximal, and was kept constant throughout the experimental session. The optimal intensity to elicit M_{max} was determined in both left and right vastus lateralis (VL) in a randomized order. During the experiment the superimposed doublet with interstimulus interval of 10 ms was delivered over the isometric torque plateau followed by potentiated doublet approximately 2 seconds after each MVC to assess maximal voluntary activation level according to the interpolated twitch technique (Merton 1954). During BL contractions the stimulation was performed in the right leg only.

7. 5 Transcranial magnetic stimulation

A Magstim 200^2 transcranial magnetic stimulator (Magstim Co., Ltd., UK) with concave double-cone coil (110-mm diameter) was used to elicit motor evoked potentials (MEPs) in the VL muscle. TMS of the knee extensors has been shown to have good reliability and small between- and within-day variability (Sidhu et al. 2009; O'Leary et al. 2015). The junction of the coil was aligned with the sagittal plane, the center of the coil was placed 1 cm lateral of the vertex and oriented to induce current in posterior-to-anterior direction (Sidhu et al. 2009). From there the coil was moved in 1 cm steps in lateral-medial and anterior-posterior direction to identify the optimal location (hotspot), which was defined as the one eliciting greatest VL MEP amplitude with minimal BF MEP amplitude (less than 50% of VL MEP). The optimal location was determined with 40-60% of the maximum stimulation output. Upon identification the hotspot was immediately marked with a permanent marker on a firmly attached electroencephalography cap. Additionally, the constant coil position was maintained with a custom-made coil holder (Figure 2) and was constantly being checked after each contraction trial. Despite using the coil holder, the same experimenter held the coil manually as well and was monitoring its position visually due to movement of the subject during maximal contractions. The optimal position was identified for both left and right leg area of the motor cortex in a randomized order. Following identification of the hotspot, resting motor threshold (rMT) was determined for both left and right leg area of the motor cortex in a randomized order. Resting motor threshold was defined as the minimum stimulus intensity that elicited reproducible MEPs of at least 50 μV in 3 out of 5 trials (Rossini et al. 1994).

Single pulse TMS was applied during MVCs over the isometric plateau. During the investigation of corticospinal modulation TMS was elicited at an intensity of 120% rMT and responses of the target muscle contralateral to the stimulating site were investigated. During BL contractions the right primary motor cortex (M1) was stimulated to elicit MEPs in the left leg. During investigation of transcallosal modulation the ipsilateral TMS technique was employed at an intensity of 180% rMT (Irlbacher et al. 2006). During UL contractions the responses from the active, non-target muscle were investigated. During BL contractions the right M1 was stimulated and the responses of the ipsilateral (right) leg were analyzed.

In two subjects we were unable to perform ipsilateral TMS technique due to high rMT. Therefore, they were excluded from the analysis of ipsilateral responses. One of them belonged to CG and BLD groups, respectively, while the other belonged to BG and BLF groups, respectively.

7. 6 Electromyography

Surface electromyography (EMG) of VL and lateral head of BF was measured using self-adhesive circular bipolar surface electrodes (Natus Neurology Inc., Middleton, WI, USA; pre-gelled Ag/AgCl material, 10 mm diameter, 20 mm inter-electrode distance, < 2 kΩ inter-electrode impedance) with the ground electrode placed on the patella. The electrodes were placed, according to the SENIAM recommendations (Hermens et al. 2000), for VL on the belly of the muscle at two-thirds of the distance between anterior supine iliaca and lateral side of the patella and oriented in the direction of the muscle fibers, and for BF on the belly of the muscle at half of the line between the ischial tuberosity and the lateral epicondyle of the tibia in the direction of this line. The BF activity was recorded to monitor antagonist activation. The skin preparation included shaving, light abrasion of the skin and subsequent cleaning with alcohol to ensure appropriate electrode resistance (< 2 kΩ). After the placement, the electrodes were additionally taped to ensure proper fixation. Cables were fixed underneath the chair to avoid movement artifacts. EMG signals were A/D converted (Micro3 1401, Cambridge Electronic Design Limited, Cambridge, UK) band-pass filtered (20-2000 Hz), amplified (x 1000) and sampled at 5000 Hz with an amplifier (D360, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) . The EMG data was stored on a computer (Spike 2 v6.17, Cambridge Electronic Design Limited, UK) and subsequently analyzed off-line (MATLAB, The MathWorks Inc. Natrick, MA, USA).

7. 7 Data analysis

7. 7. 1 Torque

Maximal (peak) torque was defined as the greatest torque achieved either before or after the stimulation. Peak torque values for BL and UL contractions were used for

determination of BLD in force production. Thereafter, the bilateral index (BI) in force was calculated as BI_F (%) = [100 x (bilateral / (right unilateral + left unilateral))] – 100 (Howard & Enoka 1991). The positive BI_F is indicative of BLF, while the negative value indicates BLD. Furthermore, average peak torque out of six best contraction trials of the same contraction mode was calculated and subsequently used to calculate average bilateral index (aBI_F), since it has been suggested that using only the peak value may favor unilateral performance and consequently affect BLD (Buckthorpe et al. 2013).

7. 7. 2 Electromyographic activity

VL EMG activity was quantified with root mean square (RMS) values of the EMG signal over a 500 ms interval prior to the stimulation point and normalized to M_{max} of the same contraction mode (VL RMS) to account for peripheral alterations (Place et al. 2007; Duclay et al. 2014). Peak VL RMS values for BL and UL contractions were considered for the analysis of BI in EMG activity (BI_E). Furthermore, average BI of EMG (aBI_E) activity was calculated by averaging VL RMS of six best contraction trials of the same contraction mode. The 'bilateral' part of BI equation was taken as the summation of the left and the right VL RMS during BL contractions. Antagonist activation was quantified with BF RMS normalized to the peak BF EMG signal over a 500 ms interval obtained during peak flexion MVC torque for each leg separately.

7. 7. 3 Voluntary activation level

According to the interpolated twitch technique voluntary activation level (VAL) was calculated with the linear equation: Voluntary activation level (VAL %) = [1 – (superimposed doublet amplitude / potentiated doublet amplitude)] x 100 (Allen et al. 1998; Place et al. 2007), with the superimposed doublet amplitude being the torque increment observed during the contraction at the point of stimulation and potentiated doublet amplitude being the torque evoked in the relaxed muscle 2 seconds after the superimposed stimulation. A correction was employed if the superimposed doublet was not delivered during the instance of the peak torque (Strojnik and Komi 1998). Typical recording of torque, EMG and VAL are depicted in Figure 12.

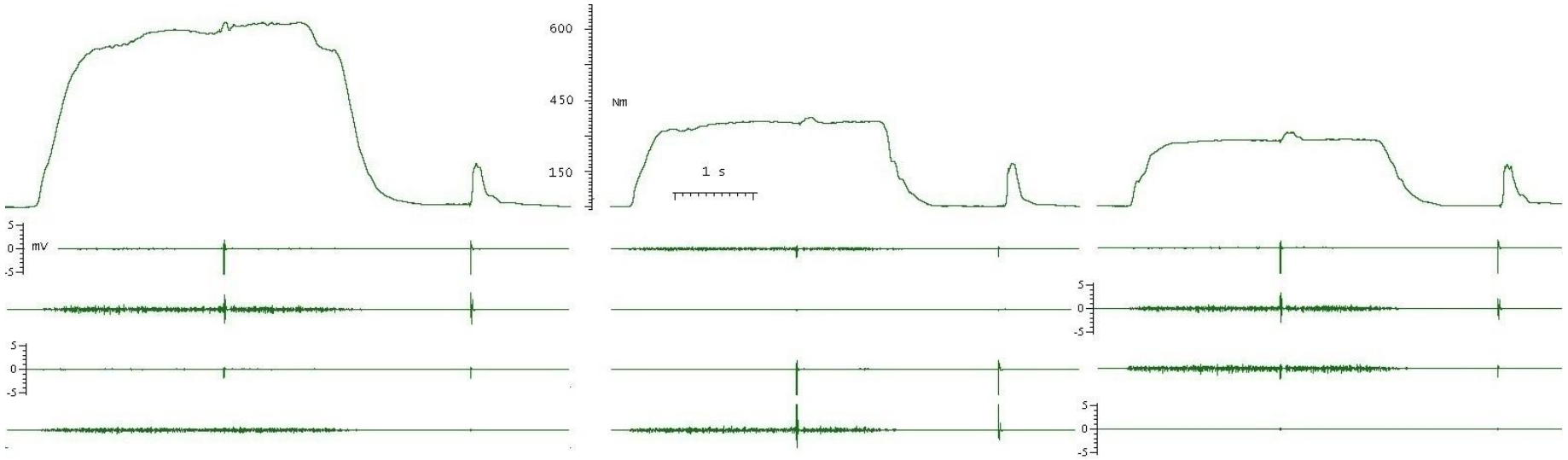

FIGURE 12. Typical torque (upper row) and filtered EMG recordings during BL (left column), UL left (middle column) and UL right (right column) contractions while electrical stimulation of the peripheral nerve was performed for one subject. Right BF, right VL, left BF and left VL in descending order are shown for EMG traces. This particular subject belonged to BG and BLF groups, respectively, exhibiting BI_F and aBI_F of 16.30 and 19.54, respectively. His VAL values were 97.52, 93.77 and 89.07, for BL, UL left and UL right, respectively. Time calibration is 1 second.

7. 7. 4 Motor evoked potentials

Peak-to-peak amplitudes and areas of motor evoked potentials induced by contralateral (MEPs) and ipsilateral stimulations (iMEPs) were calculated between initial deflection of the EMG from baseline to the second crossing of the horizontal axis (Gruber et al. 2009). Peak-to-peak amplitudes and areas were similar and correlated significantly (Spearman's rank correlation coefficient: $p < 0.001$, $r = 0.805 – 0.950$ and $p < 0.001$, $r = 0.938 – 0.942$, for MEPs and iMEPs, respectively), thus only the peak-to-peak amplitudes are reported. MEP amplitudes were normalized to M_{max} amplitudes corresponding to the same contraction mode. Due to natural occurring variability of MEPs, two best trials at each contraction mode were averaged for every subject. Additionally, the ratio R (= iMEP / MEP) was calculated (Bawa et al. 2004).

7. 7. 5 Maximum compound action potential

Peak-to-peak amplitudes and areas of M_{max} during the contractions were analyzed as the second M-wave of the doublet (Löscher et al. 1996; Matkowski et al. 2011) and subsequently used for normalization of the VL RMS, MEPs and iMEPs. M_{max} value was taken as the average of all trials of the same contraction mode.

7. 7. 6 Cortical silent period

Cortical silent periods (CSP) in the ongoing EMG activity following TMS were analyzed to assess the contribution of intracortical inhibition. The duration of CSP was defined as the time interval between the stimulus artifact and the return of the continuous EMG activity (Damron et al. 2008) (Figure 13A). CSP presented are the average value of two best trials per contraction mode (Groppa et al. 2012). In some cases CSP was interrupted by a short burst of EMG activity. To deal with ambiguity of the end of CSP the following criteria was applied: If EMG activity reached the pre-TMS level and lasted for at least 50 ms it marked the end of SP (Groppa et al. 2012).

7. 7. 7 Ipsilateral silent period

Ipsilateral silent periods (iSP) were analyzed to assess the contribution of transcallosal inhibition (Ferbert et al. 1992). Similar to SP the duration of iSP was defined between the stimulus artifact and the return of the continuous EMG activity (Figure 13B).

