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The effect of experimental and clinical musculoskeletal pain on spinal and supraspinal projections to motoneurons and motor unit properties in humans: A systematic review

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Abstract

Background and Objective: Numerous studies have examined the influence of pain on spinal reflex excitability, motor unit behaviour and corticospinal excitability. Nevertheless, there are inconsistencies in the conclusions made. This systematic review sought to understand the effect of pain on spinal and supraspinal projections to motoneurons and motor unit properties by examining the influence of clinical or experimental pain on the following three domains: H-reflex, corticospinal excitability and motor unit properties.

Databases and Data Treatment: MeSH terms and preselected keywords relating to the H-reflex, motor evoked potentials and motor unit decomposition in chronic and experimental pain were used to perform a systematic literature search using Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), Web of Science, Medline, Google Scholar and Scopus databases. Two independent reviewers screened papers for inclusion and assessed the methodological quality using a modified Downs and Black risk of bias tool; a narrative synthesis and three meta-analyses were performed.

Results: Sixty-one studies were included, and 17 different outcome variables were assessed across the three domains. Both experimental and clinical pain have no major influence on measures of the H-reflex, whereas experimental and clinical pain appeared to have differing effects on corticospinal excitability. Experimental pain consistently reduced motor unit discharge rate, a finding which was not consistent with data obtained from patients. The results indicate that when in tonic pain, induced via experimental pain models, inhibitory effects on motoneuron behaviour were evident. However, in chronic clinical pain populations, more varied responses were evident likely reflecting individual adaptations to chronic symptoms.

Andy Sanderson and Shuwfen F. Wang have equal contribution as first author.

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Significance: This is a comprehensive systematic review and meta-analysis which synthesizes evidence on the influence of pain on spinal and supraspinal projections to motoneurons and motor unit properties considering measures of the H-reflex, corticospinal excitability and motor unit behaviour. The H-reflex is largely not influenced by the presence of either clinical or experimental pain. Whilst inhibitory effects on corticospinal excitability and motor unit behaviour were evident under experimental pain conditions, more variable responses were observed for people with painful musculoskeletal disorders.

1 | INTRODUCTION

Clinical and experimentally induced pain can change motor output. Several theories of motor adaptations to pain describe changes in motor output as a primary feature. The nature and purpose of this change are unclear, with suggestions that it can be either compensatory or protective in nature (Hodges, 2014; Lund et al., 1991; Sterling et al., 2001). Motor adaptations to pain can occur at numerous levels and in order to comprehensively understand the influence of pain on motor output, it is necessary to investigate pain-related changes at all levels of the motor pathway, including supraspinal and spinal projections to motoneurons and motor unit properties (Heckman & Enoka, 2012; Mcneil et al., 2013). Pain is defined as a 'sensory and emotional experience' which involves the processing of nociceptive stimuli at the cortical level (Nathan et al., 1985; Woo et al., 2017). Within studies which investigate changes in motor output, the term pain is used in the context of nociception even with the absence of cortical processing, and this is the definition of pain which will be used in this review.

Changes in corticospinal excitability represent the behaviour of the nervous pathway from the brain to the motoneuron (Chen, 2000). Although the measure of motor evoked potentials (MEP) is not specific to motoneuron properties, it can indirectly estimate the variations in motoneuron behaviour and has been used to investigate the mechanisms underlying changes in motor output in the presence of pain. At the spinal level, the Hoffman or H-reflex is the electrical analogue of the monosynaptic stretch reflex and has been used in a number of pain studies to test excitability of spinal motoneurons (Dhand et al., 1991; Knikou, 2008; Kosik et al., 2017; Le Pera et al., 2001). Additionally, the study of motor units has provided insight into the influence of pain on motor output, as motor units convert sensory and descending inputs into muscle forces that generate movement (Heckman & Enoka, 2012). Both central (e.g. discharge rate, discharge rate variability) and peripheral (e.g. conduction velocity) properties have been studied when examining neuromuscular adaptations to pain. Taken together, these techniques provide useful information about the neural changes occurring in response to pain and hence have been extensively examined

(Calder et al., 2008; Falla et al., 2010; Farina et al., 2008; Yang et al., 2016).

