Review

A Meta-analysis of Non-local Heterologous Muscle Fatigue

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Objectives: This meta-analysis included two separate aims, 1) to perform a comprehensive search of the literature examining heterologous non-local muscle fatigue (i.e., decrement in force-production capacity of a heterologous unexercised muscle) and, 2) to determine the overall effects of non-local muscle fatigue on important parameters such as maximal voluntary force and spinal and supraspinal excitability.

Design and Methods: Exploration of all published literature investigating non-local heterologous muscle fatigue was performed. Primary requirements for data analysis were the inclusion of maximal voluntary force and spinal and supraspinal excitability measures. Using a random effects model, Hedge's *g* effect sizes and 95% confidence intervals (CI) were computed.

Results: A total of thirty-five effect sizes were computed from six studies. For all outcomes, a negative effect size indicates a decrement in the performance of the unexercised (heterologous) non-local muscle as a result of the fatiguing intervention. For the maximal voluntary force and spinal and supraspinal excitability outcomes, a trivial mean ES = -0.142 (95% CI = -0.164; -0.120, $p < 0.001$), and ES = -0.072 (95% CI = -0.096; -0.048, $p < 0.001$) were observed, respectively.

Conclusions: Heterologous non-local muscle fatigue was evident, indicating that fatiguing exercises on one muscle group can induce minor decrements (from pre-fatigue baseline) in the maximal voluntary force and spinal and supraspinal excitability outcomes of the heterologous muscle group(s). This analysis provides important quantitative insight regarding the functional consequences of non-local muscle fatigue (i.e., reduced force output and efferent neural drive).

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Key words: Quantitative ■ Spinal excitability ■ Supraspinal excitability ■ Maximal voluntary force ■ Global fatigue

INTRODUCTION

Non-local muscle fatigue (NLMF) has been characterized as a reduction in force production capacity of the unexercised muscle following a fatiguing protocol of a different muscle group(s).[1] To assess NLMF, numerous fatiguing protocols may be performed in unilateral or bilateral muscle groups and then assessment of maximal voluntary force [i.e., maximal voluntary isometric contraction (MVIC)], electromyography (EMG) [e.g., amplitude or mean frequency (MF)] and peripheral and/or supraspinal excitability measures [e.g., motor evoked potentials (MEPs), cervicomedullary motor evoked potentials (CMEPs), thoracic motor evoked potentials (TMEPs), maximal compound muscle action potential (Mmax) and voluntary activation (VA)] in the homologous contralateral or non-related heterologous muscle groups.[1] The spinal and supraspinal measures are of great importance because they allow for determination of a potential global effect of NLMF. Interestingly however, the studies investigating the aforementioned muscle groups more commonly examined the cross-over effects in homologous contralateral lower body[2-9] and/or upper body[10-14] muscles. Therefore, in order to examine NLMF in different manners, many researchers have utilized variable fatiguing protocols involving either sustained isometric, repeated isokinetic and/or isotonic, or cyclical contractions (i.e., ergometry). Remarkably, even though studies have investigated similar muscle groups and employed differing fatiguing protocols, the results across studies have been equivocal (i.e., significant or non-significant reductions in MVIC, EMGa, VA, and Mmax, or increases in CMEP, MEP, Mmax, and TMEP). With this, there is difficulty in discerning if the NLMF effect may be muscle- (i.e., KE, EF, or FDI) and/or dose-dependent (i.e., volume of fatiguing intervention), and/or due to the specific fatigue protocol utilized (i.e., maximal sustained/intermittent or submaximal). Consequently, this unfortunately raises concern toward the reproducibility of studies investigating NLMF. In an effort to more specifically examine the global effects (i.e., neurological), reduce ambiguity, and increase the likelihood of reproducible studies examining NLMF, we believe the original NLMF definition requires more specificity. The existing definition creates a complex problem in attempting to answer questions pertaining to NLMF because there are multiple possible methodological combinations examining exercised and unexercised; contralateral and ipsilateral; homologous and heterologous; muscle group(s). Additionally, the review by Halperin, Chapman, & Behm[1] was literature-based and did not examine the collective magnitude of the NLMF effect in the non-local muscles. Therefore, the focus of this study was on an explicit portion of the NLMF literature, through examination of the non-local "heterologous" muscle group(s) after a

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fatiguing intervention in the unrelated muscle group(s). In the context of this review, heterologous refers to originating from the non-local muscle group(s) that is, non-exercised muscle group(s) acting upon a completely different joint and are entirely and completely unrelated to the muscle group(s) involved in the exercise bout. This allowed us to examine the global neurological effects of NLMF in an effort to reduce equivocality in the literature.

This precise review was necessary because there are numerous fatiguing interventions but there is no standardized method nor outcome variable; that is, few studies have employed the combination of spinal or supraspinal excitability, maximal voluntary force, and EMG measures. Additionally, understanding heterologous NLMF may provide essential information for further comprehension in the mechanisms of central or peripheral fatigue, or aid in creating a widely-used fatigue protocol which could be implemented into numerous study designs. Therefore, the aim of this quantitative analysis was to collect, synthesize, extract, and disseminate information regarding heterologous NLMF using a meta-analysis. Specifically, to provide substantive information from controlled and uncontrolled within-subjects design studies regarding the heterologous NLMF effects of different fatiguing protocols and to investigate how the fatigue protocol may alter maximal voluntary force and spinal/supraspinal variables in the non-local muscle group(s).

