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Does lower-limb osteoarthritis alter motor cortex descending drive and voluntary activation? A systematic review and meta-analysis

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- *Purpose:* The aim of the study was to quantify motor cortex descending drive and voluntary activation (VA) in people with lower-limb OA compared to controls.
- *Methods:* A systematic review and meta-analysis according to the PRISMA guidelines was carried out. Seven databases were searched until 30 December 2022. Studies assessing VA or responses to transcranial magnetic stimulation (TMS; i.e. motor evoked potential, intracortical facilitation, motor threshold, short-interval intracortical inhibition, and silent period) were included. Study quality was assessed using Joanna Briggs Institute criteria and evidence certainty using GRADE. The meta-analysis was performed using RevMan inverse variance, mixed-effect models.
- *Results:* Eighteen studies were included, all deemed low-quality. Quadriceps VA was impaired with knee OA compared to healthy controls (standardised mean difference (SMD) = 0.84, 95% CI = −1.12–0.56, low certainty). VA of the more symptomatic limb was impaired (SMD = 0.42, 95% CI = −0.75–0.09, moderate certainty) compared to the other limb in people with hip/knee OA. As only two studies assessed responses to TMS, very low-certainty evidence demonstrated no significant difference between knee OA and healthy controls for motor evoked potential, intracortical facilitation, resting motor threshold or short-interval intracortical inhibition.
- *Conclusions:* Low-certainty evidence suggests people with knee OA have substantial impairments in VA of their quadriceps muscle when compared to healthy controls. With moderate certainty we conclude that people with hip and knee OA had larger impairments in VA of the quadriceps in their more painful limb compared to their non-affected/other limb.

Keywords
- exercise
- hip
- knee
- ankle
- corticospinal
- intracortical inhibition

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Introduction

Osteoarthritis (OA) is a leading cause of pain and disability globally (1). It results in substantial health expenditure in Australia, with over $3.5 billion being spent annually on OA burden (2). OA presents as pain and impaired function, causing people to leave the workforce early and frequently progress to pharmacological and surgical management (3, 4). Best practice management for OA includes exercise targeted at peripheral impairments (e.g. muscle strength, range of motion, and proprioception) (5). However, the pain experienced with OA is complex and not solely a result of nociceptive input from peripheral tissue (6). By understanding different central nervous system contributions to motor dysfunction in OA, we can provide more targeted

interventions to improve pain, muscle weakness and function.

A major misconception with OA is that pain severity and function are related to the degree of structural damage (7). Evidence actually shows that pain severity with OA has a poor relationship with the degree of structural damage visible on imaging (8). Similar to other musculoskeletal conditions (9), improvements in pain experienced can occur whilst visible 'damage' remains unchanged (10). It has been proposed that pain improvements occur due to improved neuromuscular function with exercise rehabilitation (11). However, this hypothesis has been challenged in other musculoskeletal conditions, with changes in disability being unrelated to neuromuscular function (12). Specifically in OA, improvements in muscle function, including strength, are proposed to improve the joint's capacity to absorb impact forces and thereby reduce joint load (10).

When attempting to actively contract their muscles, people with persistent pain (i.e. OA) have impaired voluntary activation (13, 14). However, we do not know the mechanism by which this impaired activation occurs. It may be that altered descending neural drive and subsequently greater inhibition contributes to impaired voluntary maximal force production in people with OA (15). This may then reduce exercise performance or reduce capacity to increase muscular strength (16), the primary aim of exercise rehabilitation. Conversely, a large meta-analysis of chronic pain conditions demonstrated disinhibition, with subsequent increases in motor cortex excitability (17). The function of the motor cortex, responsible for initiating and providing descending drive to allow voluntary muscle contraction, is typically assessed using transcranial magnetic stimulation (TMS), which provides insight into the level of motor cortex excitability and inhibition.

In knee OA, one study ($n=107$) demonstrated that decreased intracortical facilitation (ICF) and a reduced motor threshold (MT) were associated with increased pain when assessed using a visual analogue scale (16). Conversely, this same study reported that when using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scale, increased ICF and increased MT were associated with increased pain (16). These conflicting findings make interpretation of the results challenging. Therefore, a comprehensive understanding of motor cortex drive, including other measures of corticospinal and intracortical excitability, and overall neural activation of the muscle, may improve the understanding of the mechanisms contributing to motor dysfunction in OA. This may assist exercise (and other) intervention selection, dosage, and parameters to improve OA outcomes. The aim of this review was to determine the extent that people with lower-limb OA have altered neural responses implicated in descending motor drive and voluntary muscle activation.

Objectives

Our primary objective was to quantify motor cortex descending drive and voluntary activation in people with lower-limb OA compared to controls.

Methods

Guidelines and prospective registration

This systematic review and meta-analysis was designed and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (18). The protocol was registered prospectively with PROSPERO (CRD42022381635; https://www.crd.york.ac.uk/prospero/).

Data management

All records were managed and stored within Covidence (Veritas Health Innovation, Melbourne, Australia). Study data extraction utilised Microsoft Excel spreadsheets. To facilitate systematic review transparency (19, 20), all extracted data are included within this submission.