In individual studies, there appears to be some consistency with respect to pain-induced motor adaptations, for example, decreased size of MEPs (Le Pera et al., 2001; Svensson et al., 2003) or decreased motor unit discharge rate (Dideriksen et al., 2016; Farina et al., 2008; Poortvliet et al., 2015; Tucker et al., 2009a, 2012; Tucker & Hodges, 2010). However, other studies report inconsistent or contradictory findings. For example, an increased or unaltered MEP (Del Santo et al., 2007; Rice et al., 2015; Schabrun et al., 2016) or increased or unchanged motor unit discharge rates (Dideriksen et al., 2016; Minami et al., 2013; Sohn et al., 2000, 2004) have also been reported. It is relevant to discuss previous reviews which discuss the behaviour of aspects of the pathway, such as MEPs, in clinical pain (Chang et al., 2018; Parker et al., 2016) and in experimental pain (Burns et al., 2016b). However, these reviews only consider one element of the motor pathway excitability in a specific condition, and the results are conflicting and differ between reviews. Deeper insight into the influence of pain on these mechanisms would provide clearer directions for future research and would examine the viability of current experimental pain techniques for simulating chronic pain conditions.

This systematic review focuses on pain-induced changes in motoneuron excitability including the H-reflex, transcranial magnetic stimulation (TMS) induced MEP and motor unit properties during voluntary contractions in humans. The following specific questions were addressed: Does the presence of pain (either experimentally induced or clinical) change the (a) H-reflex; (b) corticospinal excitability; or (c) motor unit firing and peripheral properties during voluntary contractions?

2 | METHODS

The systematic review was conducted according to the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Methods S1) and was prospectively registered with PROSPERO (Registration CRD42018095693) (Liberati et al., 2009; Moher et al., 2009).

2.1 | Eligibility criteria

The selection criteria for study inclusion were informed by the Population, Intervention, Comparison, Outcome (PICO) framework (Shamseer et al., 2015; Smith et al., 2011).

2.1.1 | Inclusion criteria

Population (P)

- Men and women over 18 years old.
- Healthy participants experiencing experimentally induced deep soft-tissue pain or patients experiencing musculoskeletal clinical pain.
- Asymptomatic participants not undergoing experimental pain or experiencing clinical pain could be included in the context of comparative controls.

Intervention (I)

- In experimental pain studies, the intervention was the induction of pain in deep soft-tissue. In these studies, participants must have pain induced in deep soft tissue by a controlled stimulus, either thermal, mechanical, electrical or chemical.
- In clinical pain studies, the intervention of interest was the presence of chronic pain symptoms. Clinical participants were eligible if they were diagnosed with chronic musculoskeletal pain, including but not limited to nonspecific neck pain, nonspecific back pain, tendinopathy, fibromyalgia or myofascial pain.

Comparator (C)

- In experimental pain studies, a comparator of either a sham or nonnoxious stimulation may be included.
- For clinical pain studies, a comparator of either a healthy control group or testing of the asymptomatic side could be included.

Outcome (O)

- The use of neurophysiological methods such as electrical stimulation and electromyography (EMG) to measure spinal reflex circuit excitability via the H-reflex; the use of TMS and EMG to measure corticospinal excitability and the use of EMG (surface or intramuscular) and decomposition of signals to examine motor unit behaviour.

2.1.2 | Exclusion criteria

In the clinical pain sample, studies including participants with cancer, autoimmune diseases, visceral pain, central nervous system pathologies (i.e. spinal cord injury or stroke or brain injury), surgical pain, neuropathic pain, complex regional

pain or chronic fatigue syndrome were excluded to ensure the focus of studies on musculoskeletal pain (Vos et al., 2017). As the primary focus of the review was the effect of soft tissue pain, studies focused on arthritis related pain were also excluded. Additionally, any study that included participants under the age of 18 years was excluded, as were animal studies.

In the experimental pain sample, studies including cutaneous pain induced by laser, electrical or chemical stimulation or other means were excluded to ensure a focus on subcutaneous soft tissue pain (Stecco, 2014). Muscle pain induced by eccentric exercise and ischemic pain induced by deafferentiation were excluded to eliminate muscle pain with the presence of local muscle damage. Experimental studies with pain induced by mental imagery, observation and mirror pain were excluded.

Studies measuring the effects of interventions or training were excluded. Studies involving magnetic resonance imaging, functional magnetic resonance imaging, electroencephalogram (EEG), Mono-ethylene glycol (MEG) were excluded. Because the focus of this review is on motoneuron properties for the limb and trunk muscles, studies focussing on the trigemino-facial system were excluded. StretchH-reflexes were also not included due to the measurement of sensory afferent activity and peripheral receptor involvement during the evoked stretchH-reflexes (Kandel et al., 2000).