METHODS

Database Review

We explored all published literature to identify studies that examined heterologous NLMF in healthy adults (≥ 18 years of age) using online databases CINAHL Plus, Medline, SportDiscus, PubMed, ScienceDirect, EMBASE, and Google Scholar. The date of the last comprehensive literature search was January 30th, 2019. Several keyword search terms were used singularly and in combination including, non-local muscle fatigue, non-local fatigue, cross-over muscle fatigue, cross-over fatigue, upper-body muscle fatigue, lower-body muscle fatigue, contralateral muscle fatigue, and upper-and lower-body muscle fatigue.

Inclusion and Exclusion Criteria

For inclusion into the analysis the following criteria were applied: 1) Studies had to include measures of maximal voluntary force; and/or EMG; and/or spinal/supraspinal excitability; 2) Studies were required to be peer-reviewed journal articles published in the English language; 3) The target sample of healthy male and female adults aged eighteen years or older who were physically active at any level and were not considered sedentary. This age range and activity level for the population was chosen to increase the number of published articles included;[1] 4) The studies with research designs that were controlled, uncontrolled, acute, and within-subjects, were included. Of specific importance for inclusion was, 5) the nature of the intervention must have included a fatiguing protocol of at least one muscle group, followed by a performance test for a non-local heterologous muscle group. Studies were excluded from the analysis: 1) If the focus was not upon the NLMF effects by investigating homologous muscle groups; 2) If the studies examined contralateral or cross-over effects only; 3) If insufficient data were reported for proper effect size (ES) calculations; and 4) studies which involved participants with disease or illness were not included in the analysis unless specified data on healthy adults was also included. Notably, there were several NLMF studies which were excluded in the analysis due to the aforementioned reason(s).[2-10,12-34]

Quality of Selected Articles

Quality evaluation of the selected articles was based upon the Methodological Index for Non-Randomized Studies (MINORS) tool.[35] The MINORS tool includes twelve questions; the first eight refer to comparative and noncomparative studies and the last four refer to comparative studies only. Articles were scored based upon a 0 to 2 scale; specifically, if the item was not reported it would be stated as 0; if the item was reported but not clearly, it was stated as a 1; and if the item was reported and clearly understood, it was stated as a 2. As recommended by Wylie et al.[36] MINORS scores were reported as a percentage of the overall maximal point value of 24. Egger's regression intercept was examined to test for asymmetry in the funnel plot (i.e., publication bias), and asymmetry was defined as p value less than 0.05.[37]

Outcome and Moderating Variables

All outcomes for maximal voluntary force (e.g., MVIC, maximal torque, absolute and relative peak power, etc.); spinal and supraspinal excitability (e.g., MEP, CMEP, TMEP, VA, Mmax, evoked twitch, etc.); and EMG (e.g., amplitude, mean frequency, etc.) were collected by two evaluators after careful analysis of the selected articles. These variables were chosen because they represent what is reported in the literature and are considered to be valid assessments for determining the effects of NLMF.[1] Study design information was collected for analysis including, fatigued and tested muscle group(s) (i.e., EF, KF, KE, total upper and total lower body) and exercise protocol(s) (i.e., cycling, dynamic exercise, concentric only exercise, and repeated sustained MVICs) to determine the potential influence toward the overall effect size. However, if more than one muscle group in the upper or lower body was utilized during the fatiguing or testing protocol, then all muscle groups were examined collectively (e.g., Total lower body and Total upper body vs. knee extensor and elbow flexor). Exercise protocol moderators were divided on the basis of contraction type, number of sets, and intensity. In addition, testing procedure and sample characteristics were not included as moderators due to the wide variability in testing procedures and predominantly homogenous sample of all included studies (See Tables 1 and 3). Furthermore, the exercise protocol (i.e., repeated dynamic knee extension contractions) from Sambaher et al.[38] was not included in the overall moderator analyses because only one ES was included.

Table 1 Detailed study characteristics included in the analyses

Author	Study Design	Sample (N) (mean±SD)	Fatigued Muscle	Tested Muscle	Fatigue Procedure	Testing Procedure	Outcome Variables	Key Findings
Aboodarda et al.[48]	WCG WSJD	9 M/2 F (RA) [27±6.4 yrs]	BIL & UNI EF	BIL & UNI KE	Sustained UNI and BIL MVICs for 5 sets with 15-s of rest between, until force ↓ to ≤ 20% pre-fatigue MVIC, or failure	5-s MVICs at 30-s, 3-min & 5-min after fatiguing bout	EMG; ETF; Mmax; TMEP; TMEP/ Mmax; MVIC	↓ EMG, MVIC, Mmax in BIL & UNI ↑ ETF, TMEP, TMEP/ Mmax in BIL & UNI
Aboodarda et al.[49]	WCG WSJD	11 M (RA) [27.3±7.4 yrs]	Left UNI KE	Right UNI EF	Sustained MVICs for 2 sets of 100-s until task failure	Four blocks of 6-s MVICs for 3 repetitions at 5, 50, & 100% of MVIC with 10-s of rest between each	MEP; CMEP	↑ CMEP in 100, 50, & 5% ↑ MEP in 100% ↓ MEP in 50 & 5%
Bouhlel et al.[39]	NCG WSJD	10 M (Trained) [20.6±2 yrs]	LB & UB BIL Cycling	UB & LB BIL Cycling	7-sec all-out cycling tests for 6-8 sets of UB and/or LB with 5-min of rest between sets & 8-min of rest between conditions	7-sec all-out cycling tests for 6-8 sets of UB and/or LB with 5-min of rest between sets & 8-min of rest between conditions	APAP; RPAP; OPTF	↓ APAP, RPAP, OPTF in arm ↑ APAP, RPAP, OPTF in leg
Sambaher et al.[38]	WCG WSJD	14 M (RA) [24±3 yrs]	UNI KE	UNI EF	5 sets of BIL KE contractions until force ↓ to 35% pre-fatigue MVIC	5-s MVIC for 12 sets with 10-s of rest between each	MVIC; EMGa; Mmax; MEP/Mmax; CMEP/Mmax; MEP/ CMEP	↓ EMGa, MVIC ↑ Mmax, CMEP/ Mmax, MEP/CMEP, MEP/Mmax
Sidhu et al.[50]	WCG WSJD	8 M (RA) [27±1 yrs]	BIL LB Cycling	UNI EF	Sustain 80% of peak watt while cycling until task failure	3-s MVIC for 3 repetitions with 2 to 3-s of rest between each at task failure and post-fatigue	MVIC; SIT; MEP; VA	↓ VA, MVIC (task failure & post-fatigue), MEP ↑ SIT
Ye et al.[51]	WCG WSJD	10 M/9 F (RA) [26±3 yrs] [27±2 yrs]	Right EF & KE	Left KE & EF	30-s MVIC for 6 sets with 30-s of rest between	5-s MVIC for 3 repetitions with 30-s of rest between each	MVIC; EMGa	↓ MVIC KE (M only) & BB, & EMGa in BB (M & F) ↑ MVIC in KE (F only)

