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INVITED REVIEW

# Non-local muscle fatigue: effects and possible mechanisms

**Israel Halperin[1,2] · Dale W. Chapman[1,2] · David G. Behm[3]**

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**Abstract**
*Introduction* Non-local muscle fatigue (NLMF) is characterized by muscle performance impairments in a contralateral or remote non-exercised muscle(s) following a fatiguing protocol of a different muscle group(s). This topic is of interest as it affords insights into physiological determinants of muscle fatigue and may provide practical applications concerning the order of exercises in training and rehabilitation programs.
*Methods* A literature review was conducted using Web of Science, PubMed, and Google Scholar databases to evaluate the NLMF effects and possible underlying mechanisms. Overall, 35 studies with 58 outcome measures that met the inclusion criteria were identified.
*Results* The literature is conflicting with approximately half of the studies reporting NLMF effects (32 of 58 measurements). However, on closer examination 76 % of outcome measures of the lower limbs reported NLMF effects (23 of 30 measurements) compared to only 32 % in the upper body (9 of 28 measurements). Thus, it appears that NLMF effects may be muscle group dependent. Also, tests that involve prolonged or repetitive contractions provide clearer evidence of NLMF. Other variables potentially influencing the size of the NLMF effect include the fatigued muscle groups, the protocols used to elicit the fatigue, gender and training background of participants.
*Conclusion* While the NLMF literature is conflicting, certain variables appear to affect NLMF responses which can account for some of the discrepancies. Furthermore, the NLMF effects may be attributed to four different but interconnected pathways: neurological, biochemical, biomechanical and psychological.

**Keywords** Crossover fatigue · Cross-education · Contralateral muscles · Force · Endurance

**Abbreviations**

| | |
|---|---|
| 1 RM | 1 Repetition maximum |
| FDI | First dorsal interosseous |
| Mmax | Femoral nerve stimulation |
| MVC | Maximum voluntary contraction |
| NLMF | Non-local muscle fatigue |
| RPE | Rating of perceived exertion |
| TMEP | Thoracic motor evoked potential |

## Introduction

Muscle fatigue commonly refers to a transient decrease in the muscles' capacity to produce force or power (Gandevia 2001). Despite a great deal of accumulated research on this topic, uncertainty still exists as to why muscle fatigue occurs under various conditions (Enoka and Duchateau 2008). While the majority of muscle fatigue literature investigates the effects of fatigue in relation to the working muscles (Gandevia 2001; Allen et al. 2008), an emerging line of research examines the effects of fatigue on rested muscle groups (Halperin et al. 2014c; Kennedy et al. 2013).

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✉ David G. Behm
dbehm@mun.ca

[1] School of Exercise and Health Sciences, Edith Cowan University, Perth, WA, Australia

[2] Physiology, Australian Institute of Sport, Canberra, Australia

[3] School of Human Kinetics and Recreation, Memorial University of Newfoundland, St. John's, NL A1C 5S7, Canada

This aspect of fatigue has been termed crossover fatigue to denote a temporary deficit in performance of the rested, contralateral limb muscles following a fatiguing protocol to the opposite limb (Martin and Rattey 2007; Doix et al. 2013). However, the broader term of non-local muscle fatigue (NLMF) is used to indicate a temporary deficit in performance of non-exercised muscle groups that could be located contralateral, or ipsilateral, as well as inferior or superior to the fatigued muscle groups (Halperin et al. 2014c; Kennedy et al. 2013) and this definition will be used throughout this review.

The NLMF research is of interest for a number of reasons. First, it seeks to address the question of whether fatigue is specific to the working muscles or is it more of a systemic response. Answering this would greatly enhance our understanding of the mechanisms responsible for muscle fatigue and how these may then be ameliorated with training. Second, NLMF research outcomes may provide practical insights into the order of exercises used in training or rehabilitation programs. Importantly, some muscle groups may be more susceptible to NLMF and this should be considered when planning training or rehabilitation programs. However, such considerations have yet to be accounted for in the relevant literature (Simão et al. 2012) despite emerging evidence of its relevance (Halperin et al. 2014c).

This review seeks to critically discuss and summarize the relevant available NLMF literature related to four pertinent variables: (1) the type of fatiguing protocols; (2) quantification of the NLMF response; (3) muscle specific NLMF effects; (4) gender and training background of participants. Finally, we also seek to provide a hypothesis based on four potential interconnected pathways responsible for NLMF: neurological, biochemical, biomechanical and psychological.

### Search strategy

A literature search was performed independently by two co-authors using SPORT Discus, Pubmed, Web of Science and Google Scholar databases. The search time period ranged from January 1989 to June 2015 using the following-key terms: contralateral, non-local, cross-over, upper-lower in conjunction with muscle fatigue. After a relevant article was identified from the database search, the associated reference lists were carefully examined to identify any further articles not detected in the earlier search. The operational definition of muscle fatigue utilized as an inclusion criteria for studies in this review, was a voluntary reduction in the ability of a muscle to produce force or power [e.g. maximal voluntary contractions (MVC)] (Gandevia 2001). However, studies that examined a time to task failure exercises at a constant level (e.g. cycling with a given resistance) were also included. Thus the inclusion criteria for studies in this review were: (1) The investigation contained a fatiguing exercise of at least one muscle group, followed by a performance test for a non-exercised muscle group(s); (2) The non-exercised muscle group(s) could not be the antagonists to the fatigued muscle groups (e.g., elbow extensors and flexors), as co-contractions could lead to fatigue thereby confounding the rested state of the muscles. (3) Participants had to be healthy and active; (4) The manuscript must be available in the English language and published as an article in a peer-reviewed journal or conference proceeding. Further to these inclusion criteria, our primary classification variable was that the study must have reported either a muscle force response or a time to exhaustion response to the fatiguing exercise task.

### Search result

The database searches returned a total of 37 relevant articles. After reading and applying the inclusion criteria, 35 studies were retained for critical examination. Two investigations were excluded from the final analysis as one reported similar data in two journals (Martin and Rattey 2007; Rattey et al. 2006), while a second investigation (Seaward and Clarke 1992) employed a fatiguing protocol that we believe lacked sufficient intensity to elicit a NLMF response (10 min of running at submaximal intensity among trained runners). The included investigations reported quantifying NLMF with 58 different performance measures (e.g., decrements in force or time to exhaustion) with only 32 positively identifying NLMF effects (Tables 1, 2). A summary of supplementary measures used to describe the performance decrements, such as muscle activation and blood lactate levels, are also provided in Tables 1 and 2. Unfortunately, only two-thirds of the included manuscripts reported absolute values or effect sizes. Furthermore, the majority of included NLMF investigations were conducted with a small number of participants, and only 16 studies included a control condition, thereby not allowing for a robust meta-analysis. However, to provide context and support to our assessment we have reported percent differences where required, and Cohen's *d* effect sizes are reported in the Tables 1 and 2 when absolute values and standard deviations or the effects sizes were stated in studies.