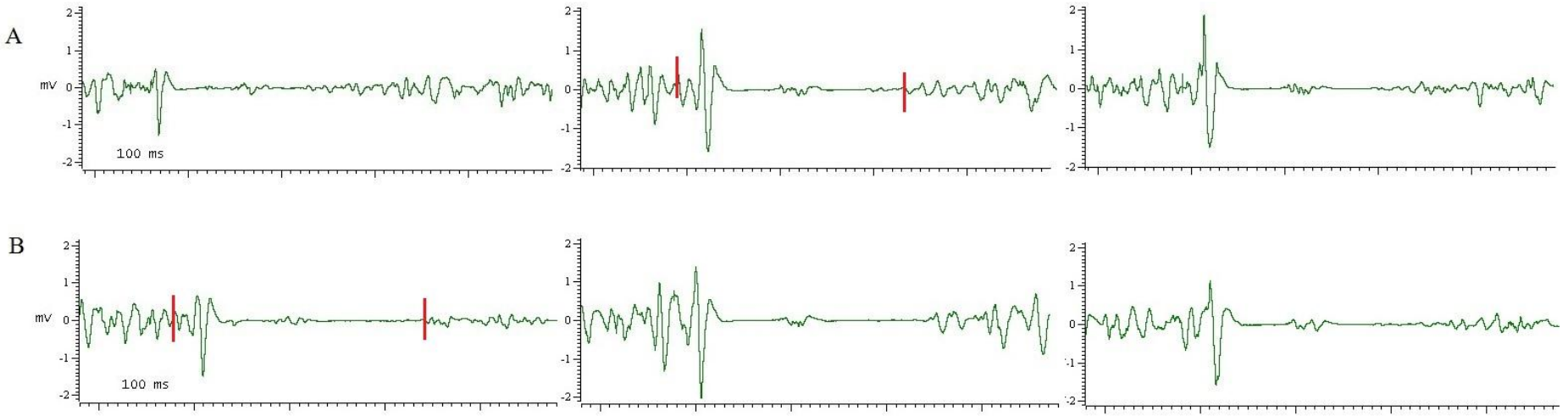

FIGURE 13. Typical electromyographic responses of vastus lateralis to contralateral (A) and ipsilateral (B) transcranial magnetic stimulation during UL left (left column), UL right (middle column) and BL (right column) contraction for one subject. The red lines denote the examples of the onset and the end of silent periods. This particular subject belonged to CG and BLD groups, respectively, exhibiting BI_F and aBI_F of – 1.72 and – 6.71, respectively. His MEP amplitudes normalized to M_{max} were 0.46, 0.75 and 0.94, and his iMEP amplitudes were 0.64, 0.74 and 0.82, for UL left, UL right and BL contractions, respectively. His CSP durations were 184.8, 200.0 and 204.5 ms, and his iSP durations were 225.6, 247.9, and 202.1 ms, for UL left, UL right and BL contractions, respectively. Time calibration is 100 ms.

7. 8 Statistical analyses

Data are presented as means ± SD unless stated otherwise. All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at an alpha level of 0.05. Normality of the data was assessed using Shapiro-Wilks test. If the data was not normal, transformations were performed. For positively skewed data common logarithm was used and natural logarithm was used to transform negatively skewed data. One-way analysis of variance (ANOVA) with Bonferroni post-hoc tests was used to compare differences between AG in the initial status of the subjects (age, height, weight, peak force and activity levels, respectively), and differences between AG in BI_F, aBI_F, BI_E and aBI_E. Independent samples T-test was used to compare training age between the two groups of athletes (BG and UG), differences between BIG in the initial status of the subjects, and differences between BIG in BI_F, aBI_F, BI_E and aBI_E . One sample T-test was used to compare BI_F and aBI_F, and BI_E and aBI_E, respectively, with zero, and R ratios with 1. Paired-samples T-test was used to compare the differences in BI_F and aBI_F, and BI_E and aBI_E. Pearson product-moment correlation coefficient was used to investigate the parallelism between BI_F, aBI_F, BI_E, and aBI_E. A 3(2) x 3 mixed ANOVA (1 between-subject factor – group – BG, UG, and CG, and BLD and BLF, respectively; 1 within-subject factor – contraction mode, i.e. unilateral left, unilateral right, bilateral) was used to compare differences in VA, MEP, iMEP, R, CSP, iSP, and TCT between groups (either AG or BIG) and a repeated measures ANOVA was used to compare the differences in VA, MEP, iMEP, R, CSP, iSP, between different contractions modes (left, right and bilateral, respectively) for ALL. A 3(2) x 2 x 3 mixed ANOVA (2 between-subject factors – group and leg dominance, 1 within-subject factor – contraction mode) was used to investigate and compare the effect of leg dominance on VA, MEP, iMEP, CSP, iSP, and TCT between groups (either AG or BIG) and a 2 x 3 mixed ANOVA (1 between subject factor – leg dominance, 1 within-subject factor – contraction mode) was used to investigate the effect of leg dominance on VA, MEP, CSP, iSP of ALL. A repeated measures ANOVA (UL left, UL right, left BL, right BL) and a 3(2) x 4 mixed ANOVA (1 between-subject factor – group, 4 within-subject factors – UL left, UL right, left BL,

right BL) was used to compare differences in VL EMG for ALL and between groups, respectively. A repeated measures ANOVA (UL left/right, UL right/left, left BL, right BL) and a 3(2) x 4 mixed ANOVA (1 between-subject factor – group, 4 within-subject factors – UL left/right, UL right/left, left BL, right BL) was used to compare differences in ipsilateral and contralateral antagonist activation for ALL and between groups, respectively. In the cases of mixed or repeated measures ANOVA, the analysis was continued with post hoc testing including pairwaise t-tests with Bonferonni correction if an interaction was found. Pearson product-moment coefficient was used to investigate correlations between cMEP and iMEP, and CSP and iSP. To investigate the possible effect of fatigue during the session a separate 1-way repeated-measures ANOVA was performed for all trials of UL left, UL right and BL contraction force, respectively. If significant effect of time was detected, the post hoc pairwise comparison was performed with a Boneferroni correction for multiple comparisons. For all analysis using ANOVA sphericity was assessed using Mauchly's test of sphericity. If it was found to be violated, Greenhouse-Geisser correction was employed. Within-session reliability of the unilateral and bilateral contractions force was calculated using 2-way mixed-effect models intraclass correlation coefficient ($ICC_{3,1}$) for absolute agreement (Shrout & Fleiss 1979). Additionally the ICC 95% confidence intervals (95% IC) were also calculated. An ICC $\geq$ 0.8 was considered good reliability and an ICC $\geq$ 0.6 was accepted as reliable (O'Leary et al. 2015). Coefficient of variation (CV) was calculated for MVC using the following formula: SD / mean x 100 (O'Leary et al. 2015). For a better representation of absolute reliability for all individuals SD of CV was also reported (Atkinson & Nevill 1998).

8 RESULTS

8. 1 Initial status of the subjects

Subject details are reported in Table 5. All three athlete groups were of similar age, height, and leg extension strength levels ($p > 0.05$). However, there were statistically significant differences in weight ($F (2, 17) = 26.303$, $p < 0.024$) and activity level ($F (2, 17) = 26.303$, $p < 0.001$). A post-hoc analysis showed that BG was significantly heavier than UG ($p = 0.024$), and both BG and UG were significantly more physically active than CG ($p < 0.001$ and $p = 0.001$, respectively). There were differences in the years of participation insofar as UG had been competing in their respective sport longer than BG ($t (10) = - 2.936$, $p = 0.015$). No differences were noted between BI groups for any of the variable ($p > 0.05$).

8. 2 Within-session reliability and variability of the force and EMG measurements

MVC. No effect of the number of trials on MVC during the experimental session was observed for UL left, UL right, and BL contractions. UL left, UL right, and BL MVC all demonstrated good reliability (ICC ≥ 0.85, ≥ 0.90, and ≥ 0.92, respectively) and small variability (CV ≤ 7.9 %, ≤ 9.0 %, and ≤ 5.3%, respectively) (Table 2).

EMG responses from vastus lateralis muscle. VL EMG data obtained from the left leg was considered reliable (ICC ≥ 0.69 and ICC ≥ 0.64 for UL and BL contractions, respectively). On the other hand, EMG obtained from the right leg did not satisfy the reliability criteria (ICC ≥ 0.53 and ICC ≥ 0.59 for UL and BL contractions, respectively). VL EMG data demonstrated lower reliability than MVC, but was consistent between the legs (Table 2).

EMG responses from biceps femoris muscle. Measures of BF RMS demonstrated good reliability with the exception being the right leg during UL contractions, which did not satisfy the reliability criteria (Table 2). However, variability of BF RMS was considered high and even very high in some cases (ULR and URL, Table 2).

TABLE 6. Within session reliability of MVC and EMG.

		Reliability indices	
Variables	Contractions	$ICC_{3,1}$ (95% CI)	CV (%, mean ± SD)
MVC	ULL	0.85 (0.74 – 0.93)	7.9 ± 4.2
	ULR	0.90 (0.81 – 0.95)	9.0 ± 4.1
	BL	0.92 (0.85 – 0.96)	5.3 ± 3.6
VL RMS	ULL	0.69 (0.52 – 0.85)	17.3 ± 9.3
	URR	0.53 (0.34 – 0.74)	18.0 ± 12.7
	BLL	0.64 (0.45 – 0.82)	21.6 ± 13.3
	BLR	0.59 (0.39 – 0.79)	19.2 ± 15.1
BF RMS	ULL	0.85 (0.75 – 0.93)	18.9 ± 16.8
	ULR	0.56 (0.36 – 0.76)	57.6 ± 31.1
	URL	0.63 (0.45 – 0.80)	54.4 ± 36.7
	URR	0.93 (0.87 – 0.97)	20.5 ± 15.2
	BLL	0.81 (0.68 – 0.92)	26.2 ± 20.4
	BLR	0.92 (0.86 – 0.97)	29.9 ± 27.7

CV – coefficient of variation; $ICC_{3,1}$ – intraclass correlation coefficient, equation 3,1; CI – confidence interval; MVC – maximal voluntary contraction force; RMS VL – Root mean square EMG of vastus lateralis muscle normalized to the M_{max}, RMS BF – Root mean square EMG of biceps femoris muscle normalized to the M_{max}; ULL – left leg during unilateral contraction of the left leg; ULR – right leg during unilateral contraction of the left leg; URL - left leg during unilateral contraction of the right leg; URL - right leg during unilateral contraction of the right leg; BL – bilateral; BLL – left leg during bilateral contraction; BLR – right leg during bilateral contraction.

8. 3 Bilateral index

Bilateral index in force. BI_F of ALL was significantly lower than 0 (t (19) = - 2.918, p = 0.009), indicating BLD, but aBI_F was not. BI_F of ALL was significantly smaller than aBI_F (t (19) = -3.917, p < 0.001). There were no between-group differences in BI_F and aBI_F for AG. None of the groups had BI_F and aBI_F significantly different than 0. BI_F was significantly smaller than aBI_F for BG (t (6) = - 4.707, p = 0.003), but not UG and CG (Table 7).

Bilateral index in EMG activity. Both BI_E and aBI_E p of ALL were not significantly different than 0 (Table 8). No differences between AG were noted both for BI_E and aBI_E. No differences were observed between BIG for BI_E and aBI_E. All athlete groups and both BI groups had BI_E and aBI_E that were not significantly different than 0. No differences were noted between BI_E and aBI_E for ALL or any of the groups taken separately. No correlations were observed between force and EMG BIs regardless of subject grouping.