APAP – absolute peak anaerobic power; BIL – bilateral; CMEP – cervicomedullary motor evoked potential; CMEP/Mmax – cervicomedullary motor evoked potential to maximal compound muscle action potential ratio; EF – elbow flexor; EMG – electromyography; EMGa – electromyography amplitude; ETF – evoked twitch force; F – female; KE – knee extensor; KF – knee flexor; LB – lower body; M – male; MEP – motor evoked potential; min – minutes; MEP/Mmax – motor evoked potential to maximal compound muscle action potential ratio; MEP/CMEP - motor evoked potential to cervicomedullary motor evoked potential ratio; Mmax – maximal compound muscle action potential; MVIC – maximal voluntary isometric contraction; NCG – no control group; OPTF – optimal force; RA – recreationally active; RPAP – relative peak anaerobic power; s – second; SIT – superimposed twitch; TMEP – thoracic motor evoked potential; TMEP/Mmax – thoracic motor evoked potential to maximal compound muscle action potential ratio; UNI – unilateral; UB – upper body; VA – voluntary activation; WCG – with control group; WSJD; within subjects' design; yrs - years

Statistical Analyses

Two separate meta-analyses were completed to compute the overall mean Hedge's *g* ESs for each outcome variable, which demonstrates how fatigue of an exercised muscle affects the maximal voluntary force and spinal and supraspinal excitability measures of the non-local heterologous muscle(s) that were uninvolved in the fatiguing bout. Specifically, for all reported ESs, a negative ES explains the existence of NLMF [from pre-fatigue (i.e., baseline)] in the non-local muscle group(s) due to the fatiguing protocol. Importantly, due to the lack of studies involving the EMG measurement (i.e., inclusion of only 4 ESs), the EMG measurement was not included in a separate meta-analysis. Pre- and post-fatigue assessment correlations for all maximal voluntary force outcomes were obtained from Bouhlel et al.[39] (i.e., arm peak power of 0.97 and leg peak power of 0.99); and Hamilton and Behm[9] (i.e., elbow flexor MVIC of 0.99). The pre- and post-fatigue correlation values for spinal and supraspinal excitability outcomes were obtained from Allen, Lamb, and Westerblad[40] [i.e., elbow flexor superimposed twitch (SIT) of 0.97 and VA of 0.89]; Calder et al.[41] (i.e., elbow flexor Mmax of 0.96); Place et al.[42] [i.e., vastus lateralis (VL) peak twitch of 0.98, root mean square to Mmax ratio (RMS/Mmax) of 0.96, Mmax of 0.99, vastus medialis (VM) Mmax of 0.86 and rectus femoris (RF) Mmax of 0.99]; and Todd et al.[43] (i.e., elbow flexor MEP of 0.99). Hedge's *g* was utilized for ES calculations due to the small sample size of all included studies. Means and standard deviations for pre- and post-fatigue measurements of maximal voluntary force and spinal and supraspinal excitability were extracted from six studies. The calculated Hedge's *g* ESs are presented as the standardized difference between means in units of the pooled standard deviation. Based upon Cohen,[44] effect sizes were categorized as trivial (< 0.2), small (0.2 to < 0.5), medium (0.5 to < 0.8), and large (> 0.8). The random effects model was computed under the assumption of between study heterogeneity. All computations were performed in Comprehensive Meta-Analysis (CMA) software (Biostat Inc., Englewood, NJ).[45]

RESULTS

Database Review

The search identified 5,892 publications and after using Boolean terms and filtering, a total of 4,481 titles were removed. A second inspection resulted in removal of 1,343 publications based upon duplicates and title. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[46] guidelines, 30 full-text publications were thoroughly read and once the inclusion criteria were applied, a total of 6 publications were included for analysis (Figure 1). There were 27 full-text publications excluded from the analysis; 5 examining contralateral homologous effects;[5,7,9-10,13], 13 examining NLMF but did not include data for proper ES calculation nor variables of interest;[15,18-20,22-24,26-30,34] 8 studies that did not examine NLMF (e.g., coactivation, tremor, concurrent contraction, stretching, training intervention);[16-17,21,25,31-33,47] and 1 study which was the review by Halperin, Chapman, and Behm.[1]

Sample Characteristics of Selected Articles

In total, the studies included 73 individuals; 62 male (84.9%) and 11 female (15.1%) adults above the age of 18 years (mean age of 25.3 ± 2.61 years). Additionally, 63 (86.3%) and 10 (13.7%) individuals were considered to be recreationally active (i.e., no structured or regimented exercise) and well-trained (i.e., structured or regimented training) adults, respectively. Main study characteristics are presented in Table 1, including author, study design, sample characteristics, procedures for the fatigue and testing protocols, the fatigued and tested limb/muscle group, key outcome variables, and main findings.