Inclusion criteria

Participants

Our pathological group included humans aged ≥18 years, who had been diagnosed with lower-limb OA (hip, knee, ankle, and/or foot). Studies whose participants had mixed presentations of joint OA were included, provided the region of OA was identified.

For studies utilising TMS or assessing voluntary activation, our control group included reportedly healthy humans aged ≥18 years who did not have lower-limb OA but were not required to have been matched for age, sex, or physical activity levels. For studies assessing voluntary activation we also included studies that assessed the contralateral non/less affected limb as a control, however these were assessed separately to healthy controls.

Outcomes

The primary outcome for this review was the assessment of measures that assess aspects of descending motor drive. We included studies that reported any measure inclusive of cervicomedullary evoked potentials (CMEP), ICF, motor evoked potential (MEP), active motor threshold (AMT), resting motor threshold (RMT), short-interval intracortical inhibition (SICI), and silent period (SP). Furthermore, studies that assessed voluntary

activation (the ability of the nervous system to drive the muscle to produce maximal force) were included. A detailed description of each of these terms is included within Appendix A (see section on supplementary materials given at the end of this article).

Types of studies

Cross-sectional, case–control, and observational studies were included. We also included randomised controlled trials (RCTs) that performed analysis at baseline (e.g. some RCTs performed a cross-sectional analysis of voluntary activation at baseline versus healthy controls). Studies were included regardless of their publication status. Reviews and case reports were excluded. We included records in all languages, which were translated as needed.

Search strategy

Search strategies using free text terms (Appendix B) were performed from inception to 30 December 2022. Searches were performed within the following electronic databases: PubMed, CINAHL (Full-text), EBSCO (Medline), Cochrane library, SPORTDiscus, Web of Science (Appendix C). Clinical trial registries were not searched as we examined cross-sectional data only. Reference lists of reviews and retrieved articles were checked for additional studies missed in the electronic database search. The ePublication lists of key journals in the field were screened to identify studies that have yet to be indexed.

Study selection

Identified studies were exported to reference management software, EndNote™ 20 (Version 20.4.1, Clarivate Analytics, Philadelphia, PA, USA) and then uploaded into Covidence, with duplicates automatically removed by the software. Two review authors (WH and MM) independently assessed the titles and abstracts of eligible studies identified by the search strategy. Articles that met the inclusion criteria were assessed in full. Disagreements were resolved by consensus.

Data extraction

Two review authors (MM and CS) independently extracted data from all included studies written in English. For studies that were translated from another language, a single study author (SM) performed data extraction directly from the manuscript to minimise errors, under the guidance of one study author (MM). Discrepancies and disagreements were resolved by consensus. The following data were extracted: primary author; year of publication; country in which study was conducted; study design; diagnosis; clinical diagnosis was reported; radiological diagnosis was reported; sample size; age; height; weight; body mass index; sex; gender; duration of pain; co-morbidities; injury history; TMS and voluntary activation assessment protocol(s); ICF; MEP; RMT; AMT; SICI; SP; voluntary activation; quality of life; disability; physical function; severity of OA on imaging (Kellgren–Lawrence grading system: 0 = none; 1 = doubtful; 2 = minimal; 3 = moderate; 4 = severe) (21).

Data management

Where presented in graphical format, data were extracted using an online software tool that provided the mean and measure of variance (https://apps.automeris.io/wpd/). Where median (interquartile range: IQR) was presented, it was converted to mean (S.D.) by assuming the median was the same as the mean and S.D. was 1.35 times the IQR (22).

Data synthesis

Demographic data were described using count, percentage, mean, S.D. (or non-parametric alternatives), as indicated. Meta-analyses of between-group outcomes were performed using an inverse variance, random-effects models in RevMan (ReviewManager program, Version 5.4, The Cochrane Collaboration, 2020). For voluntary activation, the pooled standardised mean difference (SMD) with 95% confidence intervals (95% CI) was calculated as the units of measure were not comparable for all studies. For TMS the SMD (95% CI) was calculated as one study used the lower-limb as the reference site and the other study used the upper limb.

Assessment of methodological quality

Two review authors (CL and MM) independently assessed risk of bias for each study using the Joanna Briggs Institute Checklist for Analytical Cross-sectional Studies with any disagreements being resolved by consensus or a third review author if consensus could not be reached. This scale includes eight items, and we defined criteria for each item *a priori* (Appendix D). An overall judgement of methodological quality was assigned based on a 'worst-item-counts' basis with studies being assigned 'low' quality if at least one item is reported as 'no', unclear if no items are reported as 'no' and at least one item is reported as 'unclear', and 'high' quality if all items are reported as 'yes'.

Statistical heterogeneity

A chi-square test was used to evaluate statistical heterogeneity (22). The presence of heterogeneity was assessed using the I^2 statistic, based on the P-value being <0.10 or the I^2 value being $>40\%$ (22).

Consideration of other biases

The influence of small study biases were addressed. Studies with sample sizes less than 50 cases were considered as representing high risk, studies with samples between 50 and 200 cases were classified as moderate risk, and studies with sample sizes greater than 200 cases were classed as low risk (23, 24, 25).

Funnel plots for each variable were visually inspected to explore the likelihood of reporting biases when at least 10 studies were included in a meta-analysis (26).