TABLE 7. Maximal unilateral and bilateral forces, bilateral index in force, average bilateral index in force.

	ULpF (Nm)	URpF (Nm)	BLpF (Nm)	BI_F (%)	aBI_F (%)
All	453.33 ± 119.41	467.27 ± 155.87	855.63 ± 148.19	- 8.76*† ± 13.43	- 4.60 ± 12.62
BG	495.00 ± 117.28	513.38 ± 116.26	926.16 ± 81.59	- 11.64† ± 16.05	- 5.82 ± 16.51
UG	491.00 ± 139.52	437.42 ± 133.08	857.51 ± 204.39	- 11.48 ± 10.50	- 5.07 ± 6.46
CG	408.33 ± 104.06	445.57 ± 202.34	792.75 ± 143.30	- 4.54 ± 13.10	- 3.24 ± 13.07

Values as means ± SD. All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, ULpF = peak unilateral force of the left leg contraction, URpF = peak unilateral force of the right leg contraction, BLpF = peak force of the bilateral contraction, BI_F = bilateral index in force, aBI_F = bilateral index in force – average of 6 trials per mode. *Significantly different than 0, † significantly different than aBI_F of the same population.

8. 4 Muscle activation (EMG)

EMG responses from the agonist muscle. EMG values for UL left, UL right, and BL contractions are reported in Table 8. Significant main effect for contraction mode was observed for peak VL RMS ($F(1.518, 28.835) = 4.168$, $p = 0.035$, $\eta_p^2 = 0.180$) of ALL. However, post hoc testing did not reveal any differences. There was no significant interaction between VL RMS and leg dominance of ALL. There was also no significant interaction between contraction mode and AG for peak VL RMS. Furthermore, no significant main effects were found for either contraction mode or AG. No significant

interaction was found for contraction mode and BIG for peak VL RMS. Main effects for contraction mode and BIG were also not significant. No effect of leg dominance was observed regardless of subject grouping.

TABLE 8. Peak unilateral and bilateral RMS VL values bilateral index in EMG and average bilateral index in EMG.

	UL (au)	UR (au)	BLL (au)	BLR (au)	BI_E (%)	aBI_E (%)
All	11.76 ± 0.72	12.23 ± 0.91	11.81 ± 0.94	12.09 ± 0.91	- 2.67 ± 14.22	- 3.69 ± 13.92
BG	11.55 ± 0.41	12.01 ± 0.82	11.47 ± 0.37	11.95 ± 0.77	- 2.77 ± 12.24	- 2.02 ± 12.04
UG	12.45 ± 0.66	12.89 ± 1.21	12.51 ± 1.04	12.72 ± 1.28	- 3.01 ± 17.07	- 2.03 ± 12.04
CG	11.51 ± 0.75	12.01 ± 0.65	11.66 ± 1.08	11.82 ± 0.65	- 2.37 ± 15.94	- 5.12 ± 16.51
BLD	11.77 ± 0.75	12.39 ± 0.98	11.75 ± 0.92	12.15 ± 0.97	- 5.93 ± 13.77	- 7.52 ± 13.54
BLF	11.74 ± 0.71	11.86 ± 0.65	11.93 ± 1.06	11.95 ± 0.84	4.94 ± 13.28	5.25 ± 11.11

Values as means ± SD. au = arbitrary units, All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, UL = peak VL RMS of the left leg during unilateral contraction of the same leg, UR = peak VL RMS of the right leg during unilateral contraction of the same leg, BLL = peak VL RMS of the left leg during bilateral contraction, BLR = peak VL RMS of the right leg during bilateral contraction, BI_E = bilateral index, aBI_E = bilateral index – average of 6 trials per mode. *Significantly different than 0, † significantly different than aBI of the same population.

EMG responses from the antagonist muscle. A significant main effect for contraction mode was noted for ipsilateral activation of antagonist muscle ($F(3, 57) = 3.408$, $p = 0.023$, $\eta_p^2 = 0.152$) for ALL. Post hoc testing showed that peak ipsilateral BF RMS activity was smaller during UL left compared to the right leg during BL contraction ($p = 0.030$). No significant main effect for contraction mode was found for contralateral activation of antagonist (Table 9). No significant interaction between contraction mode and AG for ipsilateral activation of antagonist was noted. A significant main effect was found for contraction mode ($F(3, 51) = 2.838$, $p = 0.047$, $\eta_p^2 = 0.143$), but post hoc

testing did not reveal any significant differences in peak ipsilateral BF RMS activity between contraction modes. No main effect for AG was noted. There was also no significant interaction between contraction mode and AG for contralateral activation of antagonist. No effect of either contraction mode or AG was noted for contralateral peak BF RMS activity (Table 9). No significant interaction between contraction mode and BIG was noted for ipsilateral activation of antagonist. A significant main effect for contraction mode for ipsilateral coactivation was observed ($F (3, 54) = 4.981$, $p = 0.004$, $\eta_p^2 = 0.217$). Post hoc testing showed that peak BF RMS activity was smaller during UL left compared to the right BL contraction ($p = 0.007$). A significant main effect for BIG was also noted ($F (1, 18) = 5.502$, $p = 0.031$, $\eta_p^2 = 0.234$) (Table 9). No significant interaction between contraction mode and BIG was also noted for contralateral activation of antagonist. No significant main effect for contraction mode was observed. A significant main effect for BIG was noted ($F (1, 18) = 10.016$, $p = 0.005$, $\eta_p^2 = 0.358$) (Table 9). No effect of leg dominance was observed either for ipsilateral or contralateral antagonist activation, respectively, regardless of subject grouping.

TABLE 9. Peak unilateral and bilateral RMS BF values.

	ULL	ULR	URL	URR	BLL	BLR
All	0.29 ± 0.23	0.50 ± 0.50	0.55 ± 0.47	0.38 ± 0.37	0.35 ± 0.21	0.46 ± 0.41*
BG	0.29 ± 0.25	0.47 ± 0.44	0.54 ± 0.56	0.37 ± 0.32	0.39 ± 0.23	0.51 ± 0.43
UG	0.22 ± 0.94	0.54 ± 0.54	0.47 ± 0.40	0.36 ± 0.32	0.33 ± 0.21	0.26 ± 0.10
CG	0.34 ± 0.28	0.49 ± 0.49	0.60 ± 0.50	0.41 ± 0.48	0.33 ± 0.20	0.54 ± 0.50
BLD	0.23 ± 0.17	0.32 ± 0.39	0.42 ± 0.39	0.25 ± 0.17	0.30 ± 0.15	0.32 ± 0.24*
BLF	0.42 ± 0.32†	0.90 ± 0.38†	0.85 ± 0.55†	0.69 ± 0.55†	0.47 ± 0.28†	0.78 ± 0.56*†

Values as means ± SD. au = arbitrary units, All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, ULL = peak BF RMS of the left leg during unilateral contraction of the left leg, ULR = peak BF RMS of the right leg during unilateral contraction of the left leg, URL = peak BF RMS of the left leg during unilateral contraction of the right leg, URR = peak BF RMS of the right leg during unilateral contraction of the right leg BLL = peak BF RMS of the left leg during bilateral contraction, BLR = peak BF RMS of the right leg during bilateral contraction. * Significantly different than ULL of the same population, † significantly different than BLD group.

8. 5 Voluntary activation level

Voluntary activation level of the whole population. Considering ALL there was a difference in the VAL between UL and BL contractions ($F(2, 38) = 4.504$, $p = 0.018$, $\eta_p^2 = 0.192$). VAL was significantly higher during BL contractions compared to the right UL ($p = 0.045$), but not left UL ($p = 0.074$) contraction, respectively (Figure 14, Table 10). A significant interaction between contraction mode and leg dominance was found for VA of ALL ($F(2, 36) = 4.592$, $p = 0.017$, $\eta_p^2 = 0.203$). Simple main effect for leg dominance was not significant. However, simple main effect for contraction mode was found to be significant for left-handed individuals ($F(2, 6) = 6.012$, $p = 0.037$, $\eta_p^2 =$

0.667), but not right-handed (p = 0.053). However, post hoc testing did not reveal any significant differences.

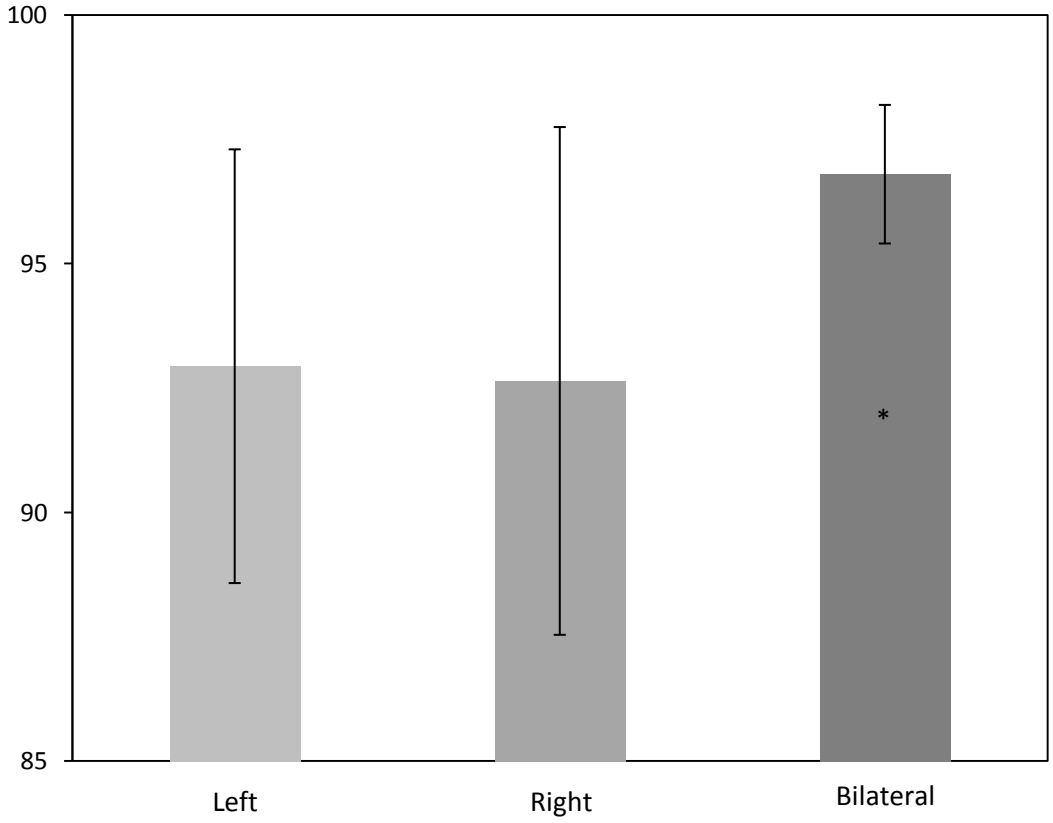

FIGURE 14. Voluntary activation level (%) of the whole population during unilateral left, right, and bilateral knee extension, respectively. * Significantly different than 'Right'.

Voluntary activation level between athlete groups. There was no significant interaction between contraction mode and AG. There was a significant main effect for contraction mode ($F(2, 34) = 4.936$, $p = 0.013$, $\eta_p^2 = 0.225$). VAL was significantly higher during BL contractions compared to right UL ($p = 0.049$), but not left UL ($p = 0.062$) contraction (Figure 15, Table 10). The main effect showed no significant difference in VAL between AG (Figure 15, Table 10). There was a significant three way interaction between contraction mode, AG and leg dominance for VA ($F(2, 30) = 3.470$, $p = 0.044$, $\eta_p^2 = 0.188$). However, there were no significant simple two-way interactions between AG and leg for any of the contraction modes.