Quality Assessment and Publication Bias

Individual study scores and MINORS criteria are presented in Table 2. Briefly, MINORS assessment of quality of the 6 included studies demonstrated a mean score of 94%, with a range of 88 – 100%. Egger's regression intercept[37] for publication bias across studies was not statistically significant for maximal voluntary force (B0) = -1.28 (95% CI = -9.44; 6.88), $p = 0.739$; or spinal and supraspinal excitability (B0) = -1.35 (95% CI = -3.71; 1.01), $p = 0.246$. The results of the Egger's test[37] indicated that publication bias did not exist in the studies included in these meta-analyses.

Overall Effect Sizes

Figures 2 and 3 display Forest plots of meta-analyses show-

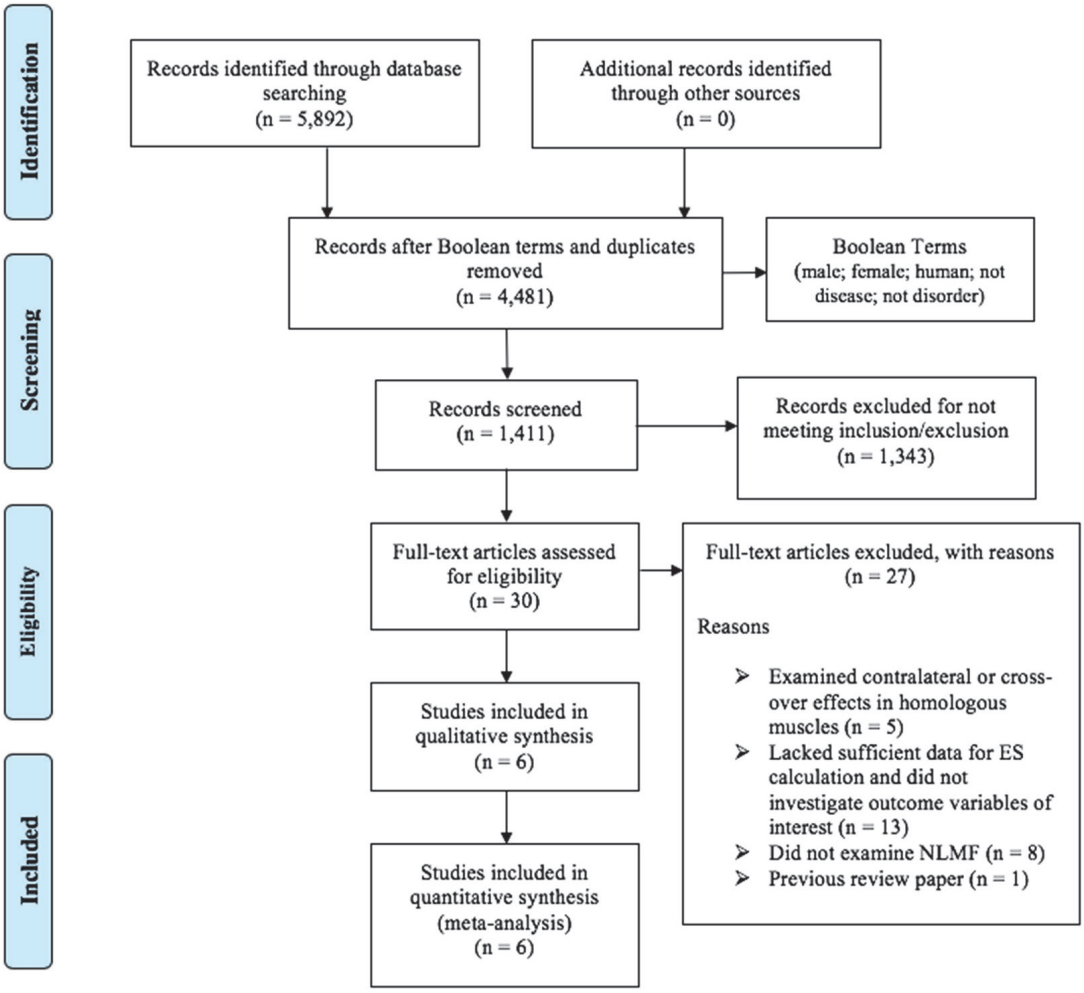

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses. ES – Effect Size

Table 2 Detailed description of the MINORS scores

Author	Aboodarda et al.[48]	Aboodarda et al.[49]	Bouhlel et al.[39]	Sambaher et al.[38]	Sidhu et al.[50]	Ye et al.[51]
Clearly stated aim	2	2	2	2	2	2
Inclusion of consecutive patients	1	1	2	2	1	2
Prospective collection of data	2	2	2	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2
Unbiased assessment of the study endpoint	2	2	2	2	2	2
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2
Loss to follow-up < 5%	2	2	2	2	2	2
Prospective calculation of the study size	2	1	1	1	1	2
An adequate control group	2	2	0	2	2	2
Contemporary groups	2	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	2
Adequate statistical analyses	2	2	2	2	2	2
Total Score	23 [96%]	22 [92%]	21 [88%]	23 [96%]	22 [92%]	24 [100%]