Assessment of the quality of the body of evidence

The quality of the body of evidence was determined using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, which was adapted for this study design. The GRADE approach involves making an overall judgement on the quality of the body of evidence based on the overall risk of bias, consistency of results, precision, directness of the evidence and publication bias.

Deviations to protocol

Analysis using individual participant data had been planned, however due to the age of included studies (most studies published prior to 2005) and only two studies assessing responses to TMS, we did not proceed with individual participant data meta-analysis.

Results

Selection of studies

A total of 1578 records were identified, and after removal of duplicates, 41 ($n=41$) records proceeded to full-text review. Finally, 18 ($n=18$) records were included in our review (Fig. 1). Reasons for full-text exclusion are reported in Appendix E.

Study information

Full study data are presented in Table 1. All studies reported that their participants were clinically diagnosed with OA (13, 14, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42); however, the criteria for diagnosis varied substantially between studies. 78% of studies also reported that radiological investigations supported the clinical diagnosis (13, 14, 27, 28, 29, 30, 31, 33, 34, 37, 38, 39, 40, 41). Knee OA was investigated in 17/18 studies (94%) (13, 14, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42), whilst the remaining study assessed hip OA (38). Nine studies (50%) compared findings of the symptomatic/most symptomatic limb to the asymptomatic/less symptomatic limb (27, 28, 34,

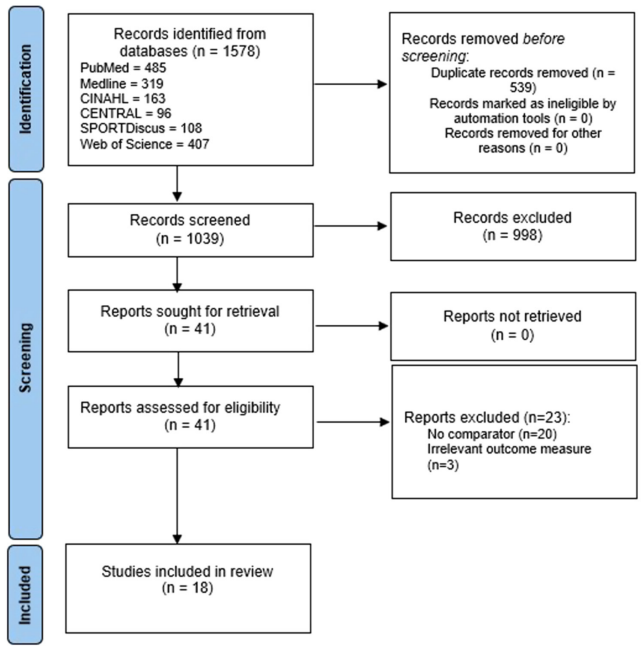

Figure 1
PRISMA flow chart.

35, 36, 37, 38, 41, 42) with 11 studies (61%) comparing the OA group to a healthy control (13, 14, 27, 28, 29, 30, 31, 32, 33, 39, 40). Voluntary activation of the quadriceps was assessed in 17/18 studies (94%) (13, 14, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42), and two studies assessed responses to TMS (32, 39) (Appendix F for a detailed description of these assessment techniques). The majority of the studies were from the USA (6/18, 33%) (32, 33, 35, 36, 37, 40), followed by those from Germany (4/18, 22%) (13, 14, 27, 34). All but one study (94%) (13, 14, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41) received financial support (Appendix G).

Participant demographics

Complete study level demographic details are presented in Tables 2 and 3. A total of 1271 participants were included in the articles (913 OA and 358 controls) with sample sizes in OA groups ranging from 10 (28) to 154 (14) participants. Female inclusion between studies varied, ranging between 29% (38) and 100% females (28). Mean OA participant ages ranged from 52.6 (33) to 67.3 (34) years, with mean control ages often being younger (e.g. two control cohorts mean ages were <35 years (32, 39)). Mean BMI also varied for OA participants, ranging from 25.1 (14) to 33.0 (40), with mean control BMI often lower (e.g. three control cohorts BMI were <25 (29, 30, 32)). The severity of OA also varied, with studies

Table 1 Study information.

Study	Country	Diagnosis	Co-morbidities	Sample injury history	Limb compared to	
					AS/LS limb*	HL of control†
Berth *et al.* (27)	Germany	Unilateral knee OA	NR	NR	Y	Y
Gapeyeva *et al.* (28)	Estonia	Unilateral knee OA	NR	NR	Y	Y
Hassan *et al.* (29)	UK	Bilateral or unilateral knee OA	NR	NR		Y
Heiden *et al.* (30)	Australia	Knee OA	NR	NR		Y
Hurley *et al.* (31)	UK	Bilateral or unilateral knee OA	NR	NR		Y
Kittelson *et al.* (32)	USA	Unilateral knee OA	NR	NR		Y
Lewek *et al.* (33)	USA	Unilateral knee OA (medial compartment) with genu varum	NR	NR		Y
Machner *et al.* (34)	Germany	Unilateral knee OA (primarily the medial tibiofemoral joint)	NR	NR	Y	
Pap *et al.* (13)	Germany	Unilateral knee OA with genu varum	NR	NR		Y
Pap *et al.* (14)	Germany	Unilateral knee OA (medial and lateral femoral and tibial condyle)	NR	NR		Y
Petterson *et al.* (35)	USA	Unilateral knee OA	NR	NR	Y	
Petterson *et al.* (36)	USA	Unilateral knee OA	NR	NR	Y	
Stevens *et al.* (37)	USA	Unilateral OA (tricompartmental)	NR	NR	Y	
Suetta *et al.* (38)	Denmark	Unilateral hip OA	NR	NR	Y	
Tarrago *et al.* (39)	Brazil	Unilateral knee OA	HT: 47.6%, DB: 9.5%, Asthma: 9.5%	NR		Y
Thomas *et al.* (40)	USA	Unilateral or bilateral knee OA	NR	NR		Y
Vahtrik *et al.* (41)	Estonia	Unilateral or bilateral mild knee OA	NR	Heavy physical work or prior trauma	Y	
Ventura *et al.* (42)	Switzerland	Unilateral knee OA (medial tibiofemoral or multicompartmental)	NR	NR	Y	