The literature focus was on published and peer-reviewed journal articles; therefore, published abstracts, nonpublished studies (e.g. graduate theses), nonprimary literature (e.g. systematic and narrative reviews), letters, editorials, commentaries, case studies, unpublished manuscripts, books and book chapters, conference proceedings, cost analyses and clinical practise guidelines were excluded.

2.2 | Search strategy and data sources

A search strategy was constructed using a combination of medical subject heading (MeSH) terms and keywords related to pain, motor behaviour and neurophysiological methods (Table 1). Searches were conducted by a single author (SFW) using the following electronic databases: Cumulative Index of Nursing and Allied Health Literature (CINAHL) (EBSCO interface), Excerpta Medica dataBASE (EMBASE) (Ovid interface), Web of Science, Medline, Google Scholar and Scopus. A complete list of search terms is included in Methods S2, and example terms for one database are listed in Table 1. Studies published in English prior to 1 March 2019 were searched initially, and the search was updated up to 13 October 2020. Search terms from each column in Table 1 were entered using the Boolean operator 'OR'. The Boolean operator 'AND' was then used to combine these searches across columns.

TABLE 1 Key words used to inform the search strategy

| Population | Intervention | Outcome | Comparisons |
|--------------|------------------------|--------------------------|------------------------------------|
| Pain | Magnetic Stimulation | Motor neuron* | EMG |
| Acute pain | Electrical stimulation | Alpha | Electromyograph* |
| Chronic pain | | Motoneuron* | MEP |
| Acute | Cranial | Motor unit* | Motor evoked potential |
| Chronic | Transcranial | Muscle unit* | Cervicomedullary evoked potential |
| Nocicept* | Cervicomedullary | Muscle fib* | CMEP |
| | TMS | Neural drive | Transmastoid |
| | Transcranial | Muscle activit* | Brainstem |
| | Magnetic stimulation | Synerg* | Corticospinal tract stimulation |
| | | Antagon* | Pyramidal tract |
| | | | Spinal excitability |
| | H reflex | Motor cortex | Spinal inhibition |
| | | Brain | Cortical inhibition |
| | | | Cortical excitability |
| | Rest | Motor adaptation | Motor excitability |
| | Voluntary | Neural adaptation | Corticospinal excitability |
| | Isotonic contraction | Neuromuscular adaptation | Discharge rate |
| | Isometric contraction | Motor control | Firing rate |
| | Isokinetic | Muscle function | Firing frequency |
| | Dynamic | Motor output | ISI variability |
| | Repetitive | Motor behaviour | Inter-spike interval |
| | Concentric | | Recruitment threshold |
| | Eccentric | | Conduction velocity |
| | Sustained | Movement strategy | IPSP |
| | Movement | | Inhibitory postsynaptic potentials |
| | | | Oscillation |
| | | | Coherence |
| | | | Force variability |
| | | | Force steadiness |
| | | | Coefficient of variation |
| | | | Synchronization |
| | | | Spatial resolution |
| | | | Motor unit recruitment |
| | | | Neurophysiological recruitment |
| | | | TMS recruitment curves |
| | | | TMS intensity |
| | | | MEP amplitude |

*Wildcard searches are indicated by an asterisk.

2.3 | Study selection

All potentially eligible studies were retrieved and stored on Endnote software (X7.7.1). Duplicates were identified and removed by a single reviewer (SFW). Two independent

reviewers (SFW, EMV) screened the studies based on the title and abstract for eligibility. Subsequently, full texts of the remaining studies were reviewed, and inclusion was determined independently (SFW, ESS). Where discrepancies occurred, a consensus meeting was held with an additional reviewer (DF) to determine inclusion. The updated search

was conducted in the same manner and using the same criteria by two reviewers (AS and EEC). In line with the PRISMA guidelines, information on excluded studies and the reasons for exclusion are collated and reported (Figure 1) (Liberati et al., 2009; Moher et al., 2009).

2.4 | Data extraction

Data extraction was completed by one reviewer per search (SFW/AS) and checked for accuracy by secondary reviewers (ESS/EEC). A standardized, prepiloted form was used to extract data including patient demographics, methodology, all outcome measurement information and results of measurement properties. The outcome variables which were extracted have been listed in Table 2.