## Fatiguing protocols

A confounding yet linked variable when critically reviewing the magnitude of NLMF is the intensity (e.g., percent of 1RM or MVC), contraction activation strategy (e.g., concentric vs. eccentric; continuous vs. discrete), and number of limbs involved (unilateral vs. bilateral) during the

**Table 1** Illustrates a comprehensive sampling of the non-local muscle fatigue (NLMF) literature investigating the non-exercised lower body muscle groups, presented based on the type of fatiguing protocol used (Isometric, Cyclical or Dynamic)

| References | Study design & subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Isometric fatiguing protocols | | | | | | | |
| Aboodarda et al. (2015) | 12 active males (2F)<br>C-W | Bilateral and unilateral EF | 5 sets of unilateral or bilateral sustained MVC to failure, or until force dropped below 20 % of pre-test | Unilateral KE | Three MVCs performed 30 s, 3 and 5 min post-fatiguing protocol | ↓ MVC 8.9 % (post 1) and 8 % (post 2) after bilateral protocol<br>↓ EMG 18 % after bilateral protocol<br>↑ TMEP 46 % after bilateral & 26 % after unilateral protocol | 0.93–1.07 |
| Arora et al. (2015) | 16 recreationally active males<br>UC-W | Unilateral KE | 15 sets of isometric contractions (16 s on and 4 s of) against 30 % of MVC | Contralateral KE | Single MVC | ↔ MVC of non-exercised KE<br>↔ EMG after fatiguing protocol | >0.1 |
| Doix et al. (2013) | 15 recreationally active males<br>UC-W | Unilateral KE | Two, 100 s continuous MVC | Contralateral KE | Two MVCs after the 1st and 2nd fatiguing protocols. Two min rest between each MVC | ↓ MVC 4.9 % (post 1) and 10.5 % (post 2)<br>↓ ITT 6 % (post 1) and 9 % (post 2) | ~0.6 |
| Halperin et al. (2014c) | 11 resistance trained males<br>C-W | Unilateral KE or EF | Two, 100 s continuous MVC with non-dominant KE (day 1) or non-dominant EF (day 2) | Contralateral KE | Single MVC interspersed by 1 min between fatiguing protocols. This was followed by 12 MVCs with work to rest ratio of 5/10 s | ↓ MVC ~6 % (4–9 %) post the EF fatiguing protocol<br>↓ ITT ~4.5 % (2–7 %) post the EF fatiguing protocol<br>↓ MVC ~8 % (6–11 %) post KE fatiguing protocol<br>↓ ITT 5.5 % (3–9 %) post the KE fatiguing protocol | 0.82<br><br>1.1 |
| Kennedy et al. (2015) | 10 recreationally active subjects (2F)<br>UC-W | Unilateral KE | 2 min continuous MVC | Contralateral KE | 8 MVCs every 25 s | ↔ MVC<br>↔ ITT | NA |
| Kennedy et al. (2013) | 14 recreationally active subjects (6F)<br>UC-W | Bilateral HG | 1. MVC until a 20 % decrement<br>2. Submaximal (30 % of MVC) until 20 % decrement | Unilateral PF | 5 MVCs | ↓ MVC 23, 10 % immediately and 2 min post the maximal<br>↓ MVC 8, 7 % immediately and 2 min post the submaximal<br>↓ ITT 15 and 2 % for maximal and submaximal fatiguing protocol, respectively | NA<br>NA |
| Martin and Rattey (2007) | 15 healthy subject (7F)<br>UC-W | Unilateral KE | One, 100 s continuous MVC | Contralateral KE | 4 MVCs each 30 s post the fatiguing protocol | ↓ MVC 10-13 % (M) & 8 % (F)<br>↓ ITT 9 % (M) 3 % (F) | 1.13 (M)<br>0.77 (F) |
| Paillard et al. (2010) | 8 healthy male subjects<br>UC-W | Unilateral KE | 10 sets of 50 isometric submaximal (10 % of MVC) repetitions. Work to rest ratio of 4/2 s | Contralateral KE | Single MVC | ↔ MVC | NA |

**Table 1** continued

| References | Study design & subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Cyclical fatiguing protocols | | | | | | | |
| Bangsbo et al. (1996) | 7 active male subjects<br>C-W | Upper body | 4 sets of 1 min and one set of 1.5 min of arm cranking exercise (137 W; 60 rpm) with 30 s rest intervals | Unilateral lower limb | Unilateral cycling task to exhaustion with dominant leg (~61 W; 60 rpm) | ↓ Time to exhaustion 27 %<br>↑ Blood lactate at onset of lower body exercise 35 % | 2.77 |
| Bogdanis et al. (1994) | 8 healthy males<br>C-W | Upper body | 5 min of arm cranking exercise | Lower body | Two 30 s maximal effort cycling sprints (Wingate's) interspersed by 6 min | ↓ PP by 5 and 10 % in 1st & 2nd Wingate<br>↑ Blood lactate at onset of Wingate | 2.1 |
| Bouhlel et al. (2010)[a] | 10 well trained males<br>UC-W | Upper or lower body | 6 sets lasting 7 s of cycling interspersed by 5 min | Upper or lower body (opposite to fatigued muscle group) | Same as the fatiguing protocol | ↓ PP ~4 % lower after upper body<br>↑ PP ~4 % upper after lower body | 0.21<br>−0.28 |
| Elmor et al. (2013)[a] | 12 competitive male cyclists<br>C-W | Unilateral lower limb | A 10 min time trial of a self-paced, maximal effort, cycling task | Contralateral lower limb | Maximal cycling test lasting ~4.5 s<br>HG MVC | ↔ PP of non-exercised leg<br>↔HG<br>↔ Blood lactate<br>↔ RPE | >0.1<br>>0.1 |
| Johnson et al. (2014) | 7 moderately trained males<br>C-W | Upper body | Eight, 1 min arm cranking cycling bouts with work rate of 1.5–2.0 W × $kg^{-1}$ interspersed by 30 s | Lower body | One maximal incremental cycling test and four constant-power cycling tests | ↓ Cycling power 8 %<br>↓ Time to exhaustion 8 %<br>↑Blood lactate and H+ | 1.42<br>1.4 |
| Nordsborg et al. (2003) | 6 recreationally trained males<br>C-W | Upper body | Four 1 min arm cranking exercise (140 W; 60 rpm) interspersed by 30 s, followed by 1.5 min interval. Post four min the 5th one min set was conducted | Lower body | Cycling to exhaustion (60 W) | ↓ Time to exhaustion 33 %<br>↑ Interstitial K+ | 4.3 |
| Dynamic fatiguing protocols | | | | | | | |
| Amann et al. (2013)[a] | 8 recreationally active males<br>C-W | Unilateral KE | Constant load KE (60 RPM, 85 % of $W_{peak}$) to task failure | Contralateral KE | Similar to the fatiguing protocol | ↔ MVC of non-exercised KE<br>↔ HG MVC<br>↓ Time to exhaustion of non-exercised KE 49 %<br>↑ RPE, cardiac output, $VO_2$, HR of non-exercised leg at onset of exercise | NA<br>0.39<br>8.8 |
| Ciccone et al. (2014) | 20 well trained males<br>C-W | Upper body | 4 × 5 Reps of squats with 80 % of 1RM and one set to failure interspersed by rest or a set of bench press and bench pull | Lower body | PP in the first four sets of squats and number of repetitions in the fifth set | ↓ PP ~5 %<br>↓ Number of repetitions 13 % | 0.3<br>0.45 |
| Grabiner and Owings (1999) | 12 recreationally active subjects (2F)<br>UC-W | Unilateral KE | 75 Dynamic concentric (day 1) or eccentric (day 2) MVCs at a constant speed | Contralateral KE | 3 MVCs | ↔ MVC post concentric protocol<br>↑ MVC post eccentric protocol 11 % | NA<br>NA |