TABLE 10. Voluntary activation level during bilateral and unilateral knee extensions.

	UL VAL (%)	UR VAL (%)	BL VAL (%)
All	92.94 ± 4.36	92.65 ± 5.11	96.81 ± 1.39*
BG	91.41 ± 6.06	94.95 ± 2.33	97.96 ± 0.28*
UG	94.02 ± 2.30	89.49 ± 8.26	96.59 ± 1.48*
CG	93.40 ± 4.18	91.88 ± 6.22	95.62 ± 2.92*
BLD	92.93 ± 4.19	92.36 ± 5.33	96.81 ± 0.92
BLF	92.98 ± 4.64	93.29 ± 4.39	96.79 ± 2.35

Values as means ± SD. All data are logarithmically transformed. All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, UL VAL = voluntary activation level during unilateral contraction of the left leg, UR VAL = voluntary activation level during unilateral contraction of the right leg, BL VAL = voluntary activation level during bilateral contractions. *Significantly different than UR of the same population.

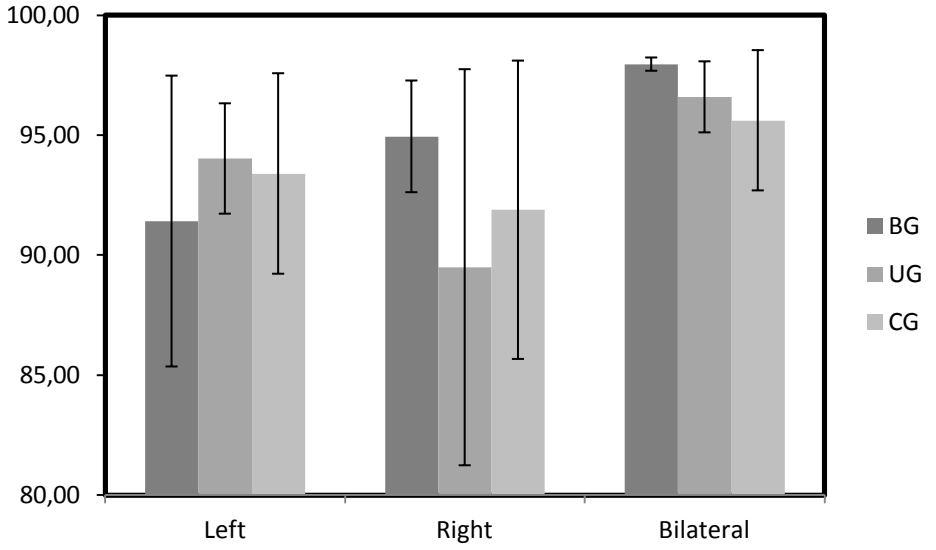

FIGURE 15. Voluntary activation level (%) between athlete groups. CG = control group, BG = bilateral group, UG = unilateral group.

Voluntary activation level between groups exhibiting bilateral deficit or facilitation. No significant interaction between contraction mode and BIG was observed. Significant main effect for contraction mode was noted ($F(2, 36) = 3.356$, $p = 0.046$, $\eta_p^2 = 0.157$). However, post hoc testing did not reveal any significant differences between contraction modes (Figure 16, Table 10). There was a significant two way interaction between

contraction mode and leg dominance for VA of BIG (F = (2, 34) = 4.598, p = 0.017, η_p^2 = 0.213). However, simple main effects were not significant.

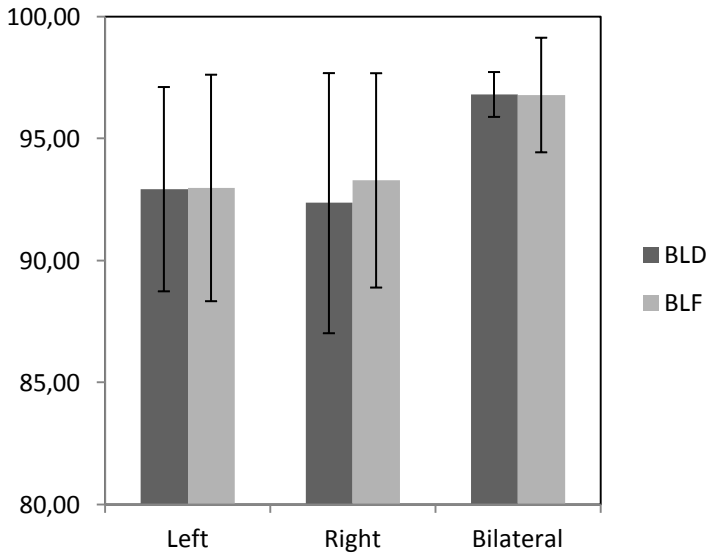

FIGURE 16. Voluntary activation level (%) between BI groups. BLD = exhibited bilateral deficit, BLF = exhibited bilateral facilitation.

8. 6 Motor evoked potentials

Motor evoked potentials of the target muscles for the whole population. Main effect of contraction mode was observed for MEP (F (2, 38) = 5.044, p = 0.015, η_p^2 = 0.210) of ALL. MEPs during UL contractions were significantly smaller than during BL contractions (p = 0.042) (Figure 17).

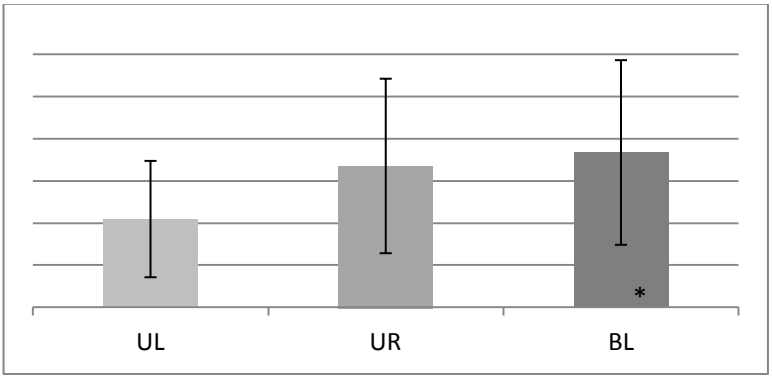

FIGURE 17. Motor evoked potentials of the whole sample size for unilateral left (UL), unilateral right (UR), and bilateral (BL) knee extensions, respectively. *Significantly different than UL.

Motor evoked potentials of the target muscles between groups. No interaction between contraction mode and neither AG or BIG was observed for MEP. A significant main effect of contraction mode was noted in the case of AG ($F(2, 34) = 3.731$, $p = 0.034$, $\eta_p^2 = 0.180$) (Figure 18) as well as BIG ($F(2, 36) = 3.786$, $p = 0.032$, partial $\eta^2 = 0.174$) (Figure 19), but post hoc testing did not reveal any differences in both cases. No interaction between contraction mode and leg dominance was found for MEP, regardless of the subject grouping.

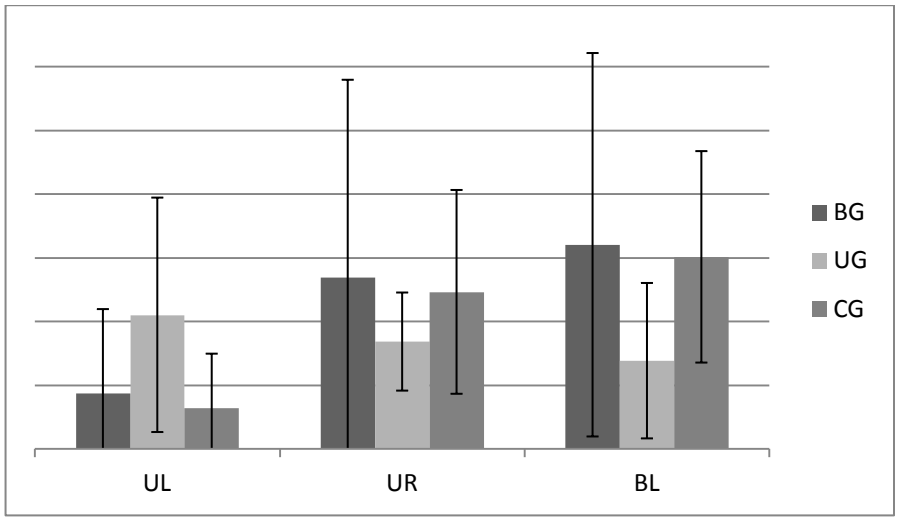

FIGURE 18. Motor evoked potentials in athlete groups. UL = unilateral left, UR = unilateral right, BL = bilateral, BG = bilateral group, UG = unilateral group, CG = control group.

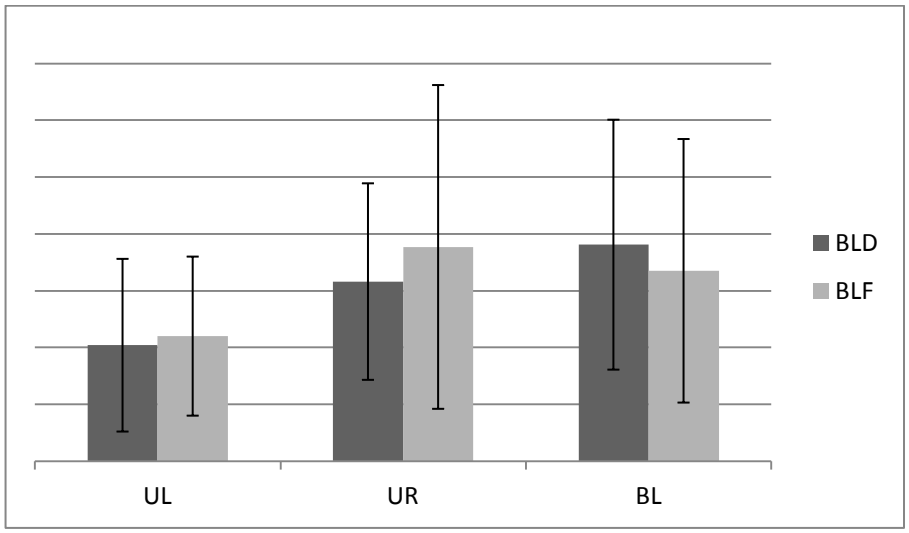

FIGURE 19. Motor evoked potentials between BI groups. UL = unilateral left, UR = unilateral right, BL = bilateral, BLD = exhibited bilateral deficit, BLF = exhibited bilateral facilitation

Motor evoked potentials of the ipsilateral muscles for the whole population. Significant main effect of contraction mode was found for iMEP ($F(2, 34) = 6.347$, $p = 0.005$, $\eta_p^2 = 0.272$). Post hoc testing revealed that iMEPs were significantly greater during BL compared to UL ($p = 0.022$). Furthermore, iMEPs were significantly bigger during UR compared to UL ($p = 0.038$) (Figure 20).