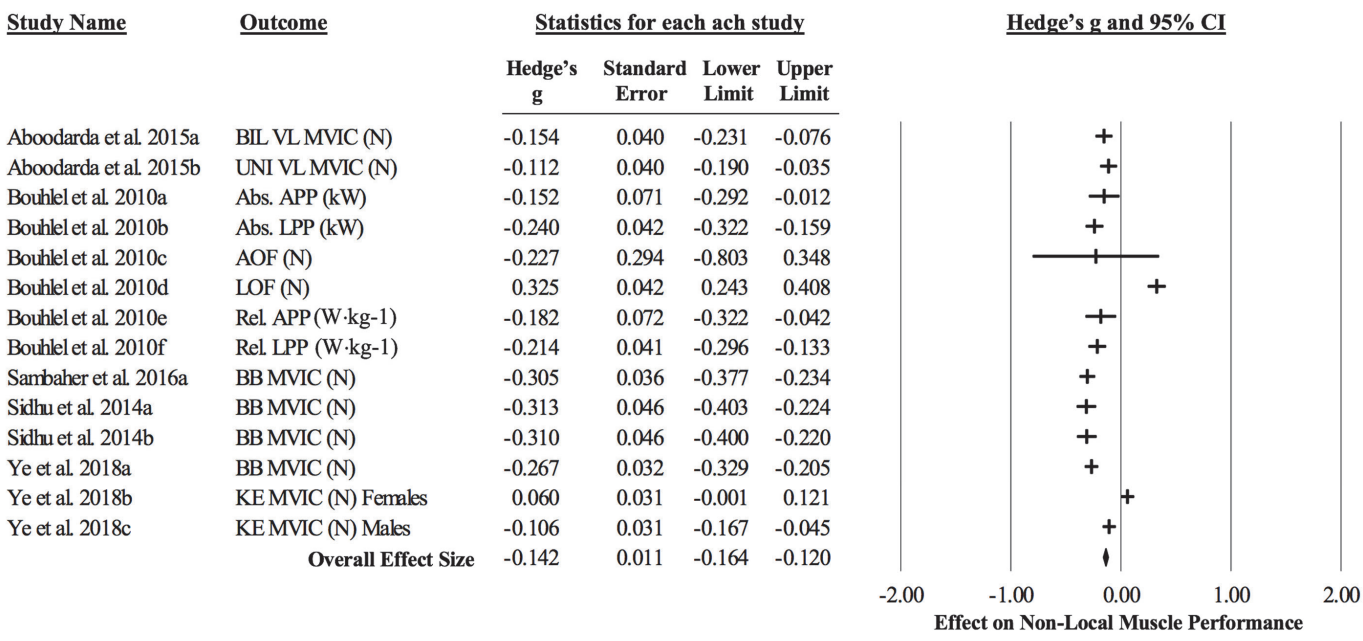

Figure 2 Forest Plot Showing Hedge's g Individual and Overall Effect Sizes for Non-Local Muscle Performance on Maximal Voluntary Force Outcomes. Hedge's g effect sizes were calculated using the difference in means divided by the pooled and weighted standard deviation in the Comprehensive Meta-Analysis software.[45] Data were pooled using a fixed-effects model. Negative effect sizes indicate post-fatigue decreases in maximal voluntary force of the Non-Local muscle(s), and were categorized as trivial (< 0.2), small (0.2 to < 0.5), medium (0.5 to < 0.8), and large (> 0.8).[44]

Abs – absolute; APP – absolute peak power; AOF – arm optimal force; BB – biceps brachii; BIL – bilateral; KE – knee extensor; kW – kilowatts; LOF – leg optimal force; LPP – leg peak power; Max – maximal; MVC – maximal voluntary contraction; MVIC – maximal voluntary isometric contraction; N – newton; Nm – newton meters; Rel – relative; UNI – unilateral; VL – vastus lateralis; W×kg-1 – watts per kilogram