*Compared symptomatic/most symptomatic limb to the asymptomatic/less symptomatic limb; †Compared the symptomatic/most symptomatic limb to the healthy limb of a control.
AS, asymptomatic; DB, diabetes; HL, healthy limb; HT, hypertension; LS, less symptomatic; OA, osteoarthritis; NR, not reported.

including participants ranging from grade II to grade IV OA. Two studies (11%) included quality of life (30, 42) and nine studies (50%) included a measure of disability (14, 28, 29, 30, 31, 37, 38, 40, 42). Only two studies (11%) reported symptom duration (14, 28).

Transcranial magnetic stimulation

Two studies assessed differences in TMS parameters (specifically ICF, RMT, and SICI) between knee OA participants ($n = 38$) and healthy controls ($n = 30$). No studies assessed AMT or CMEPs.

Intracortical facilitation

No differences were observed between knee OA cases and healthy controls (Fig. 2A); however, a non-significant moderate effect towards reduced ICF in OA cases was observed (S.M.D. = −0.43, 95% CI = −0.92 to 0.07, $P = 0.09$).

Resting motor threshold

No differences were observed between knee OA cases and healthy controls (Fig. 2B); however, a non-significant small effect towards an increased RMT in OA cases was observed (S.M.D. = 0.33, 95% CI = −0.33–0.99, $P = 0.33$), driven by a large effect from Tarrago *et al.* (2016) (39) which assessed upper limb.

Short-interval intracortical inhibition

No differences in SICI were observed between knee OA cases and healthy controls (Fig. 2C), with a non-significant, negligible effect.

Motor evoked potentials

One study assessed differences in MEP, with no differences between knee OA and healthy controls observed (39).

Silent period

One study assessed differences in SP, with a reduced silent period in OA compared to controls (39).

Voluntary activation of the quadriceps

Comparison between OA group and healthy controls

All studies comparing voluntary activation between OA participants ($n = 567$) and controls ($n = 386$) were performed in knee OA. Significant differences were seen between groups (Fig. 3), with OA cases having reduced voluntary activation compared to controls (S.M.D. = −0.84, 95% CI = −1.12 to −0.56, $P < 0.001$).

Comparison between limbs

Eight studies ($n = 321$) compared voluntary activation of the quadriceps between knee OA cases symptomatic/most symptomatic limb and non/less symptomatic limb, and one study examined hip OA ($n = 17$). Significant

Table 2 Participant baseline demographics.

Study/group	Sample size, *n*	Female (%)	Age*, years	Height*, cm	Weight*, Kg	BMI*
Berth *et al.* (27)						
OA	50	64	65.8 (NR)			31.0 (NR)
CONT	46	65	63.2 (NR)			26.2 (NR)
Gapeyeva *et al.* (28)						
OA	10	100	63.0 (52.0-74.0)	156.0 (151.0-166.0)	73.0 (55.0-101.0)	29.0 (22.0-38.0)
CONT	10	100	64.0 (52.0-75.0)	158.0 (148.0-165.0)	70.0 (60.0-84.8)	27† (NR)
Hassan *et al.* (29)						
OA	77	75	63.4 (10.3)	165.0 (8.8)	83.4 (16.5)	30.6 (NR)
CONT	63	71	63.0 (10.7)	166.0 (7.9)	68.7 (9.5)	24.9 (NR)
Heiden *et al.* (30)						
OA	54	56	65.6 (7.6)	170.0 (9.0)	81.4 (14.2)	28.1 (4.2)
CONT	27	67	64.2 (5.1)	170.0 (9.0)	71.3 (13.8)	24.4 (3.6)
Hurley *et al.* (31)						
OA	103	63	60.7 (10.3)	165.0 (10.2)	75.9 (14.63)	28.3 (NR)
CONT	25	72	65.6 (9.5)	164.0 (8.5)	74.0 (16.7)	27.5 (NR)
Kittelson *et al.* (32)						
OA	17	53	63.9 (9.0)			28.3 (5.0)
CONT	20	50	28.3 (11.2)			25.0 (11.2)
Lewek *et al.* (33)						
OA	12	42	52.6 (7.2)			31.3 (5.1)
CONT	12	50	48.9 (4.9)			28.6 (5.6)
Machner *et al.* (34)						
OA	18	61	67.3 (NR)			
Pap *et al.* (13)						
OA	47	77	64.0 (5.2)			
CONT	47	77	64.0 (5.2)			
Pap *et al.* (14)						
OA	68	60	56.7 (9.5)	164.0 (8.7)	74.0 (9.4)	27.5 (NR)
OA	154	59	65.6 (6.0)	166.0 (7.2)	76.0 (11.9)	25.1 (NR)
CONT	85	64	58.1 (8.7)	173.0 (6.8)	75.0 (9.7)	
Petterson *et al.* (35)						
OA	123	54	64.9 (8.5)	170.0 (10.0)	91.0 (16.4)	31.4 (4.8)
Petterson *et al.* (36)						
OA	61	56				
Stevens *et al.* (37)						
OA	28		63.0 (8.8)			
Suetta *et al.* (38)						
OA	17	29				
Tarrago *et al.* (39)						
OA	21	100	64.5 (7.7)			27.5 (5.1)
CONT	10	100	34.1 (11.6)			
Thomas *et al.* (40)						
OA	22	100	58.4 (3.0)	161.2 (5.6)	84.9 (16.8)	32.7 (6.6)
CONT	13	100	57.3 (2.5)	166.5 (4.7)	89.2 (13.8)	31.5 (5.4)
Vahtrik *et al.* (41)						
OA	12	100	61.0 (6.8)			33.0 (4.6)
Ventura *et al.* (42)						
OA	19	53	64.0 (6.0)	171.0 (10.0)	83.0 (17.0)	29.0 (5.0)