**Table 1** continued

| References | Study design & subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Grant et al. (2014) | 11 recreationally active males C-W | Bilateral EF | 3 × 10 reps of bicep curls and one set to failure with 70 % of 1RM interspersed by 30 s | Lower body | 2 "Wingates" interspersed by 6 min | ↓ PP by 5 and 1 % in first and second Wingate | 0.3 |
| | | | | | | ↑ Blood lactate at onset of Wingate | |
| Kawamoto and Behm (2014) | 12 recreationally active males C-W | Unilateral KE | 4 sets to task failure of KE with 40 % (light) and 70 % (heavy) of MVC | Contralateral KE | MVC | ↓ MVC 4.4 % (light) | 0.29 |
| | | | | | Isometric time to exhaustion test with 70 % of MVC | ↓ MVC 7.1 (heavy) | 0.53 |
| | | | | | | ↓ Time to exhaustion 8 % (heavy) | 0.29 |
| | | | | | | ↓ Time to exhaustion test 2 % (light) | >0.1 |
| Regueme et al. (2007) | 25 healthy male subjects UC-W | Unilateral PF | Repeated sets of 30 rebound jumps until exhaustion 3 min between each set | Contralateral PF | 3 MVCs followed by10 unilateral drop jumps | ↔ MVC and jump height of non-exercised PF | NA |

*EF* elbow flexors, *EMG* electromyography, *TMEP* thoracic motor evoked potentials, *ITT* interpolated twitch technique, *KE* knee extensors, *MVC* maximal voluntary contraction, *NA* not available, *PF* plantar flexors, *PP* peak power, *RM* repetition maximum, *RPE* rate of perceived exertion, *C* controlled condition included, *UC* uncontrolled study design, *W* within subject study design

[a] Studies reported in tables I and II

fatiguing protocols. Each of these protocol permutations serves as a fundamental tool of adjustment in training program design literature; systematic investigations of these variables are scarce within NLMF literature.

### Contraction intensity

A high intensity isometric fatiguing protocol with the hand grip muscles (100 % of MVC) to task failure was compared to a low intensity protocol (30 % of MVC) in regards to their effects on the non-exercised plantar flexors (Kennedy et al. 2013). The high intensity protocol resulted in significantly greater force reductions (23 %) compared to a low intensity protocol (8 %) (Kennedy et al. 2013). In a study by Kawamoto and Behm (2014), fatiguing the non-dominant knee extensor with loads equal to 70 % of MVC to task failure resulted in a larger NLMF effect in the contralateral knee extensor compared to a lighter load equal to 40 % MVC (7 vs. 4.4 %). Rasmussen et al. (2010) reported that a 20 min low intensity lower body cycling task did not affect elbow flexion MVC or activation. However, a high intensity cycling protocol completed to task failure decreased MVC (5 %) and activation (12 %).

Further evidence demonstrating the lack of NLMF effect following a low intensity fatiguing protocol was reported by Paillard et al. (2010) and Arora et al. (2015). Both investigations tested the non-exercised contralateral knee extensor following a low intensity fatiguing protocol of the contralateral knee extensor. Arora et al. (2015) implemented 15 sets of isometric contractions (16 s contractions with 4 s recovery) performed at 30 % of MVC until a 50 % decrease in MVC was observed, while Paillard et al. (2010) used 10 sets of 50 isometric submaximal (10 % of MVC) repetitions with a work to rest ratio of 4/2 s. In muscles of the upper body, however, similar force deficits (~9 %) were observed in rested FDI muscle after performing one of two fatiguing protocols with the contralateral FDI: a continuous 2 min high intensity (100 % of MVC) or a constant submaximal intensity (30 % MVC) contraction interspersed by a 4 s MVC every 30 s until failure (Post et al. 2008). These few studies suggest that higher intensity contractions may lead to greater NLMF in the lower body compared to lower intensity ones, and may not influence the upper body to an equivalent extent.

### Contraction activation strategy

Few studies have directly compared the effect of muscle contraction activation strategy (cyclical concentric only, repeated voluntary concentric contractions or isometric, repeated stretch–shortening cycle contractions, continuous voluntary isometric or a form of involuntary stimulated contraction) on manifestations of NLMF. In early work by

**Table 2** Illustrates a comprehensive sampling of the non-local muscle fatigue (NLMF) literature investigating the non-exercised upper body muscle groups, presented based on the type of fatiguing protocol used (Isometric, Cyclical or Dynamic)

| References | Study design and subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Isometric fatiguing protocols | | | | | | | |
| Halperin et al. (2014c) | 10 resistance trained males<br>C-W | Unilateral EF or KE | Two, 100 s continuous MVC KE (day 1) or EF (day 2) | Contralateral EF | Single MVC interspersed by one min between fatiguing protocols. This was followed by 12 MVCs with work to rest ratio of 5/10 s | ↔ MVC EF post both fatiguing protocol (<3 %)<br>↔ ITT after both fatiguing protocol (<3 %) | 0.17 (leg-arm)<br>>0.1 (arm–arm) |
| Post et al. (2008) | 15 subjects healthy subjects<br>(7F)<br>UC-W | Unilateral FDI | Protocol 1: Continuous 2 min MVC with FDI<br>Protocol 2: Constant submaximal contraction (30 % of MVC), interspersed by a 4 s MVC every 30 s until failure | Contralateral FDI | 2 MVCs repeated every 40 s for 5 min | ↓ Both fatiguing protocols led to ~9 % in MVC<br>↓ ITT 22 % post protocol and 9 % post protocol 2 | NA |
| Todd et al. (2003) | 10 healthy subjects (3F)<br>C-W | Unilateral EF | Two, 1 min sets of continuous EF MVCs with the right arm interspersed by 1 min of continuous MVCs with contralateral arm (fatigue day) or rest (control day) | Contralateral EF | Continuous MVCs | ↔ Force production between the two trials<br>↓ ITT during fatigued day 2.8 % | NA |
| Zijdewind et al. (1998) | 7 healthy subjects (4F)<br>UC-W | Unilateral FDI | Constant isometric force (30 % of MVC) with right side FDI, interspersed by a 4 s MVC every 30 s until failure | Contralateral FDI | Same as fatiguing protocol with left side | ↔ MVC<br>↔ Time to exhaustion | NA<br>−0.82 |
| Cyclical fatiguing protocols | | | | | | | |
| Bouhlel et al. (2010)[a] | 10 well trained males<br>UC-W | Upper or lower body | 6 Sets lasting 7 s of cycling interspersed by 5 min | Upper or lower body (opposite to fatigued muscle group) | Same as the fatiguing protocol | ↓ PP ~4 % lower after upper body<br>↑ PP ~4 % upper after lower body | 0.21<br>−0.28 |
| Decorte et al. (2012) | 13 moderately trained males<br>UC-W | Lower body | Lower body cycling at 80 % of maximal power output. Work to rest ratio was 6/4 min. Repeated to failure | Unilateral HG | Two HG MVCs after each round | ↔ HG MVC | >0.1 |
| Elmor et al. (2013)[a] | 12 competitive male cyclists<br>C-W | Unilateral lower limb. | A 10 min time trial of a self-paced, maximal effort, cycling task | Contralateral lower limb<br>HG | Maximal cycling test lasting ~4.5 s<br>HG MVC | ↔ PP of non-exercised leg<br>↔ HG MVC<br>↔ Blood lactate<br>↔ RPE | >0.1<br>>0.1<br>>0.1<br>>0.1 |
| Rasmussen et al. (2010) | 16 healthy male subjects | Lower body | Protocol 1: 20 min of cycling at light workload (124 ± 21 W)<br>Protocol 2: 20 min of cycling at light workload (124 ± 21 W) at hypoxic conditions<br>Protocol 3: graded cycling until exhaustion with 10 % increase in workload every 5th min | Unilateral EF | 2 MVCs repeated ~20–30 s post protocol | ↔ MVC and ITT post protocol 1<br>↓ MVC 6 % and ITT 12 % post protocol 1<br>↓ MVC 5 % and ITT 15 % post protocol 3 | NA<br>NA<br>NA |
| Sidhu et al. (2014) | 8 recreationally active males<br>C-W | Lower body | Constant-workload cycling to failure (80 % of peak work) | Unilateral EF | Single EF MVC | ↓ MVC 5 %<br>↓ ITT 5 % | 1.2 |