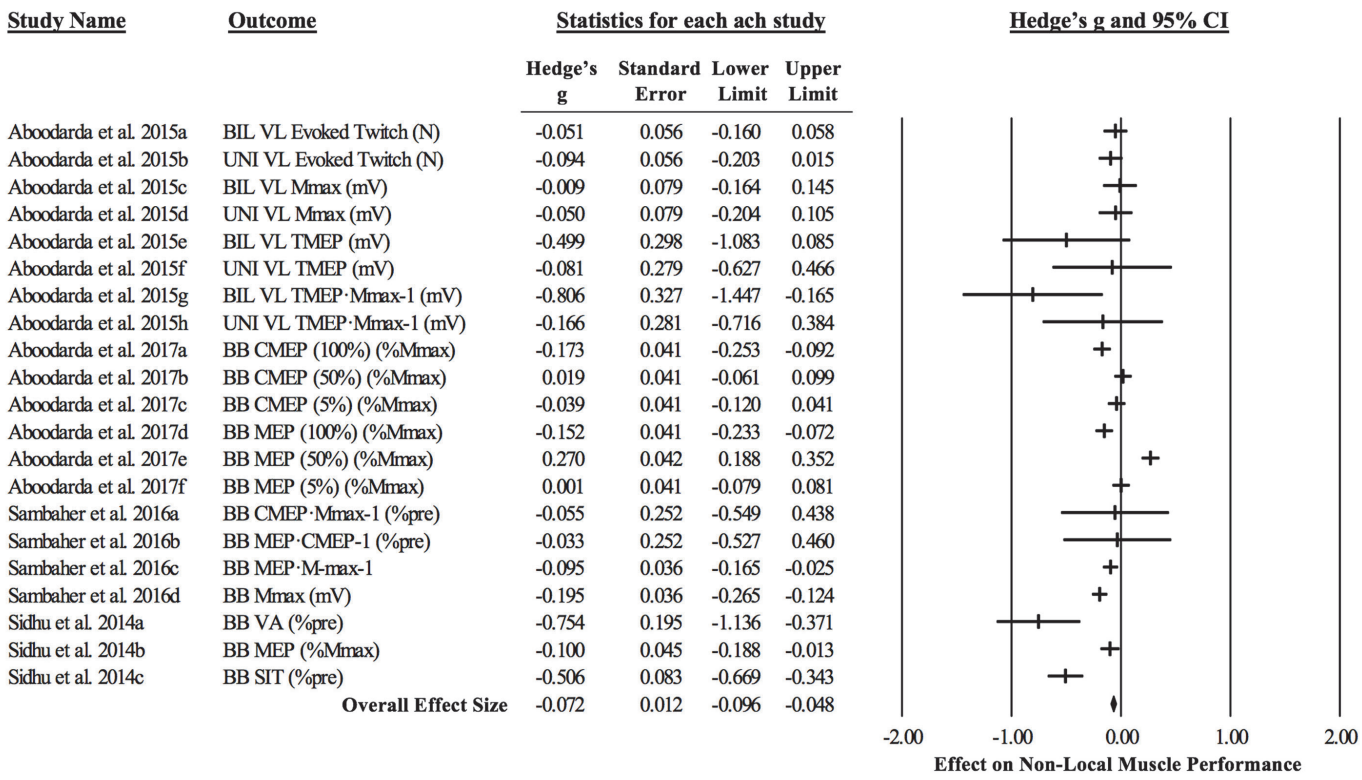

Figure 3 Forest Plot Showing Hedge's g Individual and Overall Effect Sizes for Non-Local Muscle Performance on Spinal Excitability Outcomes. Hedge's g effect sizes were calculated using the difference in means divided by the pooled and weighted standard deviation in the Comprehensive Meta-Analysis software.[45] Data were pooled using a fixed-effects model. Negative effect sizes indicate post-fatigue decreases in spinal and supraspinal excitability of the Non-Local muscle(s), and were categorized as trivial (< 0.2), small (0.2 to < 0.5), medium (0.5 to < 0.8), and large (> 0.8).[44]

BB – biceps brachii; CMEP – cervicomedullary motor evoked potential; CMEP×Mmax-1 – cervicomedullary motor evoked potential to maximal compound muscle action potential ratio; MEP – motor evoked potential; mV – millivolt; MEP×Mmax-1 – motor evoked potential to maximal compound muscle action potential ratio; MEP×CMEP-1 – motor evoked potential to cervicomedullary motor evoked potential ratio; Mmax – maximal compound muscle action potential; N – newton; SIT – superimposed twitch; TMEP – thoracic motor evoked potential; TMEP×Mmax-1 – thoracic motor evoked potential to maximal compound muscle action potential ratio; VA – voluntary activation; VL – vastus lateralis

ing individual and overall ESs for heterologous NLMF, for studies including maximal voluntary force and spinal and supraspinal excitability outcomes. Collectively, there were 35 ESs calculated from the 2 separate meta-analyses. The 6 studies included 14 and 21 ESs for maximal voluntary force and spinal and supraspinal excitability outcome variables, respectively. For the maximal voluntary force and spinal and supraspinal excitability outcomes, a trivial mean ES = -0.142 (95% CI = -0.164; -0.120, $p < 0.001$), and ES = -0.072 (95% CI = -0.096; -0.048, $p < 0.001$) were observed, respectively. The ESs indicate trivial decreases in the performance of the non-local muscle(s) after the fatiguing bout for both main outcomes; thus, the exercised limb/muscle group induced minor decrements in maximal voluntary force and spinal and supraspinal excitability outcomes of the heterologous non-local muscle group.

Moderator Analyses

The mean ES was of high heterogeneity for maximal voluntary force, Q = 239.02, $df = 15$, $p < 0.001$, $I^2 = 94.56$; and spinal and supraspinal excitability, Q = 145.85, $df = 20$, $p < 0.001$, $I^2 = 86.29$, outcomes. The mean ES for maximal voluntary force was influenced by all three moderators: fatigued muscle, Qbetween (Qb) = 92.41, $df = 3$, $p < 0.001$; tested muscle, Qb = 97.71, $df = 3$, $p < 0.001$; and exercise protocol, Qb = 63.42, $df = 4$, $p < 0.001$ (Table 3). The mean ES for spinal and supraspinal excitability was influenced by the fatigued muscle, Qb = 15.273, $df = 3$, $p < 0.002$, and exercise protocol moderator, Qb = 33.47, $df = 3$, $p < 0.001$, but not for tested muscle moderators (Table 3).

Table 3 Moderator analyses for fatigued limb, tested limb, and exercise protocol for maximal voluntary force and spinal and supraspinal outcomes