*Data presented as mean (S.D.) or as median (range); †Median value.
CONT, control; NR, not reported; OA, osteoarthritis.

differences were seen between limbs (Fig. 4), with the symptomatic/most symptomatic limb having reduced voluntary activation (S.M.D. = −0.42, 95% CI = −0.75 to −0.09, $P = 0.01$). Hip OA appeared to create a larger impairment in voluntary activation (S.M.D. = −0.71) compared to knee OA (S.M.D. = −0.30); however, the confidence intervals are broad, as only one study examines hip OA.

Assessment of clinical diversity and statistical heterogeneity

Whilst 15/18 (83%) studies did not report all demographic data, studies included cohorts which were representative of the general OA community. Most studies included both sexes and varying ages, BMI, and disability levels (Table 2). Therefore, generalisability is not a limitation of the study.

Heterogeneity (I^2 = 70%) was observed in the meta-analysis assessing voluntary activation between OA limb and healthy controls. For all other meta-analyses, when sub-grouping by the affected joints (hip or knee), statistical heterogeneity was not observed.

Assessment of quality and bias in included studies

The overall quality for each study was assessed as low (Appendix H). All studies scored low quality on at least two of the eight quality domains. Eleven studies (61%)

Table 3 QoL, Disability, OA severity scores and pain duration in the participants. Data are presented as mean (S.D.) or as median (range)

Study/group	KOOS QoL score	Disability score	OA severity, KL score	Pain duration, months
Berth *et al.* (27)				
OA			Grade 3–4	
CONT				
Gapeyeva *et al.* (28)				
OA		KKS : 56.0 (20.0–68.0)	Grade 3–4	121.2 (NR)
CONT		KKS : 91.0 (65.0–100.0)		
Hassan *et al.* (29)				
OA		WOMAC† : 36 (7.0–59.0)		
CONT				
Heiden *et al.* (30)				
OA	33.7 (15.8)	KOOS-ADLs: 60.0 (20.0)		
CONT	88.4 (15.3)	KOOS-ADLs: 96.6 (5.7)		
Hurley *et al.* (31)				
OA		MLI: 11 (10.42–12.08)*		
CONT		MLI: 1 (0-3)*		
Kittelson *et al.* (32)				
OA		WOMAC: NR		
CONT		WOMAC: NR		
Lewek *et al.* (33)				
OA				
CONT				
Machner *et al.* (34)				
OA			Grade 3	
Pap *et al.* (13)				
OA			Grade 4	
CONT				
Pap *et al.* (14)				
OA		WOMAC: 5.2 (1.6)	Grade 2	34 (NR)
OA		WOMAC: 5.5 (1.7)	Grade 4	54 (NR)
CONT		WOMAC: 0 (0)		
Petterson *et al.* (35)				
OA				
Petterson *et al.* (36)				
OA			Grade 4	
Stevens *et al.* (37)				
OA		KOOS-ADLs: 56.0 (18.0)		
Suetta *et al.* (38)				
OA			Grades 2–4	
Tarrago *et al.* (39)				
OA		WOMAC: 57.9 (13.2)	Grades 3–4	
CONT				
Thomas *et al.* (40)				
OA		WOMAC: 42.5 (18.1)	Grades 2–4	
CONT		WOMAC: 36.46 (15.26)	Grades 0–1	
Vahtrik *et al.* (41)				
OA			Grades 3–4	
Ventura *et al.* (42)				
OA	29.0 (17.0)	KOOS-ADLs: 66.0 (18.0)		

*Values in parentheses are 95% CI; †Disability score.
ADL, activity daily living; CONT, control; KL, Kellgren–Lawrence; KSS, Knee Society Score; KOOS, Knee injury and Osteoarthritis Outcome Score; MLI, median Lequesne index; OA, osteoarthritis; QoL, quality of life; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

had a sample of ≤50 OA cases (27, 28, 32, 33, 34, 37, 38, 39, 40, 41, 42), with the remaining studies having samples of <200 OA cases (13, 14, 29, 30, 31, 35, 36). Publication bias did not appear to be present on visual inspection of funnel plots of studies from the analyses of voluntary activation.