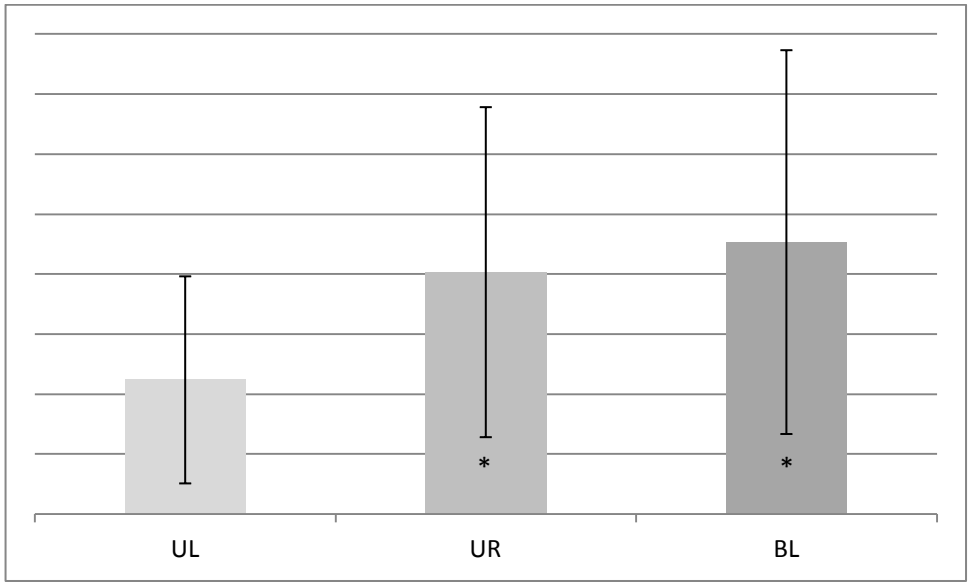

FIGURE 20. Ipsilateral motor evoked potentials of the whole sample size for unilateral left (UL), unilateral right (UR), and bilateral (BL) knee extensions, respectively. *Significantly different than UL.

Motor evoked potentials of the ipsilateral muscles between groups. No interaction between contraction mode and neither AG or BIG was observed for iMEP. A significant main effect of contraction mode was noted in the case of AG ($F(2, 30) = 5.678$, $p = 0.008$, $\eta_p^2 = 0.275$). Post hoc testing showed that iMEPs were significantly bigger during BL compared to UL ($p = 0.040$) (Figure 21). A significant main effect of contraction mode was also noted for BIG ($F(2, 32) = 4.408$, $p = 0.020$, $\eta_p^2 = 0.216$), but post hoc testing did not reveal any differences (Figure 22). No interaction between contraction mode and leg dominance was found for iMEP, regardless of the subject grouping.

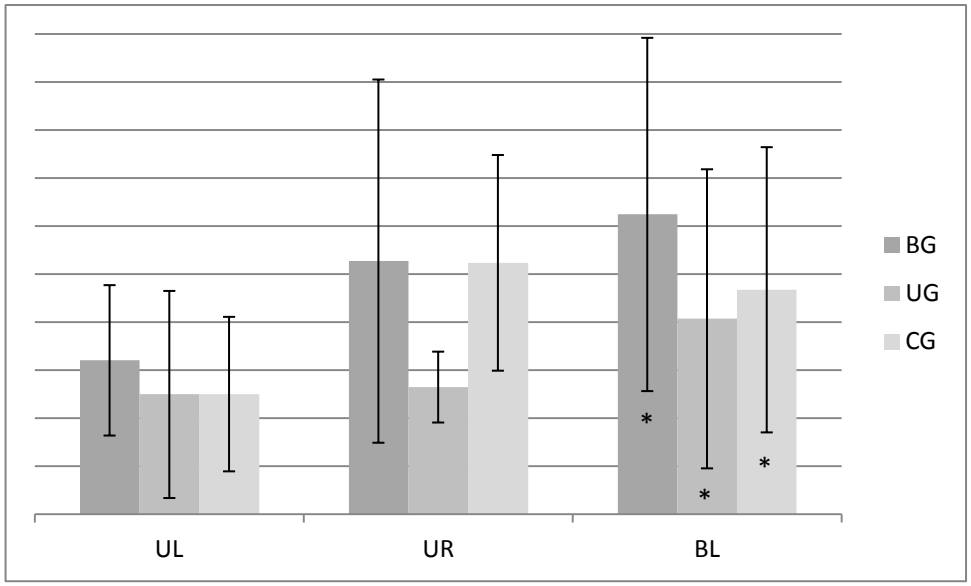

FIGURE 21. Ipsilateral motor evoked potentials among athlete groups. UL = unilateral left, UR = unilateral right, BL = bilateral, CG = control group, BG = bilateral group, UG = unilateral group. *Significantly different than UL.

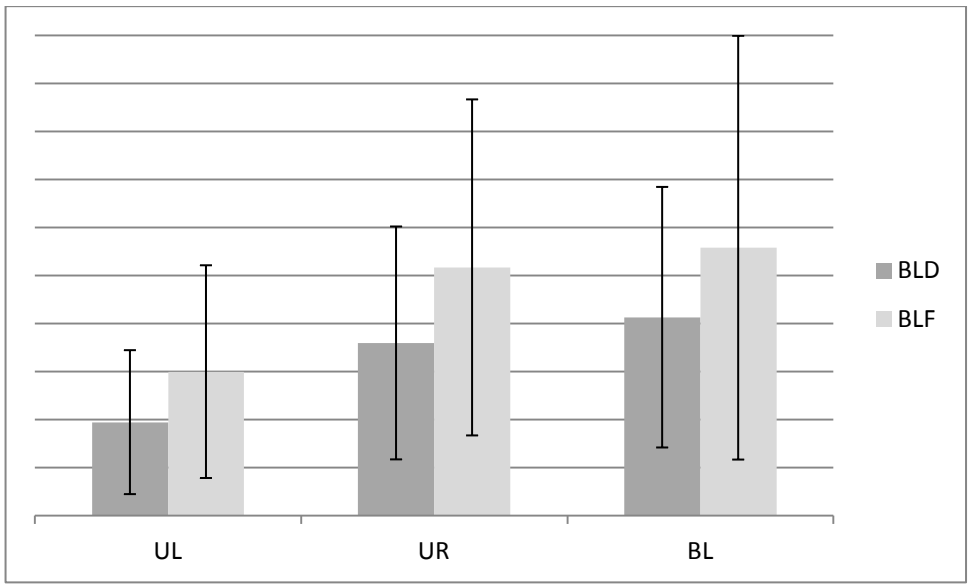

FIGURE 22. Motor evoked potentials between BI groups. UL = unilateral left, UR = unilateral right, BL = bilateral, BLD = exhibited bilateral deficit, BLF = exhibited bilateral facilitation.

Relationship between motor evoked potentials of the target and ipsilateral muscles. MEP and iMEP strongly positively correlated for all contraction modes, i.e. for left UL ($p = 0.004$, $r = 0.612$), right UL ($p < 0.001$, $r = 0.784$), and BL ($p = 0.007$, $r = 0.611$). No significant main effects were found for contraction mode and there was no difference between groups for R. R was significantly different from 1 for UL of ALL, and UL and UR of UG (Table 11).

TABLE 11. R ratios for unilateral left, right, and bilateral contractions.

	UL R	UR R	BL R
All	0.83 ± 0.39*	0.98 ± 0.38	1.04 ± 0.45
BG	1.06 ± 0.31	0.93 ± 0.28	1.04 ± 0.34
UG	0.71 ± 0.19*	0.81 ± 0.13*	1.19 ± 0.71
CG	0.95 ± 0.24	1.15 ± 0.52	0.92 ± 0.32
BLD	0.88 ± 0.28	0.97 ± 0.40	0.97 ± 0.29
BLF	1.03 ± 0.27	1.00 ± 0.36	1.19 ± 0.75

Values as means ± SD. All data are logarithmically transformed. All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, UL R = R ratio of unilateral contraction of the left leg, UR R = R ratio of unilateral contraction of the right leg, BL R = R ratio of unilateral contraction of bilateral contractions. *Significantly different than 1.

8. 7 Silent periods

All silent period durations are reported in Table 12.

Cortical silent periods. Considering ALL there was no main effect of contraction mode on CSP. There was no significant interaction between contraction mode and AG. No significant main effect was found both for contraction mode and AG. No significant interaction between contraction mode and BIG was found. Furthermore, no main effect of either contraction mode or BIG was found. No interaction between contraction mode and leg dominance was found for CSP regardless of the subject grouping.

Ipsilateral silent periods. No significant main effect of contraction mode was noted for iSP of ALL. A significant interaction between contraction mode and leg dominance was found for iSP of ALL ($F (2, 32) = 4.020$, $p = 0.028$, $\eta_p^2 = 0.201$). However, simple main effects for leg dominance and contraction mode, respectively, were not significant. There was no significant interaction between contraction mode and AG. No main effect of either contraction mode or AG was noted. Also, no significant interaction between contraction mode and BIG was noted. Main effects of either contraction mode or AG were not significant. No effect of leg dominance was found for iSP, regardless of the subject grouping

.

TABLE 12. Silent periods during unilateral and bilateral contractions

	UL CSP	UR CSP	BL CSP	UL iSP	UR iSP	BL iSP
All	169.3 ± 83.8	172.3 ± 93.6	166.8 ± 70.0	202.9 ± 94.1	181.4 ± 77.8	189.6 ± 85.6
BG	190.0 ± 119.0	193.8 ± 143.4	168.1 ± 96.5	213.1 ± 145.7	205.8 ± 103.0	205.8 ± 110.4
UG	160.0 ± 84.0	155.7 ± 77.3	160.3 ± 70.6	230.6 ± 52.3	172.4 ± 51.7	192.0 ± 96.1
CG	156.9 ± 47.1	163.9 ± 44.6	169.8 ± 49.4	174.4 ± 62.4	166.9 ± 74.9	173.9 ± 62.2
BLD	164.7 ± 90.7	173.5 ± 105.1	169.0 ± 75.0	208.3 ± 98.9	180.5 ± 79.7	182.9 ± 81.2
BLF	180.1 ± 71.5	169.5 ± 67.4	161.7 ± 63.0	188.8 ± 89.1	183.7 ± 81.6	206.8 ± 104.2

Values as means ± SD. All values in ms. All data logarithmically transformed. All = all subjects taken together, BG = bilateral group, UG = unilateral group, CG = control group, UL CSP = cortical silent period during unilateral contraction of the left leg, UR CSP = cortical silent period during unilateral contraction of the right leg, BL CSP = cortical silent period during bilateral contraction, UL iSP = ipsilateral silent period during unilateral contraction of the left leg, UR iSP = ipsilateral silent period during unilateral contraction of the right leg, BL iSP = ipsilateral silent period during bilateral contraction.

Relationship between cortical and ipsilateral silent periods. CSP and iSP strongly positively correlated for all contraction modes, i.e. for left UL ($p = 0.001$, $r = 0.732$), right UL ($p = 0.001$, $r = 0.723$), and BL ($p = 0.001$, $r = 0.711$).

9 DISCUSSION

This study showed inconsistency of BIs, i.e. BLD was observed only for ALL, but not for any of the subgroups, and differences in BI_F and aBI_F, which suggests that BLD in knee extension is a highly variable phenomenon. Unaltered SPs demonstrate that inhibition at the cortical level may not be related to BLD. Rather, higher MEP, iMEP, and VAL values during BL compared to UL contractions suggests the possibility of cortical facilitation. Based on the existing literature we present an argument that this behavior may be specific to the lower limb musculature and do not exclude the possibility of sub-cortical or higher-order neural alterations.