**Table 2** continued

| References | Study design and subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Dynamic fatiguing protocols | | | | | | | |
| Amann et al. (2013)[a] | 8 recreationally active males<br>C-W | Unilateral KE | Constant load KE (60 RPM, 85 % of $W_{peak}$) to task failure | Contralateral KE | Similar to the fatiguing protocol | ↔ MVC of non-exercised KE | NA |
| | | | | | | ↔ HG MVC | 0.39 |
| | | | | | | ↓ Time to exhaustion of non-exercised KE 49 % | 8.8 |
| | | | | | | ↑ RPE, cardiac output, VO2, HR of non-exercised leg at onset of exercise | |
| Alcaraz et al. (2008) | 10 trained males<br>C-W | Lower body | 5 sets of leg extension and PF extension (6RM) or rest | Upper body | Five sets of bench press (6RM) interspersed by lower body exercises or rest | ↔ Number of repetitions | >0.1 |
| | | | | | | ↔ PP | >0.1 |
| Halperin et al. (2014b) | 18 resistance trained males<br>C-W | KE | Five sets submaximal knee extensions to failure (50 % of single leg MVC). One min rest between sets | Unilateral EF | Immediate post-test single MVC. 2 min post followed by 12 MVCs with work to rest ratio of 5/10 s | ↔ Immediate post-test MVC with EF | >0.1 |
| | | | | | | ↓ MVC Only in last 5 repetitions during the 12 repeated protocol ~5 % | 0.58 |
| | | | | | | ↑ Blood lactate post-fatiguing protocol | |
| Humphry et al. (2004) | 6 healthy male subjects<br>UC-W | Unilateral EF | EF with a 3.5 kg dumbbell at a constant pace until failure | Contralateral EF. HG | Three MVCs with EF & HG | ↔ EF MVC 3 % | NA |
| | | | | | | ↓ HG MVC 5 % | NA |
| Millet et al. (2003) | 12 competitive male runners<br>UC-W | Lower body | Thirty km running race | Unilateral HG | 2 MVC | ↔ Handgrip MVC | >0.1 |
| Place et al. (2004) | 9 competitive triathletes<br>UC-W | Lower body | Five hour run at a pace consistent with 55 % of maximal aerobic velocity | Unilateral HG | 2 MVCs every hour | ↔ MVC | NA |
| Ross et al. (2007) | 9 experienced runners (gender unclear)<br>UC-W | Lower body | Full marathon (42.2 km) | Unilateral HG | 2 MVC | ↔ MVC | >0.1 |
| Ross et al. (2010) | 7 competitive male runners<br>UCW | Lower body | Self-paced 20 km run | Unilateral HG | 2 HG MVC post 5 and 10 km | ↔ MVC | NA |

**Table 2** continued

| References | Study design and subjects | Fatigued muscles groups | Fatiguing protocol | Tested muscles groups | Testing protocol | Key findings | Effect sizes (*d*) |
|---|---|---|---|---|---|---|---|
| Triscott et al. (2008) | 8 healthy (1F)<br>8 Strength-endurance (2F)<br>8 Resistance trained males<br>UC-W | Unilateral EF | *Day 1* Dynamic unilateral EF with 3.5 kg to exhaustion<br>*Day 2* Dynamic EF 4.5 kg to exhaustion | Contralateral EF | *Day 1* Three MVCs<br>*Day 2* EF with 3.5 kg to exhaustion | ↔MVC<br>↓ Time to exhaustion 20 and 25 % in healthy and resistance groups. No change in strength-endurance group | NA<br>0.65 (healthy)<br>0.71 (resistance)<br>>0.1 (strength-endurance) |

*EF* elbow flexors, *EMG* electromyography, *ITT* interpolated twitch technique, *KE* knee extensors, *MVC* maximal voluntary contraction, *NA* not available, *PF* plantar flexors, *PP* peak power, *HG* handgrip, *FDI* first dorsal interosseous muscle, *RM* repetition maximum, RPE rate of perceived exertion *C* controlled condition included, *UC* uncontrolled study design, *W* within subject study design

[a] Studies reported in both tables

Grabiner and Owings (1999), fatiguing the knee extensors with concentric contractions prior to testing the contralateral limb knee extensors led to no observed NLMF effects, whereas force production actually improved (~11 %) following an eccentric fatiguing protocol (Grabiner and Owings 1999). The use of isometric and cyclical muscle contractions shows a greater consistency towards observable NLMF (Table 1). In contrast, there is greater variation in reported results after repeated dynamic contractions with resistance (concentric and eccentric). For example, none of the four studies utilizing a fatiguing running intervention reported NLMF effects with the rested grip muscles (Ross et al. 2007, 2010; Place et al. 2004; Millet et al. 2003). This could potentially be the reflexive and mechanical benefits of the stretch–shortening cycle (Komi and Bosco 1978) with short transient recovery periods (flight phase) between contractions helping to alleviate NLMF when running. The higher incidences of NLMF with isometric contractions and cycling (no recovery periods) compared to the repeated dynamic and running studies suggest that inter-repetition recovery periods may play an important role NLMF effects. However, the lack of effect could also be explained by the fact that participants in these studies were trained endurance athletes, or that the tested muscle groups were located in the upper body which demonstrate a reduced susceptibility to NLMF. While in two separate studies, Halperin et al. (2014b, c) employed similar testing protocols for the rested elbow flexors but reported conflicting results. Whereas using five sets of bilateral, dynamic knee extensions to task failure elicited a small NLMF-induced MVC force loss with the contralateral elbow flexors (Halperin et al. 2014b), two sets of 100 s unilateral, isometric contractions did not elicit a NLMF response (Halperin et al. 2014c). This inconsistency might be attributed to differing contraction types (dynamic vs. isometric), the dissimilar number of participants in each study, or to a lower extent of muscle activation with bilateral versus unilateral contractions (see bilateral and unilateral tasks below). Thus, with the very few studies directly comparing contraction activation strategies and the variability between single contraction type studies, a definitive conclusion cannot be formulated.

## Bilateral and unilateral tasks

Results of a recent study suggest that bilateral isometric fatiguing protocols may lead to a greater NLMF effect compared to unilateral fatiguing tasks (Aboodarda et al. 2015). Aboodarda et al. (2015) had participants' complete five sets of continuous MVCs to task failure (a force reduction below 20 % of pre-test) with either one or both elbow flexors, prior to performing a number of MVCs with the rested knee extensors. Whereas no NLMF effects were found after the unilateral fatiguing protocol, force production of knee extensors was reduced by 8 % following the bilateral protocol, however statistical significance was not reached despite large effect sizes (0.93–1.07) observed. This bilateral performance decrement has been previously observed and is reported to result from a reduction in neural drive (Van Dieen et al. 2003). Importantly, there are reports that bilateral contractions activate inter-hemispheric inhibitory mechanisms (Oda and Moritani 1996, 1995), which may subsequently affect the neural drive to the rested muscles. The inconsistent results of the Halperin et al. (2014b, c) studies could also be explained with a similar underlining reasoning. Whereas Halperin et al. (2014b) implemented a bilateral knee-extension fatiguing protocol and observed a NLMF with the elbow flexors, Halperin et al. (2014c) implemented a unilateral knee-extension fatiguing protocol and did not record any NLMF effects.