Outcome	Moderator		# Effect Sizes	ES	SE	CI	Z	P
Maximal Voluntary Force	Fatigued Muscle	Unilateral Elbow Flexor	4	-0.065	0.017	-0.099 – -0.031	-3.760	<0.001*
		Unilateral Knee Extensor	2	-0.284	0.024	-0.330 – -0.237	-11.855	<0.001*
		Total Lower Body [a]	5	-0.269	0.027	-0.322 – -0.216	-9.919	<0.001*
		Total Upper Body [b]	3	-0.047	0.024	-0.094 – 0.000	-1.942	0.052
		Total Between	Qb = 92.405	*df* = 3	*p* = <0.001*			
	Tested Muscle	Unilateral Elbow Flexor	4	-0.294	0.019	-0.331 – -0.256	-15.220	<0.001*
		Unilateral Knee Extensor	4	-0.065	0.017	-0.099 – -0.031	-3.760	<0.001*
		Total Lower Body [a]	3	-0.047	0.024	-0.094 – 0.000	-1.942	0.052
		Total Upper Body [b]	3	-0.169	0.050	-0.266 – -0.071	-3.392	<0.001*
		Total Between	Qb = 97.711	*df* = 3	*p* = <0.001*			
	Exercise Protocol	Cycling at 80% Peak Watt	2	-0.312	0.032	-0.375 – -0.248	-9.627	<0.001*
		Sustained 30-s MVIC-6 sets	3	-0.103	0.018	-0.138 – -0.067	-5.672	<0.001*
		Maximal Cycling	6	-0.070	0.022	-0.112 – -0.027	-3.226	<0.001*
		Sustained MVIC-5 sets	2	-0.133	0.028	-0.188 – -0.067	-4.754	<0.001*
		Total Between	Qb = 68.415	*df* = 4	*p* = <0.001*			
Spinal and Supraspinal Excitability	Fatigued Muscle	Unilateral Elbow Flexor	4	-0.081	0.044	-0.168 – 0.006	-1.835	0.067
		Unilateral Knee Extensor	10	-0.054	0.014	-0.081 – -0.026	-3.835	<0.001*
		Total Lower Body [a]	3	-0.213	0.039	-0.289 – -0.138	-5.533	<0.001*
		Total Upper Body [b]	4	-0.062	0.045	-0.149 – 0.026	-1.384	0.166
		Total Between	Qb = 15.273	*df* = 3	*p* = <0.002*			
	Tested Muscle	Unilateral Elbow Flexor	13	-0.072	0.013	-0.098 – -0.046	-5.491	<0.001*
		Unilateral Knee Extensor	8	-0.072	0.031	-0.133 – -0.010	-2.276	0.023*
		Total Between	Qb = 0.000	*df* = 1	*p* = 0.989			
	Exercise Protocol	Cycling at 80% Peak Watt	3	-0.213	0.039	-0.289 – -0.138	-5.533	<0.001*
		Dynamic Contractions	4	-0.143	0.025	-0.192 – -0.093	-5.688	<0.001*
		Sustained MVIC-2 sets	6	-0.014	0.017	-0.046 – 0.019	-0.805	0.421
		Sustained MVIC-5 sets	8	-0.072	0.031	-0.133 – -0.010	-2.276	0.023*
		Total Between	Qb = 33.47	*df* = 3	*p* = <0.001*			

[a] Total Lower Body refers to inclusion of several lower body muscles (e.g., knee extensors/flexors, triceps surae, etc.) and/or a bilateral movement.

[b] Total Upper Body refers to inclusion of several upper body muscles (e.g., elbow flexors/extensors, pectorals, etc.) and/or a bilateral movement.

CI – Confidence Interval; df = degrees of freedom; ES – Effect Size; MVIC – maximal voluntary isometric contraction; SE – Standard Error; QB – Q between

* Denotes significance at $p < 0.05$

DISCUSSION

The aim of this study was to provide a quantitative analysis of the existing literature regarding exercise-induced fatigue effects on maximal voluntary force and supraspinal and spinal excitability in the non-local heterologous muscle group(s). This study differs from the review by Halperin, Chapman, and Behm[1] in that, a collective analysis to determine the overall effect(s) was performed and changes in maximal voluntary force and spinal and supraspinal excitability were examined. The primary findings of this study revealed negative effects on non-local heterologous muscle performance outcomes of maximal voluntary force and spinal and supraspinal excitability. Specifically, immediately post-exercise there were trivial to small and trivial reductions in non-local heterologous maximal voluntary force and spinal and supraspinal excitability, respectively. When considering moderators, it was revealed that the fatigued muscle, tested muscle, and exercise protocol influenced the magnitude of the effect on non-local muscle performance for post-fatigue maximal voluntary force. Specifically, fatiguing the lower body musculature either bilaterally or unilaterally, testing the upper body unilaterally, and cycling at 80% of peak watts had the greatest effects on maximal voluntary force. However, the non-local muscle performance regarding spinal and supraspinal excitability was influenced by the fatigued muscle and exercise protocol only. That is, fatiguing the lower body musculature by cycling at 80% of peak watts had the greatest effect on spinal and supraspinal excitability of the upper body. Since this meta-analysis specifically focused on heterologous NLMF involving six studies, our discussion focuses on the potential mechanisms of NLMF regarding the moderating variables (i.e., fatigued and tested muscle and exercise protocol) for maximal voluntary force and spinal and supraspinal fatigue. It is important to mention that the discussion is speculative in nature due to the lack of convincing evidence regarding NLMF. Nevertheless, we hope to provide greater insight into the global effects of heterologous NLMF and provide greater clarity toward future study design examining heterologous NLMF.