Assessment of the certainty of the body of evidence

Transcranial magnetic stimulation between OA cases and healthy controls

The certainty of the body of the evidence was reported as 'very low'. Only two studies were included, with limited TMS-based measures assessed. The number of OA cases in both studies was fewer than 25 participants, presenting wide confidence intervals, so the evidence was downgraded twice for imprecision. The methodological quality for both studies was recorded as low; therefore, the certainty of the evidence was downgraded for risk of bias. Due to a substantial I^2 statistic the certainty of the evidence was downgraded for inconsistency. Indirectness and publication bias were not judged as reasons to downgrade the evidence.

Quadriceps voluntary activation comparison between OA cases and healthy controls

The certainty of the body of the evidence was reported as 'low'. The methodological quality for all studies was recorded as low; therefore, the certainty of the

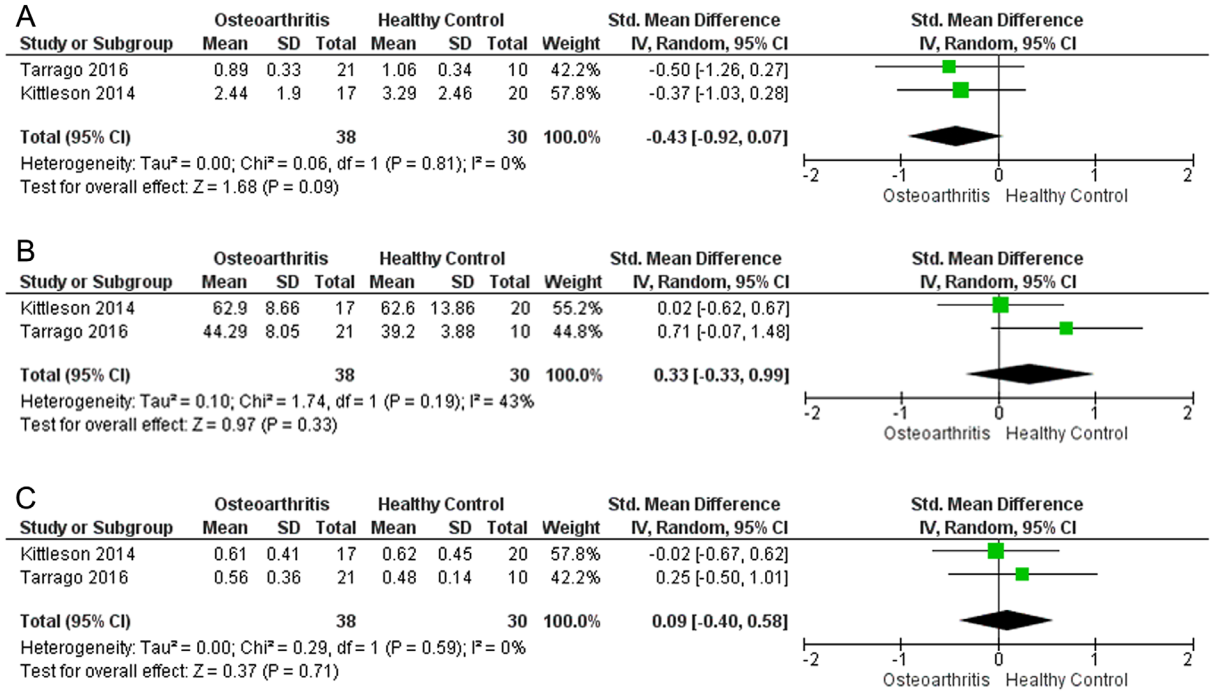

Figure 2

(A) Intracortical facilitation comparison between OA cases and healthy controls. (B) Resting motor threshold comparison between OA cases and healthy controls. (C) Short-interval intracortical inhibition comparison between OA cases and healthy controls.

evidence was downgraded for risk of bias. Due to a substantial I^2 statistic the certainty of the evidence was downgraded for inconsistency. Indirectness, imprecision, and publication bias were not judged as reasons to downgrade the evidence.

Quadriceps voluntary activation comparison between OA cases symptomatic/most symptomatic limb and non/less symptomatic limb

The certainty of the body of the evidence was reported as 'moderate'. The methodological quality for all studies was recorded as low; therefore, the certainty of the evidence was downgraded for risk of bias. Inconsistency, indirectness, imprecision, and publication bias were not judged as reasons to downgrade the evidence.