**Summary**

Higher intensity muscle contractions seem to lead to greater NLMF effects in the lower body compared to lower intensity contractions, however, contraction intensity does not seem to influence the upper body to a comparable extent. Furthermore, isometric and cyclical contractions tend to increase NLMF effects compared to dynamic contractions. Finally, bilateral fatiguing protocols may lead to a larger NLMF effect compared to unilateral protocols.

## Testing protocols for non-exercised muscle groups

Most NLMF studies employ either (1) a single post-fatiguing test MVC; ii) repeated MVCs interspersed by long rest duration (≥30 s) or (2) submaximal exercise to exhaustion. Using time to exhaustion and repetitive MVC protocols, investigators are more commonly able to observe a larger NLMF response compared to a single MVC. Indeed, NLMF deficits with individual muscle contractions for force and power of only 3–10 % are common (Humphry et al. 2004; Halperin et al. 2014b, c; Doix et al. 2013; Paillard et al. 2010; Sidhu et al. 2014; Karageorghis and Priest 2012; Aboodarda et al. 2015), in contrast NLMF measured with time to exhaustion tests elicit decrements of 10–50 % (Bangsbo et al. 1996; Nordsborg et al. 2003; Amann et al. 2013; Triscott et al. 2008; Johnson et al. 2014). However, it is challenging to compare the different outcomes as they represent different constructs. Studies that tested for muscle fatigue did so by employing units of force and power, whereas exhaustion test studies are quantified by units of time. Additionally, an uneven number of studies measured force/power (31 studies with 48 measures) compared to those recording time to exhaustion (six studies with nine measures).

For instance, after performing a unilateral fatiguing protocol with the elbow flexors, the contralateral arm elbow flexor MVC remained unaffected, but significant decrements (~20 %) were observed in time to exhaustion tests with the same arm (Triscott et al. 2008). Amann et al. (2013) reported similar findings in which a unilateral fatiguing protocol of the knee extensors did not affect the contralateral knee extensors MVC, but the subsequent submaximal knee extensions to exhaustion was ~50 % shorter compared to control conditions. Halperin et al. (2014b) tested the rested elbow flexors with a single 5 s MVC, and after 2 min of rest, a strength-endurance protocol was conducted (12 MVCs at a rate of one 5 s contraction every 10 s). No NLMF effects were observed with the single MVC, but force decrements were recorded in the last 5 MVCs of the strength-endurance protocol. This suggests that NLMF effects in the upper body may appear with repeated MVCs with short rest durations and less so with a single MVC, or repeated MVCs with long rest durations.

Indeed, most time to exhaustion tests were completed at submaximal intensities, which are longer in duration compared to maximal intensity activities. The higher incidence and magnitude of NLMF with prolonged and repetitive testing procedures might stress a number of physiological systems (e.g., neural and biochemical) to a greater extent than single contractions. For example, prolonged testing contractions demand more persistent neural input, which could augment global neural fatigue (e.g. inter-hemispheric and/or corticospinal inhibition), and afferent inhibition of spinal and cortical motoneurones (Behm 2004). Prolonged or repetitive testing contractions may lead to a greater accumulation of metabolic by-products in the tested muscles, while activating type III and IV muscle afferents leading to inhibition of the central motor drive (Amann 2012, 2011; Sidhu et al. 2014; Amann et al. 2013) (see Mechanisms of NLMF below). Disruptive metabolic by-products could also be distributed globally directly affecting remote muscle(s) performance that is more reliant upon efficient energy expenditure (e.g., prolonged contractions, time to exhaustion tests) (Bangsbo et al. 1996; Bogdanis et al. 1994; Halperin et al. 2014b; Johnson et al. 2014; Grant et al. 2014; Nordsborg et al. 2003).

Lastly, the differences in effects between time to exhaustion and the discrete MVC tests may be related to participant's knowledge of exercise endpoint (e.g., number of repetitions, distance or time of activity). In contrast to discrete MVC testing, participants are not provided with an exercise endpoint in the time to exhaustion tests. Lack of exercise endpoint has been shown to hinder performance in various exercise activities (Mauger et al. 2009; Billaut et al. 2011; Faulkner et al. 2011; Halperin et al. 2014a). This hindrance is suggested to be caused by the inability to develop a pacing strategy (e.g., how to distribute the work and energy throughout the task), which could decrease the motivation to complete the task in an optimal manner (Halperin et al. 2014a; Mauger et al. 2009). Such decrements in motivation with time to exhaustion tests may be exacerbated after performing a fatiguing task with a different muscle group.

**Summary**

Time to exhaustion and repetitive MVCs protocols typically record a greater NLMF response compared to discrete MVCs. This could stem from a greater continuous stress on the different systems (neural, biochemical and psychological). However, due to the smaller number of studies investigating time to exhaustion compared to strength/power outcomes, and the different units of measurements (time vs power/force), these conclusions should be interpreted with care.

## Is NLMF muscle specific?

Not all muscle groups may be equally susceptible to NLMF. The combined outcomes from the identified research suggest that the lower body musculature has a greater susceptibility to NLMF (Tables 1, 2). Indeed, 76 % of all performance outcome measurements of the lower limbs observed NLMF (23 of 30 measurements) (Table 1). In contrast, only 32 % of all measurements testing the upper body observed evidence for NLMF (nine of 28 measurements) (Table 2). There was no evidence of upper body muscle differentiation with most studies demonstrating a lack of NLMF whether single muscle groups [elbow flexors, handgrip, first dorsal intersosseous (FDI)] or multiple muscle groups (upper body cycle ergometry) were tested. The only study comparing the effects of fatiguing different muscles groups on the magnitude of NLMF within the same muscle group is the recent work of Halperin et al. (2014c). These investigators utilized a continuous 100 s MVC with either the elbow flexors or the knee extensors resulting in force (~7 %) and muscle activation (~5 %) decrements in the non-exercised knee extensors. In contrast, these authors observed that NLMF was not replicated when the two fatiguing protocols were repeated prior to testing the non-exercised elbow flexors. Thus concluding that the elbow flexors are less susceptible to NLMF than the knee extensors, an observation, which is supported by studies implementing multi-joint exercises as well (Alcaraz et al. 2008; Ciccone et al. 2014). For example, when comparing upper body exercise in recreational resistance trained men, the number of completed bench press repetitions was unaffected when performed following lower body exercises compared to control conditions (Alcaraz et al. 2008). In related contrasting work, trained participants completed fewer repetitions and produced lower peak power with the squat exercise when performed following upper body exercise compared to control condition (Ciccone et al. 2014).

Whereas the quadriceps were the predominant lower limb muscle group investigated with NLMF studies, there were two plantar flexors studies. While Regueme et al. (2007) reported no change in plantar flexors MVC force following rebound jumps to exhaustion, Kennedy et al. (2013) detailed an impairment of plantar flexor MVC force following fatiguing isometric handgrip exercise. There were also a number of studies reporting NLMF in the lower limbs when using cycling to exhaustion tests after fatiguing the upper body musculature with a cycling task (Bogdanis et al. 1994; Bangsbo et al. 1996; Johnson et al. 2014; Nordsborg et al. 2003). Bouhlel et al. (2010) examined if fatiguing the lower limbs with a cycling task influenced cycling performance with the upper body, and reversed the exercise order on a different day. In their study trained subjects completed six maximal effort cycling sets lasting 7 s with the upper and the lower body. While no significant differences were observed between conditions, there were reductions in peak power when the lower body was tested after the upper body compared to the reverse. Furthermore, very long rest periods between sets (5 min) were provided which may have negated some of the NLMF effects.