9. 1 Bilateral index

BLD in maximal force was observed only when the whole sample was taken into account (BI: – 8.76). However, when BI was calculated using the average value of all trials (aBI_F) no deficit was noted. It has been noted previously that investigations of BLD utilize only a small number of contractions and take into account only the maximal values, thus this approach may be biased towards UL performance (Buckthorpe et al. 2013). While we showed that variability of repeated maximal contractions was small, it was higher during UL compared to BL actions (CVs of 7.9 ± 4.2, 9.0 ± 4.1, and 5.3 ± 3.6, for UL left, UL right and BL contractions, respectively). Therefore, our results indicate that the notion proposed by Buckthorpe et al. (2013) has some merit. Furthermore, BI_F and aBI_F were shown to be different not only for the whole sample (– 8.76 vs. – 4.60, respectively), but also in the case of BG when subjects were split based on their activity (– 11.64 vs. – 5.82, respectively). What is interesting is that in the latter case, no BLD was noted (i.e. BI was not significantly different from 0), but BI_F and aBI_F were still different, which suggests that BLD is not a robust phenomenon. Indeed, BLD has been shown to be highly variable (Jakobi and Chilibeck 2001). Moreover, even when the same movement is utilized, such as isometric knee extension, BLD is not always evident (Howard and Enoka 1991; Jakobi and Cafarelli 1998; Owings and Grabiner 1998b; Khodiguian et al. 2003; Van Dieën et al. 2003; Matkowski et al. 2011). While the results of Howard & Enoka (1991) can be explained by different populations

investigated, the variability of other studies is more perplexing. A range of joint angles, thereby muscle lengths, has been used in studies. It has been shown that joint angle, and thereby muscle length, may have an effect on quadriceps activation during knee extensions (Becker and Awiszus 2001; Kubo et al. 2004). Our subjects performed contractions at 60 degrees of knee flexion as BLD in isometric knee extension has been most consistently shown at intermediate muscle lengths (Kuruganti et al. 2011; Matkowski et al. 2011; Botton et al. 2013, 2015; Teixeira et al. 2013). Since we showed BLD when a common methodological approach was applied, i.e. when peak values are used for calculation of BI, this reinforces the notion that BLD in isometric knee extension is more likely exhibited at intermediate muscle lengths. Postural stabilization requirements may also play a role in the expression of BLD (Magnus and Farthing 2008) insofar as greater stability requirements may result in greater BLD. In an effort to control for stabilization our subjects were strapped in the knee extension chair at the pelvis, chest and over the distal part of the thigh, and had their arms folded across the chest. Recently, Simoneau-Buessinger et al. (2015) hypothesized that the ability to use counterbalances during UL performance, may result in greater net torque about a joint, and therefore superior performance of one leg during UL condition. By using a specially-designed dynamometer they were able to show that BLD is only evident when torque can be added from other joints during UL contractions; therefore, BLD may simply be a result of configuration of the dynamometer used in studies. This may also explain greater consistency of BLD in combined hip and knee extension compared to knee extension (Jakobi and Chilibeck 2001), as the ability to use counterbalance is greater in the former. While we tried limiting the ability of the subjects to use counterbalances by additionally strapping them into a chair, it is still possible that our setup allowed some subjects a certain degree of trunk torsion to the contralateral leg during UL performance, and the observed deficit was the result of it. It would seem that some subjects may have been better able to take advantage of the counterbalances since the variability of BLD between subjects was high (SDs, Table 7).

The results of Howard & Enoka (1991) suggests that training adaptations play a role in BLD expression. Indeed, it has been shown repeatedly that bilateral and unilateral training reduce and increase the magnitude of BLD, respectively (Weir et al. 1995; Häkkinen et al. 1996b; Taniguchi 1997, 1998; Kuruganti et al. 2005; Janzen et al. 2006; Beurskens et al. 2015). Furthermore, Howard & Enoka (1991) showed BLD only in

untrained group, but BLF in weightlifters, who should be accustomed to performing bilateral actions almost exclusively. However, we were not able to show that to be the case, as BG, which consisted of experienced weightlifters and powerlifters, exhibited neither BLD nor BLF. Moreover, BI of BG was not different from the control group. It has to be noted that in the study of Howard & Enoka (1991), the subjects had been accustomed to performing maximum bilateral knee extensions at least one year prior to the study. This was not the case with our subjects who, despite performing maximal BL contractions in the years prior to the study, had done so rarely in open-chain, single joint motions, such as knee extension. This is supported by the findings of Secher et al. (1988), who observed that familiarity with the task plays a great role in the expression of BLD. We also hypothesized that athletes involved in sports, where performance is ultimately limited by UL force production, may exhibit a greater magnitude of BLD. We could not accept this hypothesis as UG, which consisted of long jumpers and a high jumper, did not exhibit BLD and their BI was not different from either control or BG. It has to be noted that their training regimen involves BL activities, such as BL jumping and resistance exercises, which may have positively influenced their ability to produce force bilaterally. Another issue with the type of testing employed in our study is that of joint angle specificity. Specifically, we used 60 degrees of knee flexion, which is different from angles where these athletes are commonly required to produce maximal knee extension torque. For example, weightlifting consists of the squatting movement pattern, and in powerlifting the squat is one of the competition lifts. The greatest knee torque requirements have been shown to be in the deepest portion of this exercise (Wretenberg et al. 2007; Bryanton et al. 2012), i.e. between 105 and 119 degrees of knee flexion (Bryanton et al. 2012). On the other hand, jumping disciplines of track and field are characterized by small knee flexion angles, i.e. about 40 and 30 degrees at maximum knee flexion and take-off point, respectively (Graham-Smith and Lees 2005). The issue of testing specificity is further supported by the fact that we found leg extension strength to be no different between all three AG. It seems unlikely that experienced athletes, especially those forming BG, are generally just as strong as subjects forming CG, and not stronger.

It has been suggested that variability of BLD could be explained by inadequate reproducibility of the strength tests used in the studies of BLD (Jakobi and Chilibeck 2001). Our results suggest that variability between trials was small (7.9, 9.0 and 5.3%

for left unilateral, right unilateral and bilateral contractions, respectively). Moreover, reliability of force measures was considered good (O'Leary et al. 2015), as ICCs of all contraction modes were well above 0.80. Nevertheless our results suggest that variability of BLD itself between subjects was high (SDs, Table 7). It is possible that this variability affected statistical power and thus BI that was not significantly different from 0 when subjects were grouped. Additionally grouping the subjects substantially reduced the sample size which may have been underpowered to detect significance.

A limitation needs to be noted in regard to torque recordings. We measured forces using only one force transducer and thus it is unclear to what extent did the contralateral extension contribute to the UL torque and whether there was a discrepancy in torque production, i.e. either onset of torque production, time to peak torque, or maximal force production of each leg (Matkowski et al. 2011), between the legs during BL contractions. However, the former was likely not significant as we observed no differences in EMG activity of leg extensor muscles between the legs.

9. 2 Electromyography

To assess the contribution of neural changes to BLD, investigations have often compared EMG activity between UL and BL contractions. While some investigators have shown BLD in force to parallel that in EMG (Ohtsuki 1983; Oda and Moritani 1994, 1995a; b, 1996; Hernandez et al. 2003; Post et al. 2007; Cengiz 2015), many others have not observed such coupling (Schantz et al. 1989; Howard and Enoka 1991; Matkowski et al. 2011; Cornwell et al. 2012). Our results agree with the latter studies as we showed BI in EMG activity not to be different than zero. Furthermore, no correlation between force and EMG bilateral indices were noted. These results alone cannot be taken as evidence that there is no neural contribution to BLD as EMG amplitude is not a direct indicator of muscle activation (Farina et al. 2010). Also, as Howard & Enoka (1991) warned, the force-EMG relationship is not well defined for small changes in force and since differences in force production between UL and BL contractions are small it would be more difficult to detect this difference with EMG. Furthermore, Howard & Enoka (1991) showed that changes in force and EMG vary greatly across subjects as well as between UL and BL contractions. Indeed, we observed great variability of BLD in EMG as noted by standard deviation (BIs in EMG, Table 8).

Worthy of mention is also that variability of the EMG signal in our study was high (Table 6). Furthermore, reliability criteria were satisfied only for the left leg, but not for the right (Table 6). This could have been a factor in our inability to detect correlations between force and EMG bilateral indices. Overall, our EMG findings should be interpreted with caution due to their high variability and small reliability.

Often, EMG measures are performed only on one muscle of the muscle group. As in our case, we performed EMG measures only on vastus lateralis muscle, but not on other muscles of the rectus femoris group which contribute to the extension of the knee. Some investigators have tried to circumvent this issue by summing the activity of more than one muscle of the muscle group (Kuruganti and Murphy 2008; Kuruganti et al. 2011; Botton et al. 2015). In spite of that, only two of the three studies that used this approached showed differences in EMG activity between UL and BL contraction (Kuruganti and Murphy 2008; Botton et al. 2015), while one did not (Kuruganti et al. 2011). Regardless, future studies should consider measuring EMG activity from more than one muscle of the muscle group in question and either summing the activity or calculating BI for each of the muscles.

Interpretation of EMG findings is also greatly influenced by quantification of EMG amplitude and the time period of integration. Indeed, different studies have used different methodological approaches to quantify the EMG signal. In our case, EMG signal was root-mean-squared in a time-window of 500 ms before the stimulation point and subsequently normalized to maximal M-wave during the maximal contractions of the same contraction mode (UL vs. BL). The latter was done as it discounts possible peripheral alterations of the signal, such as action potential propagation or changes at the skin-electrode interface (Neyroud et al. 2015). Considering other literature on knee extension, Matkowski et al. (2011) and Buckthorpe et al. (2013) used a similar approach to ours and noted no difference in EMG activity between UL and BL actions. Other investigations however did not normalize the amplitude to the maximal M-wave, which makes it possible that EMG measures were affected by peripheral alterations of the signal and thus pure changes in neural drive cannot be inferred.

The role of antagonist activation has been examined by many investigators. If it has any effect on BLD, greater antagonist activation would be expected during BL compared to UL contractions as it would result in reduced net torque production by the agonist

during BL actions. However, many studies did not find any difference in antagonist activation between UL and BL contractions (Howard and Enoka 1991; Koh et al. 1993; Jakobi and Cafarelli 1998; Cresswell and Overdal 2002; Behm et al. 2003; Van Dieën et al. 2003; Kuruganti et al. 2011; Buckthorpe et al. 2013). Moreover, some evidence suggests that activation may be even greater during UL contractions (Koh et al. 1993; Simoneau-Buessinger et al. 2015). We found differences in antagonist activity between the left UL contraction and the right leg during BL action. However, this significance is not meaningful since it does not represent the activity of the same leg. Therefore, our results agree with the findings of aforementioned studies that antagonist activation is not different between UL and BL contraction and thus has no effect on BLD (Jakobi and Chilibeck 2001). This is further supported by our finding that the group exhibiting BLF had even higher antagonist activation levels than the group exhibiting BLD.

We found no presence of contralateral activation of the antagonist. This is in contrast to some of the investigators who have observed such behavior (Howard and Enoka 1991; Cresswell and Overdal 2002), and is most likely due to our subjects being instructed not to do so. It is important that activation of contralateral antagonist is constrained by instruction as it could potentially lead to greater UL performance and thus contribute to the existence of BLD. This is supported by findings of Cresswell & Overdal (2002) who observed that the subjects who activated the hamstrings in the contralateral leg during UL knee extensions exhibited greater BLD compared to the subjects who did not (BLD of 21 vs. 14%, respectively).