2.5 | Methodological quality assessment

The methodological quality of each study was assessed independently by two reviewers (SFW, ESS). A custom quality checklist (Methods S3) (Burns et al., 2016b) adapted from the Downs and Black Quality Index (Downs & Black, 1998) was used to incorporate the specific needs of the objectives of this review into the quality assessment process. Amongst the 17 items, selection bias, performance bias, attrition bias, reporting bias and detection bias were assessed. The quality of each of the references included is reported as the total score by combining the score of each item (Table 3).

Inter-rater reliability between the assessors rating the methodological quality of each study was calculated in Statistical Package for the Social Sciences (SPSS) statistics 24 and

TABLE 2 Outcomes of interest for studies included in the systematic review, arranged by the type of measurement

| Measurement type | Outcome of interest | Abbreviation |
|---------------------------------|--------------------------------------|----------------|
| H reflex | H-reflex amplitude | HA |
| | Amplitude of the M-wave | MA |
| | H-reflex/M-wave ratio | H/M |
| | Latency of the H-reflex | HL |
| | Threshold of the H-reflex | HT |
| Corticospinal excitability/MEPs | Amplitude of MEP | MEPA |
| | MEP latency | MEPL |
| | Resting motor threshold | RMT |
| | Active motor threshold | AMT |
| | Duration of the silent period | SP |
| | Spatial distribution of the MEP | MEP area |
| | Spatial volume of the MEP map | Map volume |
| | Number of discrete cortical peaks | Cortical peaks |
| Motor unit behaviour | Discharge rate | Discharge rate |
| | Coherence of cumulative spike trains | Coh |
| | Conduction velocity | CV |
| | Action potential amplitude | Amplitude |

Abbreviation: MEP, motor evoked potential.

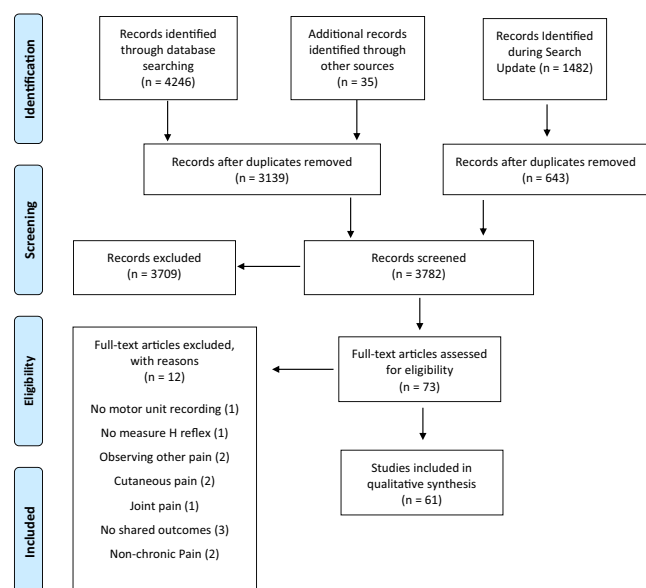


FIGURE 1 Study selection process

presented as a k Statistic (Cohen's Kappa) (McHugh, 2012). Accordingly, inter-rater reliability was interpreted as follows, poor (<0.0), slight (0.00–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8) or almost perfect (0.81–1.0) (Landis & Koch, 1977).

2.6 | Data synthesis and meta-analysis

Previous systematic reviews of the influence of pain on the results of individual methodologies (e.g. MEPs) have included detailed quantitative meta-analyses of the results (Burns et al., 2016b; Chang et al., 2018). To fully explore the potential for meta-analysis, two reviewers (AS/EEC) performed subgrouping of included studies into homogenous groupings. These groupings were completed in terms of the type of pain (experimental/clinical), location of pain (muscle group), pain mechanism or condition, outcome muscle group and then finally the variables considered. In order to be considered for further meta-analysis,