When considering mechanisms to explain the greater NLMF susceptibility of the lower compared to the upper body, current literature does not have the investigative control or statistical power necessary to provide a conclusive outcome. However, we would contest that the literature does provide the basis for a working hypothesis, which describes a transient neuromuscular impairment, especially for the quadriceps (predominant lower body muscle tested). Muscle fatigue is reported to decrease the ability to fully activate the exercised muscle (Gandevia 2001), with the quadriceps more difficult to fully activate compared to the biceps brachii (Behm et al. 2002). Thus, we propose that the fatiguing exercise hinders the nervous systems ability to fully activate the non-exercised quadriceps. This hypothesis is supported by reports of decrements in muscle activation in the non-exercised legs, highlighting deficits in central activation (Doix et al. 2013; Halperin et al. 2014c; Martin and Rattey 2007; Kennedy et al. 2013; Aboodarda et al. 2015).

It is accepted that the quadriceps are larger (Miller et al. 1993) and produce greater force (Izquierdo et al. 1999) than the upper body muscles, suggesting a possibility in which the mass of the quadriceps influences the neural drive required to fully activate and consequently, affects the magnitude of NLMF. Indeed, the rate of perceived exertion was found to be higher when completing five sets to task failure in the squat exercise compared to the bench press, even when relative intensity (% of 1RM) and rest periods were controlled (Mayo et al. 2014). Thus, activation of larger muscle mass found in the lower limbs may be associated with greater perception of effort, making the subsequent tests for the non-exercised lower body seem harder, which may lead to a greater NLMF effect. However, there is no evidence of muscle mass differentiation among the upper body muscles (elbow flexors vs. handgrip vs. FDI), or considering the lack of convincing evidence for NLMF of the plantar flexors with a similar lack of evidence for the larger mass of multiple upper body muscle groups when cycling (e.g., coordinated use of biceps brachii, triceps brachii, pectoralis major, latissimus dorsi). Furthermore, Humphry et al. (2004) observed NLMF in the smaller mass handgrip muscles versus no NLMF in the larger mass elbow flexors in the contralateral limb following dynamic elbow flexion contractions with a 3.5 kg resistance until failure.

In addition, compared to the elbow flexors, the knee extensors possess a slightly higher percentage of fast twitch high threshold muscle fibres (average of 8 studies ~45 vs. 54 %, respectively) (Miller et al. 1993) and more motor units (Galea et al. 1991). Importantly, the lower limbs serve as locomotion generators in humans (MacKay-Lyons 2002; Guertin 2012) and as such there is potential for the lower body to possess a modified neural and reflex connectivity compared to the upper body. The upper body muscles have also been shown to be activated more frequently than the lower body muscles during every day activities (Kern et al. 2001), which may differentiate the neural network of the upper and lower body. We speculate that such differences affect the susceptibility of the quadriceps to NLMF. This suggests that the quadriceps are more difficult to activate and are therefore more susceptible to NLMF, which may be related to fatigue-induced alterations in the lower body spinal connectivity. A caveat on this rationale of greater central drive required to activate high threshold fast twitch motor units is that currently this can only be applied to investigations comparing knee extensors to the elbow flexors muscle groups. However, both are the most frequently tested muscle groups within the NLMF literature.

### Summary

Lower body muscle groups (mainly quadriceps) seem to be more susceptible to NLMF compared to the upper body (mainly elbow flexors). Decrements in the nervous systems ability to activate the non-exercised lower limb muscles are a probable cause. This lack of activation could be related to fact that the lower body muscles are larger, have more motor units, possess a greater percentage of fast twitch muscle fibres, and have a modified neural and reflex network compared to the upper body muscle groups. Furthermore, fatiguing exercises with the lower body lead to a greater perception of effort compared to the upper body exercises, thus potentially affecting performance of the non-exercised muscles.

## Confounding participant factors

There are a substantial number of factors that may confound a study's design and thus the data interpretation (Halperin et al. 2015). The two major factors observed in the NLMF literature are a bias in the gender and training background of participants involved in the reported investigations.

### Gender

Only one study directly compared NLMF effects between genders (Martin and Rattey 2007) observing that both genders demonstrated NLMF measured by a reduction in MVC force, however, effects were larger with males (males: 13 %; females: 8 %). An important novel outcome in this study was that central activation decreased by 9 % in males and only 3 % in females. While it should be noted that out of an overall 439 participants in NLMF studies, only 36 were females and muscle fatigue has been demonstrated to be gender specific (Hunter 2009). According to a review by Hicks et al. (2001) females tend to be more fatigue resistant due to lower absolute muscle forces generated when performing the same relative work as males, leading to a lower muscle oxygen demand and less mechanical compression of the vasculature. Furthermore, males have a greater reliance on glycolytic pathways than females and tend to exhibit a greater impairment in neuromuscular activation after fatiguing exercise (Hunter 2009; Hicks et al. 2001). Hence the greater vascular compression and higher glycolytic-based metabolite release might contribute to a global reduction in muscle activation with fatigue and contribute to possible NLMF gender differences. However due to the dearth of comparative studies, it is suggested that future studies use female participants due to the disproportionate ratio of males to females in NLMF studies or recruit a sufficient sample to provide a direct gender comparison as part of the study design.

### Training background

Currently only a single study has compared the NLMF response between groups with differing training backgrounds: healthy, strength-endurance and resistance trained (Triscott et al. 2008). In this investigation after fatiguing the elbow flexors, the contralateral arm MVC was unaffected in all groups regardless of training history, however using a submaximal task to failure both the healthy and resistance trained participants demonstrated significant deficits whereas the strength-endurance trained subjects were immune to such effects. Strength-endurance trained subjects might accumulate less metabolic by-products due to their lesser reliance on glycolytic pathways resulting in less inhibitory metaboreceptor afferent input to the central nervous system (Lattier et al. 2003). Similar to NLMF studies, training status has also been shown to influence the magnitude of maximal eccentric exercise-induced muscle damage of the elbow flexors, with male strength trained participants not experiencing the same magnitude of effect and recovering faster than untrained males (Newton et al. 2008). This was suggested to result from training induced muscle structure changes (elimination of susceptible fibres or the addition of sarcomeres in series) (Morgan and Allen 1999), biochemical efflux changes such as a reduced heat shock protein release (Koh 2002) or an enhanced neural adaptation such as greater motor unit activation per unit of torque (McHugh et al. 2000). Although the eccentric exercise model is an extreme muscle contraction model it does provide suggestive evidence for support of training status as a confounding factor in NLMF. However, considering that trained and untrained participants demonstrate different muscle fatiguing profiles, the NLMF effect should be investigated in future studies with greater consideration of training backgrounds.

### Summary

Based on the results of only two studies, but supported by relevant literature, it is suggested that males have a greater susceptibility to NLMF. While only a single study has directly compared the effect of training status, it appears that specific training backgrounds (i.e. strength-endurance) can protect against a NLMF effect when the non-exercised muscle groups are tested in a relevant and specific manner.

## Mechanisms of NLMF

### Neurological

The ability to fully activate a muscle depends on the contributions of supraspinal and spinal excitatory and inhibitory influences (Gandevia 2001). Fatigue of such structures can result in a progressive exercise-induced reduction in voluntary activation or neural drive to the muscles (Gandevia 2001). We propose that fatigue-induced nervous system alterations can account for some of the observed NLMF effects.