Discussion

Our systematic review and meta-analysis comprehensively synthesised the evidence regarding motor cortex descending drive and voluntary activation for people with lower-limb OA. The majority of included studies

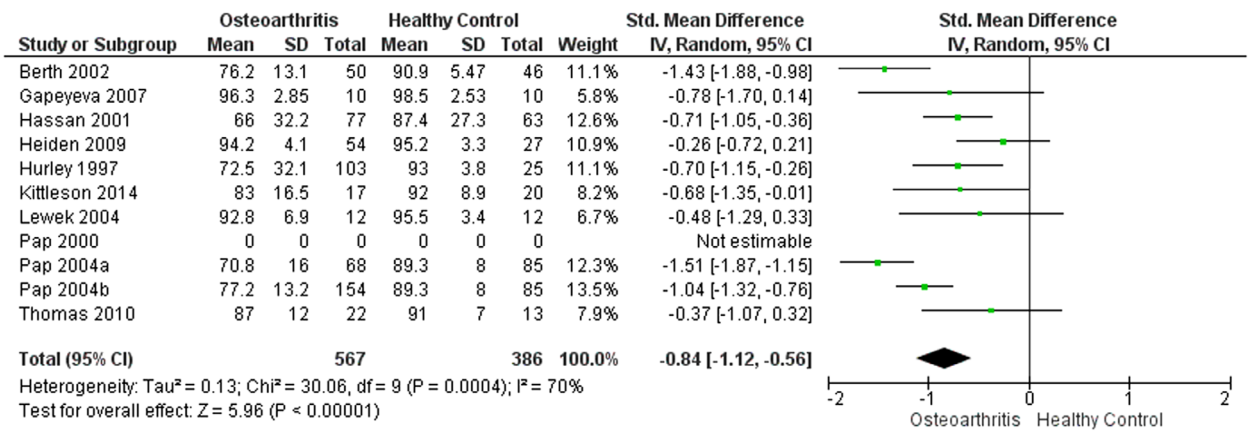

Figure 3

Voluntary activation comparison between OA limb and healthy controls.

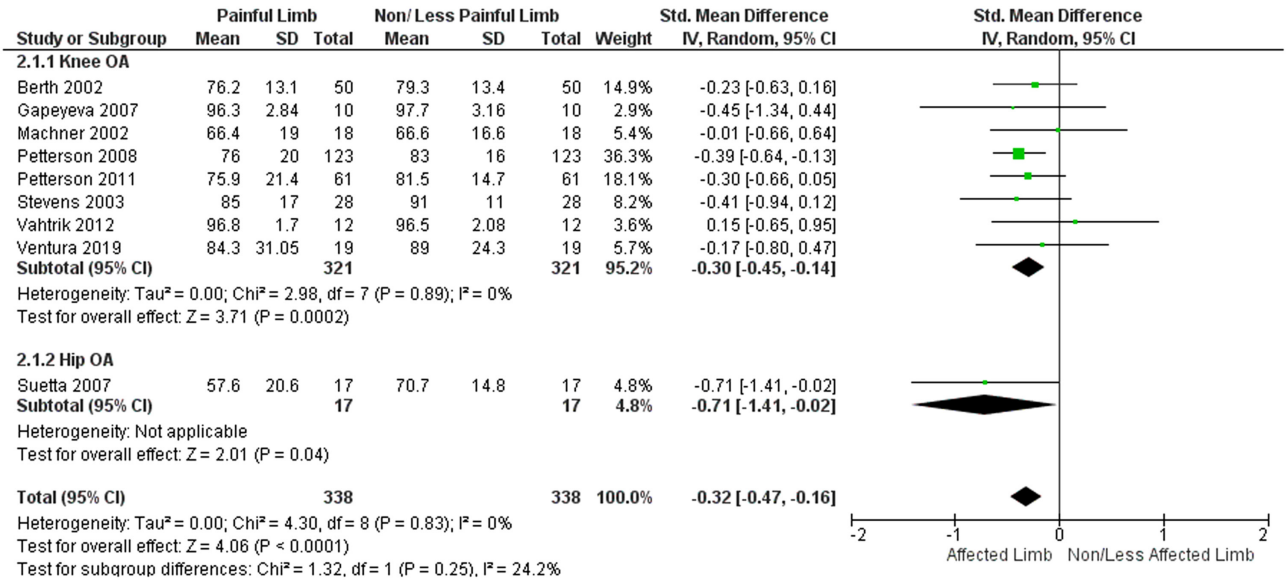

Figure 4
Comparison of voluntary activation of the quadriceps between painful/most-painful and non/less-painful limb.

assessed voluntary activation (94%) with only two studies using TMS (11%). Our findings indicate that: people with knee OA had large impairments in voluntary activation of their quadriceps muscle compared to healthy controls; people with hip and knee OA have moderate impairments in voluntary activation of the quadriceps on their more painful limb compared to their other limb; trends suggest that cortical excitability/inhibition assessed using TMS may differ in those with knee OA compared to controls, but these findings were not statistically significant. A single study found reduced SP in knee OA compared to controls. Limitations of the current body of evidence and methodological considerations regarding neural assessment are also discussed.