Our current understanding of the central nervous system's role in fatigue is applicable to heterologous NLMF. Briefly, central fatigue entails a diminished ability to voluntarily drive motor neurons which may occur at the supraspinal (e.g., motor cortex output) and/or spinal (e.g., motor axons, α-motor neurons, γ-motor neurons) levels. In turn, this causes a reduction in the ability to activate all motor units, consequently decreasing maximal voluntary force output.[52] For example, during sustained maximal fatiguing contractions (which are

lower duration but higher intensity) there is a decrease in motor neuron discharge as a result of an onslaught of repetitive firing and motor cortex excitation to the muscle due to supraspinal fatigue.[50] Similarly, sustained submaximal fatiguing contractions result in greater descending drive due to peripheral fatigue accumulation and a reduction in spinal excitability via group III and IV afferent induced inhibition.[53] Both of the aforementioned concepts were shown in this study. Most importantly, the greatest decrement (i.e., small effect) in non-local exercise performance was a result of cycling at 80% of peak watts. However, interestingly, sustained maximal exercise commonly results in less supraspinal fatigue, albeit small,[54] compared to sustained submaximal exercise.[53] This same concept applies to fatigue encompassing larger muscle masses,[51,55] which was evidenced in our study by the greatest decrement (i.e., small effect) in non-local exercise performance occurring in the lower body musculature. These theories align with our results specifically because excitability at the spinal and supraspinal levels of the non-local muscle(s) was shown to be reduced, which would also reduce maximal voluntary force. This potentially indicates a reduction in voluntary output at the spinal and supraspinal levels, possibly due to the inability to fully activate all motor units within the motor neuron pool.

In contrast to the above, sustained maximal isometric contractions and maximal cycling exercise protocols had trivial effects on the non-local exercise performance, regarding maximal voluntary force and spinal and supraspinal excitability outcomes. For clarity, the sustained maximal isometric contraction moderator included intermittent sustained and prolonged sustained contractions. Thus, a plausible reason for the lack of heterologous NLMF was possibly due to the intermittent nature of the exercise protocols regardless of the muscle group involved in the fatiguing bout. For example, one study[39] performed six to eight sets (i.e., 7 second sprints of upper or lower body cycling) with five minutes of recovery between sets, and eight minutes of recovery between the lower and upper body cycling exercise; the results demonstrated no heterologous NLMF for the upper or lower body. The proposed theory if there were to be heterologous NLMF is as follows. It is well known that metabolic by-product accumulation (e.g., hydrogen, potassium, lactate) occurs in the exercising muscle during prolonged maximal effort, potentially resulting in peripherally mediated fatigue due to the metabolic by-products being trapped in the contracted muscle. As a result, a decrease in central drive to the heterologous non-local muscles may occur. Pertaining to intermittent maximal exercise bouts, it is possible that the recovery period (i.e., depending upon length) mitigated metabolic by-product accumulation (i.e., allowed for clearance into the system) and any potential increase in centrally mediated fatigue. However, if the metabolic by-products are cleared from the exercising muscle, it may be possible for them to be circulated to the heterologous non-local muscle[15,18,28] thereby, activating the group III and IV afferents which may send inhibitory signals to the central nervous system. In turn, this may cause inhibition of the Ia afferents, inhibition at the presynaptic level of the spinal cord, and inhibition within various motor neuron pools.[56] Thus, it is possible that maximal voluntary force and spinal and supraspinal excitability of the heterologous non-local muscle would be less affected during a bout of intermittent maximal contraction, when compared to a prolonged maximal contraction. However, it is difficult to make any conclusive statements because of great variability in experimental methodology among the few studies (see Table 1). Specifically, only one study[49] performed prolonged sustained contractions involving the lower body (e.g., unilateral knee extensors). Interestingly, regarding dynamic contractions, there was a trivial effect (which was greater than any sustained maximal isometric contraction protocol) on non-local exercise performance for spinal and supraspinal fatigue. As mentioned above it is difficult to mechanistically explain this, except, the protocol was performed in the lower body and this meta-analysis has provided evidence of greater heterologous NLMF when lower body fatiguing exercise was performed, and the upper body was tested.

We cannot speculate any further than discussed in the review by Halperin, Chapman, and Behm[1] regarding how gender or training background may confound heterologous NLMF effects. Specifically Ye et al.[51] is the only other study since Martin and Rattey[2] which directly involved sex comparisons and both studies demonstrated no gender differences in heterologous NLMF. In addition, we did not use gender as a moderator in these meta-analyses due to the inequality in males to females within the study samples. Regarding training background, nearly all subjects of the included studies were considered recreationally active (i.e., 86.3%) thus, it is purely speculative in saying that heterologous NLMF was evident in recreationally active individuals. However, due to only one previous study[57] investigating NLMF and training background, did so in resistance trained individuals. Therefore, more heterologous NLMF research involving females and comparisons of differing training backgrounds is warranted.

Limitations

During the literature search and subsequent assessment of eligibility criteria, numerous studies did not provide sufficient data for calculating ESs for the outcome variables. Potential moderator variables such as sex were unable to be explored because 86.2% of the entire sample from all studies were young males. When interpreting the current results, it is also important to realize that our age inclusion criterion was above 18 years old, which may not necessarily represent the NLMF effects in adolescents. In fact, a recent study by Othman et al.[33] reported more prevalent NLMF effects in male children aged 10-13 years than young adults. This result is interesting as it may provide insight on mechanisms of motor development across the lifespan; however, there is a dearth of research investigating NLMF in the youth.

CONCLUSION

Previously, Halperin, Chapman, and Behm[1] took great care in discussing the rarity of these results however, here we pro-

vide evidence quantifying the importance of the exercise protocol and muscle chosen to be fatigued with regards to examining changes in maximal voluntary force, and spinal and supraspinal excitability. Therefore, careful consideration for future studies should be taken, when designing studies focusing on examining heterologous NLMF. Furthermore, there is still uncertainty regarding heterologous NLMF in the female population exemplifying the need for better inclusion in future studies.

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WM drafted the manuscript and performed the statistical analyses; MK assisted with the analyses and revised the manuscript methodology; XY revised the manuscript for intellectual content; and SJ assisted with the comprehensive search of the literature.

Conflicts of interest

The authors report no affiliations that could be interpreted as conflicts of interest.

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