The fatiguing protocols can alter the metabolic environment in the working muscles leading to activation of group III and IV muscle afferents (Amann 2012, 2011; Amann et al. 2013; Martin and Rattey 2007). Through a feedback loop, the muscle afferents provide an inhibitory effect to the central nervous system leading to decrements in central drive to the working muscle and potentially to the non-exercised muscles as well (Amann 2012, 2011; Sidhu et al. 2014; Amann et al. 2013). The termination of high intensity constant load exercise has been suggested to occur once an individual's sensory tolerance limit has been reached (Amann 2012; Amann et al. 2013). Such a sensory tolerance limit may have global or NLMF effects and can be associated with a certain level of peripheral fatigue and metabolic by-products (Amann 2012, 2011; Amann et al. 2013). Once approached or reached, inhibition of central drive will take place. Thereafter, when testing the non-exercised muscle group, the afferent feedback from the fatigued muscle could still remain high. Accordingly, the afferent feedback coming from the working tested muscle group in combination with the previously fatigued muscle group, could lead to a more rapid central drive inhibition due to reaching the sensory tolerance limit (Amann et al. 2013). Support for this model came from Sidhu et al. (2014) who compared the effects of cycling to exhaustion with and without sensory feedback from lower limbs on force production and activation of the elbow flexors. Gradual reduction in the responsiveness of the motor cortical cells and/or spinal motoneurons were found during the control day, whereas no changes occurred when the same exercise was performed with blocked lower limb muscle afferents. This suggests, group III and IV muscle afferents exert inhibitory influences on the corticospinal motor pathways of the upper limb in the presence of lower body muscle fatigue.

However, recently reported results suggest that the NLMF effects of group III and IV afferent are unlikely (Kennedy et al. 2015). In this study participants completed a series of MVCs with the contralateral knee extensors after completing a two minute continuous unilateral MVC of the knee extensors on two occasions. On 1 day a sphygmomanometer cuff was placed around the fatigued leg after the fatiguing protocol, and prior to testing the rested limb, while on the alternative testing day no cuff was placed around the fatigued limb. Since blood occlusion is expected to increase the firing frequency of group III and IV afferents within in the fatigued muscle, and lead to decrements in central drive, greater deficits in performance and activation are to be expected in the contralateral limb. However, no differences were observed between conditions, and no NLMF effects were recorded compared to pre-test values. Thus, further investigation is required to confirm the contribution of group III and IV afferents to NLMF effects.

Interestingly, the NLMF effects can excite or inhibit components of the corticospinal pathway depending on the time of measurement and the muscles involved. A number of studies have illustrated increased motor evoked potentials (MEP: assessment of corticospinal excitability) of the non-fatigued muscles during fatiguing contractions of the affected muscle (Takahashi et al. 2011; Stedman et al. 1998; Matsuura and Ogata 2015). However, MEPs elicited from the non-fatigued muscles have also been reported to decrease (Bonato et al. 1996; Takahashi et al. 2009, 2011). As MEP responses are indicative of corticospinal excitability, further measures are necessary to more specifically highlight the most predominant site of action. Aboodarda et al. (2015) examined spinal (thoracic motor evoked potentials (TMEPs) and peripheral [femoral nerve stimulation (Mmax)], knee extensor MVCs and EMG) excitability following unilateral and bilateral fatiguing elbow flexion MVC. Although vastus lateralis EMG activity was reduced by 18 % following the bilateral fatiguing protocol, spinal excitability as measured with a TMEP·Mmax$^{-1}$ ratio significantly increased (46 %). Since the decrement in EMG activity could not be ascribed to spinal inhibition, it was surmised that supraspinal motor output must have been reduced. Takahashi et al. (2009, 2011) made similar deductions based on a decrease in short interval intracortical inhibition (SICI: assessment of excitability of intracortical inhibitory circuits) that matched the time course of MEP decreases in both studies (fatigue of hand grip muscles and quadriceps respectively with examination of FDI and biceps brachii). More specifically, it has been postulated that an increased tonic level of inter-hemispheric or transcallosal inhibition could be a contributing factor (Takahashi et al. 2009, 2011). Furthermore it is also conceivable that indirect connections from pre-motor areas (Byblow et al. 2007, Takahashi et al. 2011) or upstream of the motor cortex (Matsuura and Ogato 2015) could also play an important role with NLMF responses.

There is also evidence for a shared neural network between contralateral limbs as evident by the cross-extensor reflex (Sherrington 1910) and cross-education phenomena (Carroll et al. 2006). Such neural networks may affect the NLMF found in the contralateral fatigue studies. Indeed, unilateral fatigue has been shown to decrease the intracortical facilitation of the motor cortex in control of the non-exercised contralateral muscle (Bäumer et al. 2002). A unique neural network connecting to upper and lower body has been demonstrated to exist (Huang and Ferris 2004; de Kam et al. 2013) potentially influencing the NLMF effects. For example, it was reported that cyclic tasks with the upper body elicit muscle activation in the lower limbs as a function of cycling intensity (Huang and Ferris 2004). Such muscle activation values (~55 % of MVC) could potentially induce muscle fatigue in the lower limbs leading to NLMF as was demonstrated by implementing an upper body cycling task prior to testing the lower body muscles. However at this juncture more research is needed to verify this assumption.

An additional potential pathway hindering neural drive to the non-exercised muscles includes perturbations to cerebral oxygenation and metabolism. During maximal effort exercise cerebral oxygenation has been shown to decrease (Nybo and Rasmussen 2007). Rasmussen et al. (2010) observed the effects three lower body cycling tasks had on the rested elbow flexors MVC: (1) a 20 min light intensity task, (2) a hypoxic 20 min light intensity task, and (3) maximal effort task to exhaustion. Whereas the elbow flexors remained unaffected after the light protocol, MVC and activation decreased to a similar extent following the light hypoxic and high intensity protocol. These decreases were associated with lowered cerebral oxygen delivery, which is suggested to hinder central drive to the rested muscles (Rasmussen et al. 2010).

The neural influence in the extent of NLMF is further supported by recent evidence of NLMF-like effects occurring following extensive passive stretching. Impairments in jump height were found following a passive stretching protocol of the contralateral limb (da Silva et al. 2015) or the upper body limbs (Marchetti et al. 2014). Passive stretching would not have resulted in any substantial accumulation of metabolites, and thus cardiovascular dispersion of metabolites or metaboreceptor-related afferent inhibition would have to be mediated by a different neural pathway. However, not all non-local stretching studies observed NLMF-like effects. Chaouachi et al. (2015) employed unilateral hip flexion static and dynamic stretching, reporting that the contralateral non-stretched hip flexors experienced 6–8 % range of motion increase, but no significant decrements with isokinetic torque. Overall, further investigation and comparisons of passive and active muscle actions on non-local effects will assist in eliciting greater insight into the NLMF mechanisms.

## Summary

Fatiguing protocols activate group III and IV muscle afferents, which is speculated to decrease central drive the non-exercised muscles. The neural pathways accounting for NLMF most likely include the shared network connecting to upper and lower body and the contralateral limbs. Emerging evidence suggests that the motor output reduction is located supraspinally. A decrease in cerebral oxygenation occurring during intense exercise could also lead to subsequent NLMF. Indirect support of the neural pathways leading to NLMF includes the non-local effects of stretching different muscles on non-stretched muscles.