We observed higher relative values of antagonist activation compared to some other studies employing the same contraction type (Grabiner et al. 1989; Krishnan and Williams 2008, 2009, 2010). It has been suggested that even when cross-talk is minimal, it can account for as much as third of what is considered antagonist EMG (Kellis 1998). Despite the fact that great care was taken when applying the electrodes, the possible effect of crosstalk cannot be discounted and may have possibly been responsible for the higher relative values observed. Additionally, having to transform our data due to its non-normal distribution may have produced higher values; however, this could not have affected the difference between UL and BL actions that we investigated. There is also some evidence to suggest that electrical stimulus may increase the activation levels of the antagonist muscles (Krishnan and Williams 2008). However, this increase does not appear to be clinically meaningful (Krishnan and

Williams 2008). Also, our EMG was analyzed in a period of 500 ms prior to the stimulation and hence the stimulation itself could not have affected the results. Antagonist activation has also been shown to be higher for lateral hamstrings (Aagaard et al. 2000; Krishnan and Williams 2009) and since we recorded activity from biceps femoris, this could have contributed to larger values obtained in our study. Comparison of studies investigating antagonist activation is also difficult due to differences in interpretation of EMG signal between studies. Factors such as amplification and rectification of the signal, smoothing technique, EMG parameter during data processing, and normalization procedure can all influence EMG results and therefore quantification of antagonist coactivation (Kellis 1998). We used a root-mean-square value obtained in the 500 ms window prior to the stimulation and normalized it to the root-mean-square value of 500 ms during MVC knee flexion at the same joint angle, while other aforementioned studies have used different approaches, which makes our results difficult to compare.

Important to consider is what is the actual mechanical contribution of the antagonist to the net knee joint moment. Although EMG may provide an indication of antagonist activity, the extent to which it can be taken as an indicator of muscle force, and therefore joint mechanics, is limited (Kellis 1998). It is unlikely that countermoments associated with antagonist activity mathematically cancel out across sides (Krishnan and Williams 2010), especially due to significant variability in antagonist activity between the legs during isometric testing (Krishnan and Williams 2009). High variability of antagonist EMG is also noted in our experiment (CVs, Table 6). Therefore, even if differences in antagonist activation between UL and BL contractions were observed, whether this has a meaningful impact on torque production and/or a difference in torque production with different contraction modes and thus any effect on BLD, is questionable.

9. 3 Voluntary activation level

Voluntary activation level (VAL) as assessed by the interpolated twitch technique is useful when trying to deduce the neural mechanism and is complementary to EMG recordings (Matkowski et al. 2011). The literature on BLD when VAL has been studied remains equivocal. While some have shown greater VAL during UL compared to BL

contractions (Herbert and Gandevia 1996; Van Dieën et al. 2003), others have showed no difference (Jakobi and Cafarelli 1998; Matkowski et al. 2011) or even greater VAL during BL contractions (Behm et al. 2003). Our results agree with the latter study as VAL during BL contraction was ~ 97% compared with ~ 93% during UL contractions. However, this was not different between groups (Table 10). We used a potentiated doublet torque on a passive muscle as a reference to calculate VAL and additionally M-wave characteristics were analyzed. Since no differences were found between contraction modes for both variables the peripheral factors had likely no influence on the observed findings. Therefore, it could be concluded that VAL observed was strictly due to neural factors.

Previous studies noted great variability between subjects, and it has been suggested that this variability could possibly explain inconsistent findings (Jakobi and Chilibeck 2001). In our case variability was minimal during BL contractions, but a bit more prominent during UL contractions as noted by standard deviations (Table 10), and it is possible that this variability is responsible for differences between UL and BL contractions observed. It is also possible that during BL action the subjects were able to use the chair as a counterbalance, thereby having greater stability and greater ability to maximally activate the muscle (Behm et al. 2002a). This could potentially explain greater variability during UL contractions, and greater VAL during BL actions observed. In this case the observed differences in VAL between UL and BL contraction cannot be considered as an effect of contraction mode per se, but rather a result of configuration of testing device (Simoneau-Buessinger et al. 2015). Pain associated with noxious evoked stimuli may affect the ability to maximally activate the muscle (Hortobágyi et al. 1992) and it is unclear if there were differences as to the degree of pain associated with noxious stimuli between BL and UL contraction. During BL actions only the right leg was stimulated and it is unclear whether contraction of contralateral homonymous, i.e. non-stimulated muscle, had any effect on the reduction in perception of pain associated with noxious stimuli, which could potentially result in higher VAL levels. It is also unclear to what extent, if any, would have the noxious stimuli pain increased had the subjects received stimulation of both legs during BL contractions and subsequently to what extent would have VAL values been affected by it.

Our VAL values (~ 93% and 97% for UL and BL actions, respectively) are a bit higher than in other studies implementing this measure during knee extension. For example, Jakobi & Cafarelli (1998) showed VAL of 93.6% vs. 90.1% for UL and BL contractions, respectively, while Matkowski et al. (2011) showed VAL of roughly 91% for both modes. The latter study was unique as it implemented concurrent stimulation of both limbs during BL contraction, while the rest, including ours, have stimulated only one leg at a time. It is possible that in the study of Matkowski et al. (2011) an additional pain from noxious stimuli was present during BL contractions and this resulted in smaller VAL. However, this seems less likely due to short latency of the responses to peripheral nerve stimulation. It is also possible that methodological approaches influenced the values, especially in regard to the calculation of VAL. Which approach is the most appropriate has been extensively debated in the literature (Shield and Zhou 2004), and there have been suggestions that the conventional ITT overestimates VAL (Yue et al. 2000). In our case we were inclined to use a correction equation (Strojnik and Komi 1998) in more than half of the cases, instead of the classical one (Allen et al. 1998; Place et al. 2007), and this may have overestimated the final value. Furthermore, due to our data being negatively skewed we needed to transform it appropriately in order to make statistical analyses. This may have possibly overestimated our values even further. However, it seems unlikely that this could have had an effect on the observed difference between UL and BL contractions.

9. 4 Responses to TMS

We found iSP, a measure of transcallosal inhibition, not to be different between UL and BL contractions. This suggests that BLD observed for the whole population is not caused by transcallosal inhibition as suggested before (Oda and Moritani 1995b). Perez et al. (2014) observed increased iSP depth and area during BL as compared to the UL contractions of the elbow flexors. While we analyzed only iSP duration, and not its depth and area, our results could still be considered in contrast to them. An important distinction that needs to be noted is that Perez et al. (2014) investigated the arm muscles and it is possible that bilateral control of upper and lower limbs differs. Indeed, interhemispheric activation patterns of lower and upper limb movements have been shown to be different (Luft et al. 2002; Volz et al. 2015) and hence comparison with

studies using the upper limbs is difficult (Chiou et al. 2013). Specifically, Volz et al. (2015) showed that during isolated unilateral movements interhemispheric inhibition accompanied movements of the hand, while foot muscles exhibited interhemispheric facilitation. Furthermore, Luft et al. (2002) showed no ipsilateral activity during elbow movement, but knee movement was characterized by activation of ipsilateral almost as much as the contralateral areas. Our responses to ipsilateral stimulation (iMEPs) were found to be ~24% greater during BL compared to UL contractions. This suggests involvement of a facilitatory mechanism during BL contractions, and it is possible that this behavior is specific to lower limb musculature. It seems reasonable to assume that during BL contractions increased facilitatory response may have been caused by increased excitatory drive from ipsilateral and contralateral hemisphere during contralateral and ipsilateral stimulation, respectively, as a result of the activation of contralateral muscles (Hess et al. 1986). Ipsilateral excitatory responses have also been shown to be more easily obtained in the lower limb muscles with the thresholds being similar to the contralateral responses, while in the upper limb muscles the amplitudes are either significantly smaller or the thresholds higher (Brouwer and Ashby 1990). However, in contrast to Perez et al. (2014) as well, when BL contractions, albeit at lower force levels than in our study, are performed with arm muscles, similar behavior has been observed insofar as transcallosal inhibition noted during UL contractions is removed and/or replaced with mutual facilitation of the two hemispheres (Bawa et al. 2004). However, the authors also noted great subject-dependency of facilitatory ipsilateral responses, and greater ability to obtain these responses in trapezius and pectoralis muscles (Bawa et al. 2004). Perez et al. (2014) on the other hand recorded responses from biceps and triceps muscles and it could be that ipsilateral facilitatory responses are muscle-dependent. Since we were, to the authors' knowledge, the first to record ipsilateral responses of the quadriceps muscle to TMS during 100% MVC in healthy subjects, the results are difficult to compare to others and would eventually need replication, possibly in comparison with upper limbs, to be classified as a distinct behavior of lower limb musculature.

Based on R ratios our results suggest that ipsilateral connections and crossed cortical connections are of similar strength. This is in contrast to studies investigating arm muscles where significantly smaller R ratios have been shown compared to us (Wassermann et al. 1991a, 1994; Carr et al. 1994; Khedr and Trakhan 2001; Bawa et al.

2004). Thus, the observed similarity in strength between ipsilateral and cortico-cortical connections may be specific to lower limb muscles. Data from Luft et al. (2002) supports this hypothesis as no ipsilateral activity was found during elbow movement, but similar activation of ipsilateral and contralateral areas were noted for knee movement. It may also be that this behavior is specific to proximal musculature. Bawa et al. (2004) noted that ipsilateral responses can be more readily obtained in the proximal muscles during BL contractions; however they recorded responses only from the upper limb muscles. In contrast, there is evidence to suggest that corticospinal projections differ in the lower limb muscles insofar as the population of cortical neurons to more proximal muscles may be less readily excitable by magnetic stimulation than projecting to more distal muscles (Brouwer and Ashby 1992). However, whether this excitability differences during rest translate to different levels of contraction remains uncertain. It is therefore unclear whether the responses are specific to proximal musculature, and additional comparison with distal muscles of the lower limbs would need to be conducted to confirm it.

Some evidence suggests that iSP is a result of inhibition at the cortical level (Ferbert et al. 1992; Di Lazzaro et al. 1999; Daskalakis et al. 2002). It is thought that iSP is modulated by excitatory axons that cross the corpus callosum and act on contralateral inhibitory neurons in the contralateral motor cortex and thus suppress the activity of corticospinal elements (Daskalakis et al. 2002; Trompetto et al. 2004). It may be that during BL actions of the lower limbs the firing rate of these excitatory axons is reduced, which would result in smaller activation of contralateral inhibitory neurons and thus the net effect is bigger facilitation as evidenced by bigger MEPs and iMEPs in our study. We showed strong correlations between MEPs and iMEPs, and CSPs and iSPs, respectively. This correlation between ipsilateral and contralateral responses has been shown before in hand muscles (Verstynen and Ivry 2011), and suggests an interaction between corticospinal and transcallosal fibers. However, there is also conflicting evidence suggesting that transcallosal are not collaterals of corticospinal fibers, but they belong to distinct neuronal populations (Lee et al. 2007). It has also been argued that iSP is actually not an aftereffect of iMEP, but arises from different stimulation of different set of cortical neurons (Wassermann et al. 1994). Direct oligosynaptic ipsilateral pathways, such as corticoreticulospinal or corticopropriospinal projection, thus cannot be discounted as a source of ipsilateral facilitatory responses (Ziemann et al.

1999). However, due to high stimulation intensity that was used during ipsilateral stimulation (180% of rMT, which corresponded to 86 ± 15 % of the stimulator output, range 42 – 100 %) there is also a possibility that we activated cortico-bulbo-spinal pathways (Bawa et al. 2004). On the other hand, branching of corticomotoneuronal axons, a transcallosal projection and a slow-conducting monosynaptic ipsilateral pathway have been excluded as a mechanism of ipsilateral facilitatory responses (Ziemann et al. 1999).