The contributions of motor cortex descending drive to voluntary activation deficits in people with lower-limb OA are still largely unknown

Whilst voluntary activation of the quadriceps was found to be impaired in people with hip and knee OA, cortical excitability and inhibition (one of the mechanisms that might contribute to impaired voluntary activation) did not significantly differ between people with and without OA in our review. However, since this judgement is based on a low number of included studies at a high risk of bias, and hence very low-certainty evidence, our results are likely to be substantially different than the true effect size. Beyond the negative influence of imprecision, inconsistency, and risk of bias on the certainty of the evidence, two significant methodological concerns need highlighting when interpreting the results of the included studies that assessed TMS. First, Tarrago *et al.* (2016) (39) recorded responses from the hand muscle, not the limb directly impacted by OA (e.g. quadriceps), meaning all data collected were from TMS assessment to the regions of the cortex responsible for upper limb motor responses. Second, Kittelson *et al.* (2014) (32) placed electrodes over the vastus lateralis muscle only, rather than all components of the quadriceps muscle group, with muscles other than vastus lateralis also playing an important functional role in hip and knee OA (43). Therefore, whilst some preliminary studies have not shown a significant difference in RMT, ICF, and SICI between knee OA and healthy controls, there is little certainty in these outcomes and no studies have explored other variables such as AMT or CMEP. Finally, both included studies were performed in knee OA, with no studies examining hip or ankle OA, meaning motor cortex responses implicated in descending motor drive in people with these conditions are unknown.

Voluntary activation of the quadriceps is impaired in people with lower-limb OA

Our review found that voluntary activation of the quadriceps was impaired (large effect size) in people with knee OA compared to healthy controls (SMD = −0.84, 95% CI = −1.12 to −0.56). Furthermore, voluntary activation of the more symptomatic limb was impaired (moderate effect size) compared to the other limb in people with hip and knee OA (SMD = −0.32, 95%

CI = −0.47 to −0.16). These findings provide guidance for clinicians to specifically target voluntary quadriceps activation in exercise rehabilitation programs. Only one study compared quadriceps voluntary activation between limbs in people with hip OA, with all other studies examining knee OA. This represents a significant gap in the literature, especially considering that hip OA is the fastest growing body region for joint OA in terms of prevalence (44). Furthermore, the considerable societal and healthcare burden of hip OA is projected to rise exponentially in the near future (45). It cannot be assumed that knee OA findings are generalisable to other regions of lower-limb OA and based on the findings of our meta-analysis, the extent of quadriceps inhibition on the symptomatic side appeared greater for participants with hip OA than knee OA (Fig. 4). Therefore, an urgent need is required for future research to investigate whether similar impairments in voluntary activation exist in other regions of OA, such as the hip, ankle, and foot.

Methodological recommendations for future research

Methodological quality of future studies assessing TMS and voluntary activation in lower-limb OA could be improved with the use of more robust outcome assessments. Only five studies (28%) reported potentially confounding variables (30, 32, 33, 38, 39), and only two studies (11%) actively implemented strategies to then deal with variables that may influence TMS or voluntary activation (30, 33). Therefore, we provide some suggestions for future research. First, although basing TMS parameters off motor threshold is accepted and appropriate for some measures, it may not be the most suitable approach for paired-pulse outcomes where a set conditioning and test pulse intensity can produce large heterogeneity of responses amongst individuals. Using a test pulse that elicits a common MEP amplitude (e.g. 1 mV or even 0.5 mV for quadriceps) may offer greater normalisation as levels of inhibition and facilitation can be affected by the size of the test MEP. Additionally, although common to set a standard conditioning pulse intensity (e.g. 70–80% of motor threshold), this approach may not provide the most sensitive information. An alternative approach would be to determine the maximal amount of inhibition or facilitation (e.g. SICI and ICF) achievable in each individual by assessing a range of conditioning stimulus intensities (46). As for voluntary activation, it is evident that many studies did not use (or at least report) muscle/nerve stimulation intensities that were supramaximal (how data were normalised was also infrequently reported). In addition to this, the same intensity was often applied for all individuals. This presents a problem for the true assessment of voluntary activation levels as submaximal stimulation intensities may underestimate or overestimate voluntary activation as not all muscle fibres are excited during stimulation. A common stimulus intensity across participants (or between limbs) is also problematic as electrically evoked activation of the muscle tissue under the electrodes is likely to be affected by muscle and fat mass, skin resistance, and deconditioning. We also note that no research has examined cervicomedullary stimulation, to delineate spinal from supraspinal activity. This may provide even more focal ability for determining the origin of any central nervous system changes in OA. Our systematic review also demonstrates poor reporting of baseline characteristics in most studies as well as clear differences between OA and control groups in some baseline characteristics (e.g. age). This is a problem as age (amongst other variables such as certain medications) can significantly impact voluntary activation (47) and TMS (48) outcomes and should be controlled for in future studies.

Conclusion

Low-certainty evidence demonstrated people with knee OA had substantial impairments in voluntary activation of their quadriceps muscle when compared to healthy controls, with no studies comparing people with other lower-limb OA regions (or other muscle groups). With moderate certainty we conclude that people with hip and knee OA have larger impairments in voluntary activation of the quadriceps in their more painful limb compared to their non/other limb. Finally, whilst trends are demonstrated, very low-certainty evidence was found that cortical excitability/inhibition assessed using TMS did not significantly differ between knee OA cases and controls, meaning the cause of voluntary activation deficits are still unknown. Methodological quality (assessment techniques and data synthesis) of the studies requires improvement to increase certainty of findings and assist clinicians managing people with OA.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-23-0092.

ICMJE Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

MCM conceived the study and MCM, CL, EKR, and ABM designed the study. MCM conducted the search, MCM and WH screened studies, SM translated and performed data extraction for non-English studies. MCM and CL performed quality appraisal, and MCM and CS performed data extraction. All authors contributed to interpretation of data analysis and writing the final manuscript.

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