## Biochemical

The greater NLMF effect with prolonged, high intensity contractions can lead to blood mediated migration of metabolic by-products originating in the fatigued muscles. Such metabolites can also be distributed to remote muscles via the cardiovascular system and directly influence its ability to contract. Indeed, increments in potassium (Johnson et al. 2014; Nordsborg et al. 2003), hydrogen (Bangsbo et al. 1996; Johnson et al. 2014) and blood lactate (Bangsbo et al. 1996; Bogdanis et al. 1994; Halperin et al. 2014b; Johnson et al. 2014; Grant et al. 2014), were reported at the initiation of the testing procedure of the non-exercised muscles. The importance of blood lactate and hydrogen in relation to muscle fatigue is disputed (Lamb and Stephenson 2006) and suggested to have been overestimated (Allen et al. 2008); however, these metabolites may still hinder the muscles' ability to contract. Hydrogen ions have been shown to reduce the force per cross bridge in both fast and slow fibers (Fitts 2008; Knuth et al. 2006), and reduce myofibrillar $Ca^{2+}$ sensitivity (Fitts 2008). The latter may have a significant contribution to the decline in force in the late stages of fatigue when the amplitude of the $Ca^{2+}$ transient is reduced (Allen et al. 1989).

Additionally, induced acidosis can aggravate fatigue in intact humans (Kowalchuk et al. 1984; Hultman et al. 1985). It was also demonstrated that repeated activation of a muscle increases the extracellular levels of potassium (Sejersted and Sjøgaard 2000), which could potentially migrate to the non-exercised muscles. Indeed, repeated muscle activation can result in alteration of electrochemical gradients for potassium, which can lead to considerable reduction in force (Juel 1986). In relation to NLMF, it is suggested that accumulation of extracellular potassium can reduce the excitability of the active muscle leading to fatigue (Nordsborg et al. 2003). An alternative transient metabolite is the known response of heat shock proteins to exercise (Koh 2002). Exercise results in these metabolites being present in non-exercised systems or organs (Jammes et al. 2012) and the implicated effects of heat shock proteins as a immunomodulator at a central level (Heck et al. 2011). Elevated levels of heat shock proteins, in particular HSP 70, is also reported to have detrimental effects on force recovery and low frequency fatigue (Thomas and Noble 1999). It should be noted, however, that the produced metabolites exert interactive effects on muscle force and performance and need to be considered together (Cairns and Lindinger 2008).

#### Summary

During and after the completion of the fatiguing protocols, different metabolites such as potassium, hydrogen, lactate and heat shock proteins can be circulated to remote non-exercised muscles via the cardiovascular system, and possibly hinder their contractile ability.

### Biomechanical

Some effects of NLMF could be attributed to deficits in the ability of the fatigued muscle groups to optimally stabilize the body while the non-exercised muscles are tested. For example, Baker and Davies (2009) reported that the handgrip muscles have a key role in power production during maximal cycling test. When participants were required to cycle without gripping the handlebar during a 30 s cycling sprint, peak power was 20 % lower (Baker and Davies 2009). It is possible that observed NLMF during high intensity lower body cycling tasks performed after an upper body fatiguing protocol may actually result from an inability of the handgrip muscles to optimally stabilize the upper body due to accumulated fatigue (Bogdanis et al. 1994; Grant et al. 2014). Indeed, fatiguing the elbow flexors prior to testing the non-exercised lower limbs with a maximal cycling test also led to muscle fatigue of the handgrip muscles (Grant et al. 2014). Similarly, the trunk muscles (abdominal and lower back) are suggested to act as stabilizers during upper and lower body movements, thereby creating an efficient proximal to distal patterning of force generation (Kibler et al. 2006). High muscle activation of the trunk muscles has been reported during upper (Tarnanen et al. 2008) and lower (Danneels et al. 2001) body activities. Thus, in some occasions NLMF effects may simply be due to participant's inability to optimally stabilize themselves with the fatigued muscles in order to produce the required outputs with the rested muscle groups. This explanation, however, can only account for exercise modalities in which the fatigued muscles are needed to work as stabilizers (e.g., grip muscles during cycling).

#### Summary

Specific fatiguing protocols may activate the stabilizer muscles to a larger extent which subsequently hinders their ability to stabilize during testing of the non-exercised muscle groups, thereby leading to muscle force decrements and an observation of indirect NLMF.

### Psychological pathways

Mentally fatiguing cognitive tasks are reported to hinder performance in subsequent physical tasks, especially with repeated and/or continuous efforts (Dorris et al. 2012; Marcora et al. 2009; Pageaux et al. 2014, 2013; Martin Ginis and Bray 2009; Graham et al. 2014). It was demonstrated that such mentally fatiguing tasks lead participants to perceive the activity as more strenuous, and thus to disengage from it earlier (Pageaux et al. 2013, 2014; Marcora et al. 2009). It should be noted that physical tasks also include a cognitive demand such as inhibiting the natural response to quit when exercise becomes uncomfortable, or sustained attention to maintain the required force when using submaximal tasks with force feedback. These cognitive demands can lead to mental fatigue and increase ratings of perceived exertion and impair performance in the subsequent task with the non-fatigued muscle. It can thus be speculated that performing a physically fatiguing task before testing for NLMF effects in the rested muscle may be analogous to performing a mentally or cognitively fatiguing task. This hypothesis is partially supported by Amann et al. (2013) who reported greater perceived exertion scores at the onset of exercise with the rested muscle group after completing the fatiguing protocol, but only marginal, non-significant differences in the overall exertion scores in the study by Elmer et al. (2013) who also failed to find a NLMF effect. Additionally, both Pageaux et al. (2013) and Rozand et al. (2014) observed that discrete MVCs with the knee extensors remained unaffected by a previous mentally fatiguing task. However, Pageaux et al. (2013) also observed that a subsequent submaximal isometric time to exhaustion test with the knee extensors was shortened after the mentally fatiguing task. This last finding supports the NLMF literature reporting larger effects with time to exhaustion tests compared to single, discrete MVCs. Future studies should further examine this hypothesis by including motivational, affect and/or exertion scales after the completion of the first fatiguing task, and before initiating the second physical task with the rested muscle groups, and compare the results to a control condition.

## Summary

Fatiguing protocols can lead to mental fatigue, which may then decrease motivation to complete the subsequent motor task with the non-exercises muscles. Alternatively, mental fatigue may increase the sensation of effort during the following physical activities. This is especially the case during submaximal and continuous tasks such as steady state cycling.

## Conclusion

While the overall literature is conflicting, there is evidence that NLMF is more prevalent when certain factors are taken into consideration. Particularly, NLMF effects tend to be more predominant when the lower body (primarily the quadriceps) rather than the upper body is tested, which could be a manifestation of differences in the neural network of the upper and lower body. In particular, the greater difficulty in activating the quadriceps results in a greater susceptibility to NLMF. Additionally, isometric and cyclical fatigue protocols appear to lead to a higher incidence and magnitude of NLMF. Performance of these protocols requires prolonged or repeated motor command function, which might stress a number of physiological systems (e.g., neural and biochemical) to a greater extent than protocols requiring repeated dynamic or stretch–shortening cycle contractions. Extended and submaximal testing tasks with the rested muscle groups seem to lead to greater NLMF effects compared to short and discrete maximal contractions. It can be speculated that the combination of the previous fatiguing exercise with the accumulated metabolic by-products produced in the longer duration time to exhaustion test leads a greater observable NLMF effect. However the gender, training background of the participant, and which muscle group is fatigued all influence these outcomes. There is evidence for NLMF effects to be attributed to a dominant neurological mechanism however there is biochemical, biomechanical and psychological factors influencing the outcome to various degrees and these are likely to be inter-related. Considering the importance and relevance of this topic, more research is needed to clarify the size of the effects using adequate methods, and with an attempt to account for some of the described confounding variables.

**Compliance with ethical standards**

**Conflict of interest** There are no known conflicts of interest involving the authors of this article.

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