Additionally, suggestions have been made that ipsilateral responses can be mediated at the sub-cortical level (Gerloff et al. 1998). Volz et al. (2015) who noted interhemispheric differences between upper and lower limbs also found effector-specific differences in the premotor areas and thus suggested that this may be due to a stronger impact of spinal cord circuits during lower limb movements. In line with research implying stronger influence of spinal neurons to motor function of the lower limbs (Danner et al. 2015), they speculated that lower limb function may be associated with a weaker control at the cortical level compared to upper limbs (Volz et al. 2015). Therefore, we cannot exclude the possibility that the observed facilitatory responses are not due to alterations at the sub-cortical level.

Similarly to iSP, no changes were observed in CSP. Despite the mechanisms of the CSP induced by TMS being poorly understood, it is generally accepted that CSP is a quantitative measure of mainly cortical inhibitory functions (Säisänen et al. 2008; Rossini et al. 2015), and probably reflects the activity of inhibitory interneurons within the cortex (Taylor et al. 1997). Since contraction intensity plays an insignificant role in CSP duration (Taylor et al. 1997; Säisänen et al. 2008), a small difference in the level of force between BL and UL contractions could not have confounded our results. Based on our findings it seems that intracortical inhibition is not different during UL and BL contractions. It has been suggested previously that MEP and CSP behave in a similar manner (Taylor et al. 1997). Furthermore, correlations between them have been observed and subsequently it has been suggested that the mechanisms between the two variables are not distinct (Säisänen et al. 2008). There is some evidence that MEPs of higher amplitude tend to lead to longer CSP, as both MEP and amplitude and area have been shown to predict SP (Orth and Rothwell 2004). However, when we additionally calculated CSP/MEP ratios the results remained the same, i.e. no differences were found between contraction modes. We also observed no correlations between CSP and MEPs

and thus they should represent inhibitory and excitatory cortical mechanisms, respectively.

The duration of silent period may be affected by the voluntary activity after the stimulus (Taylor et al. 1997) and it has indeed been shown that when subjects were instructed to 'pull through' the stimulus, i.e. maintain a constant force level despite stimulation, the duration of CSP decreased (Cantello et al. 1992; Wilson and Lockwood 1993). Our subjects were instructed to do just that and qualitative observations from the experiment suggest that subjects who were better at maintaining a constant force, despite the stimulation, also exhibited the shortest silent periods. Whether the ability to maintain a constant force level differs between UL and BL contraction and to what extent this could have affected these results remains unclear.

Similarly to ipsilateral responses, corticospinal excitability (MEP amplitude) was found to be greater during BL compared to UL contractions. If we assume that transcallosal and corticospinal fibers belong to distinct neuronal populations (Lee et al. 2007), these results suggests that BL contractions are accompanied by facilitatory responses in both populations of neurons. It is believed that MEPs are evoked through activation of corticospinal neurons and some of these neurons make direct connections with spinal motoneurons (Rothwell et al. 1987; Benecke et al. 1988). By normalizing MEP amplitude to the maximal compound action potential during the contraction, we also controlled for any potential alterations of transmission at the level of muscle or peripheral nerve (O'Leary et al. 2015).

We found no effect of leg dominance for any responses to TMS and this is consistent with the literature showing symmetrical responses in vastus lateralis muscle (Al Sawah et al. 2014). Similarly, rMT was not significantly different between the hemispheres as shown before (Civardi et al. 2000).

Taken together, the responses to TMS in our study suggest that BL contractions were not characterized by inhibition at the cortical level; rather, facilitation was observed. This behavior may be specific to muscles of the lower limbs and possibly limited to proximal ones. Our findings do not support the hypothesis that BLD is caused by inhibition at the level of primary motor cortex. However, isolated movements of both the upper and the lower limbs activate a number of motor areas such as supplementary motor area, premotor cortex and primary motor cortex (Luft et al. 2002; Volz et al.

2015). Post et al. (2007) showed that the inhibition underlying BLD is cortical, but its origin may lie upstream of the primary motor cortex. Specifically to lower limb movements, Noble et al. (2014) showed that bilateral control is distributed over cortical, cerebellar and subcortical brain regions. Thus, not observing changes at the level of primary motor cortex does not exclude the possibility that some sort of inhibition (or facilitation) is occurring at other levels of neural hierarchy during BL contractions and may (or may not) have an effect on BLD.

Comparison of TMS responses between groups. Corticospinal (Adkins et al. 2006) and transcallosal projections (Shim et al. 2005) may exhibit plastic changes with different movement practice. For example, professional musicians, who are thought to be highly skilled in complex finger movements, exhibit reduced interhemispheric inhibition (Ridding et al. 2000), and intracortical inhibition and facilitation (Nordstrom and Butler 2002), respectively. We were not able to show any difference between groups in corticospinal and transcallosal modulation during UL and BL contractions. In regard to BG this is consistent with the findings that strength training does not induce reorganization of movement representation unlike skill training (Adkins et al. 2006). Furthermore, resistance-trained individuals have not been shown to be different in terms of corticospinal excitability in comparison with untrained counterparts (del Olmo et al. 2006; Tallent et al. 2013). Considering our results demonstrating no difference between groups, the change in magnitude of BLD due to unilateral or bilateral training, respectively, is likely due to reorganization of spinal cord circuitry (Aagaard et al. 2002), rather than at the level of primary motor cortex. This is further supported by the evidence from short-term strength training interventions showing no changes, or even a decrease, in corticospinal excitability (Carroll et al. 2002, 2009; Jensen et al. 2005). Conversely, ballistic training, which is a type of training that subjects from UG would typically perform, seems to increase corticospinal excitability if the experimental is matched with training task (Beck et al. 2007a) or when a new task is presented (Schubert et al. 2008). We did not observe any difference in either corticospinal or transcallosal modulation for UG. However, looking at figures an argument could be made for between-group differences for MEP behavior between different contraction modes insofar as BG and CG show an increasing trend of MEP amplitude from left UL, to right UL, to BL action, while UG shows a reversal of this trend, i.e. decreasing in that particular order (Figure 18). Specifically, in BG and CG, MEPs during BL were ~15%

and ~3% bigger compared with UL left and UL right contractions, respectively, while the difference between UL contractions was ~11%. Conversely, in UG, MEPs during BL were ~5% and ~3% smaller compared with UL left and UL right contractions, respectively, while the difference between UL contractions was ~3%. This behavior may reflect a specific adaptation of the corticospinal system to the demands of the sport, where maximal force production is required to be produced unilaterally and explosively, which may be the ultimate performance limiting factor. However, these responses were accompanied by large variation and may have been, in conjunction with small sample size, responsible for inability to detect significance.

9. 5 Limitations

Some limitations had been noted throughout the discussion; however there are a few others that need to be considered. Firstly, in relation to studying responses to TMS it has to be noted that only a small number of trials was performed, i.e. our subjects performed only 2 to 3 contractions per each contraction mode for each type of stimulation. Due to intrinsic variability of neural excitability a greater number of trials is usually recommended to ensure reliability of recordings (Rossini et al. 2015). However, available evidence also suggests that this variability can be reduced with contracting muscle (Darling et al. 2006). In our case keeping the amount of trials to a reasonable minimum was of paramount importance to ensure that the performance of contraction was truly maximal, i.e. that no fatigue was induced, since the primary purpose of the experiment was to study TMS responses in relation to BLD. This phenomenon is likely limited to maximal force production or its mechanisms at least differ in submaximal contractions. Secondly, the use of iSP as a measure of transcallosal function needs to be considered. It has been suggested that both iSP and interhemispheric inhibition, the latter being a paired-pulse paradigm, represent transcallosal inhibition (Ferbert et al. 1992). However, it has also been suggested that they may not represent the same phenomenon and that they may be modulated by a different neuronal population in the motor cortex or by different sets of target neurons in the contralateral cortex (Chen 2002). Thirdly, during BL contractions the right M1 was always stimulated. In the case of contralateral and ipsilateral stimulation, the responses of the left and the right leg, respectively, were then compared. Thus, an argument could be made that comparison

between UL right and BL CSPs, and UL left and BL iSPs, is not valid since different limbs are being compared on top of different contraction modes. However, even when analysis was performed only on the muscles of the same leg, i.e. iSP of BL compared to iSP of right UL action and CSP of BL compared to CSP of left UL action, the results remained the same insofar as no significant interaction or main effect of either mode or group was found for both groupings (mixed ANOVA) as well as no significant difference was observed for ALL (paired samples t-test). Fourthly, Brouwer & Ashby (1990) observed differences in the ability to obtain ipsilateral excitatory responses between upper and lower limbs. However, they also noted that since latencies of contralateral and ipsilateral responses were the same, it is likely that cortical neurons of non-stimulated hemisphere are excited by the spread of current rather than transcallosal effects (Amassian and Cracco 1987). Bawa et al. (2004) observed that facilitatory ipsilateral responses were frequently observed when a large double-cone coil was used, likely due to stimulation of the contralateral motor cortex with peripheral edge of the coil. It could be argued that bigger ipsilateral facilitatory responses observed in our study were due to the spread of current, especially because high stimulation intensities were used, and/or stimulation of the contralateral cortex with peripheral edge of the coil. Indeed we observed facilitatory responses bilaterally regardless of stimulation intensity and site of stimulation, i.e. contralateral or ipsilateral. However, this does not explain the significant difference in facilitatory responses observed between UL and BL contractions as the spread of current would have likely affected responses during both contraction modes to the same extent. Fifthly, we used a double-cone coil and the responses should be interpreted within the constraints of this specific type of coil as different coils may activate different cortical elements (Taylor et al. 1997). Lastly, a limitation that needs to be noted in regard to UG is that the measures were performed on a knee extensor muscle. For this particular group plantarflexors would have been more appropriate and it is unclear if changes would have been observed had this particular muscle group been investigated

9. 6 Conclusions/summary

In summary, we showed that BLD is an inconsistent and highly variable phenomenon, which is consistent with the literature, especially in regard to isometric knee extension.

Postural stabilization requirements and the ability to use counterbalances may have played a role in high variability of BIs. Neither BLD nor BLF were shown for any of the groups likely due to poor testing specificity. No BLD in EMG activity was observed and no parallelism between force and EMG bilateral indices were noted. These findings may be specific to the methodology for quantification of EMG signal employed in this study. Furthermore, interpretation may have been skewed due to high variability and low reliability of the signal. Consistently with the literature, activation of the antagonist muscle was not found to be different between UL and BL contractions. The literature on VAL in relation to differences between UL and BL contractions remains equivocal. In our study greater VAL was observed during BL as compared to UL contractions with no differences between groups. This may have been caused by higher variability of UL contractions and the ability to use chair as a counterbalance, thereby providing subjects greater stability and greater ability to activate the muscle during BL contractions. No differences in SPs were found between contraction modes regardless of subject grouping, which is in contrast to previous studies. Moreover, greater MEPs and iMEPs were observed during BL when compared to UL contractions. This would suggest that inhibition at the cortical level is not related to BLD, but rather some facilitatory mechanisms may be involved. Based on the existing literature this behavior may be specific to lower limb musculature and further investigations comparing the lower with the upper limbs are needed to confirm this hypothesis. The exact origin of these responses remains unclear. Involvements of transcallosal and corticospinal neurons, and direct oligosynaptic pathway, have been considered. However, alterations at the sub-cortical level or at the higher levels of neural hierarchy, i.e. upstream of the primary motor cortex, cannot be excluded.

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11 APENDIX 1. ACKNOWLEDGMENTS.

Master's studies of the author were supported by 'Ad Futura' scholarship of Slovene Human Resources Development and Scholarship Fund.

The author would like to thank the personnel of Laboratory of Cognitive Neuroscience, Department of Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia, for the opportunity to conduct this experiment in their laboratory.