TABLE 3 Risk of Bias scores and key outcomes for each included study

| Experimental pain | | | Clinical pain | | |
|-------------------------------|----------|-------|---------------------------------|----------|-------|
| Author and year | Outcome | Score | Author and year | Outcome | Score |
| | | R1/R2 | | | R1/R2 |
| Schabrun et al. (2013) | H-reflex | 11 10 | Pazzinatto et al. (2019) | H-reflex | 12 12 |
| Park and Hopkins (2013) | H-reflex | 13 13 | Thompson et al. (2019) | H-reflex | 13 13 |
| Svensson et al. (2003) | H-reflex | 11 11 | Kosik et al. (2017) | H-reflex | 9 11 |
| Le Pera et al. (2001) | H-reflex | 11 10 | De Oliveira Silva et al. (2016) | H-reflex | 13 12 |
| Matre et al. (1998) | H-reflex | 9 9 | Wang et al. (2011) | H-reflex | 13 11 |
| Summers et al. (2020) | MEP | 13 13 | Ginanneschi et al. (2007) | H-reflex | 8 11 |
| Alhassani et al. (2019) | MEP | 13 13 | Mazzocchio et al., 2001 | H-reflex | 12 11 |
| Seminowicz et al. (2019) | MEP | 11 14 | Salerno et al. (2000) | H-reflex | 9 11 |
| Summers et al. (2019) | MEP | 14 13 | Leroux et al. (1995) | H-reflex | 10 12 |
| Larsen et al. (2018) | MEP | 15 14 | Dhand et al. (1991) | H-reflex | 7 11 |
| Schabrun et al. (2016) | MEP | 10 10 | Humphreys et al. (1989) | H-reflex | 8 11 |
| Burns et al. (2016) | MEP | 9 10 | Hoehler and Buerger (1981) | H-reflex | 9 12 |
| Rice et al. (2015) | MEP | 12 11 | Cardinal et al. (2019) | MEP | 16 15 |
| Schabrun et al. (2013) | MEP | 11 10 | Elgueta-Cancino et al. (2019) | MEP | 12 14 |
| Schabrun and Hodges (2012) | MEP | 13 10 | Te et al. (2017) | MEP | 11 11 |
| Tsao, Tucker, et al. (2011) | MEP | 11 10 | Massé-Alarie et al. (2017) | MEP | 13 10 |
| Del Santo et al. (2007) | MEP | 10 11 | Burns et al. (2017) | MEP | 10 11 |
| Martin et al. (2008) | MEP | 5 4 | Kosik et al. (2017) | MEP | 9 11 |
| Svensson et al. (2003) | MEP | 11 11 | Schabrun et al. (2017) | MEP | 9 10 |
| Le Pera et al. (2001) | MEP | 11 10 | Rio et al. (2016) | MEP | 15 12 |
| Martinez-Valdes et al. (2020) | MU | 14 14 | Massé-Alarie et al. (2016) | MEP | 12 11 |
| Dideriksen et al. (2016) | MU | 15 10 | Burns et al. (2016) | MEP | 9 14 |
| Yavuz et al. (2015) | MU | 14 10 | Schabrun et al. (2015) | MEP | 12 10 |
| Poortvliet et al. (2015) | MU | 14 11 | Ngomo et al. (2015) | MEP | 12 11 |
| Tucker et al. (2012) | MU | 14 10 | Massé-Alarie et al. (2012) | MEP | 13 11 |
| Tucker and Hodges (2010) | MU | 9 10 | Tsao, Tucker, et al. (2011) | MEP | 11 10 |
| Tucker et al. (2009) | MU | 10 10 | Mhalla et al. (2010) | MEP | 11 12 |
| Hodges et al. (2008) | MU | 10 10 | Tsao et al. (2008) | MEP | 11 11 |
| Farina et al. (2008) | MU | 10 11 | Strutton et al. (2005) | MEP | 9 9 |
| Farina et al. (2005) | MU | 10 10 | Salerno et al. (2000) | MEP | 9 11 |
| Farina et al. (2004) | MU | 11 10 | Gallina et al. (2018) | MU | 12 12 |
| | | | Yang et al. (2016) | MU | 12 11 |
| | | | Falla et al. (2010) | MU | 13 11 |
| | | | Calder et al. (2008) | MU | 12 11 |
| | | | Kallenberg and Hermens (2006) | MU | 12 12 |

Abbreviations: MEP, motor evoked potential; MU, motor unit firing rate; R1, reviewer 1; R2, reviewer 2.

these groupings must contain a significant number of studies; in this instance, grouping of five or more studies was considered significant. Where these subgroups were identified, specific data for the outcome of interest were extracted and if data were in graphical format, values from published figures were estimated using 'WebPlotDigitizer 4.2' by AS and checked by EEC. Where specific data were not reported or plotted, the study was excluded from the meta-analysis grouping. Mean and standard deviation (*SD*) for each study were used to calculate an odds ratio (*OR*) and indicate homogeneity in the form of an I^2 using Review Manager (RevMan 5.4; The Cochrane Collaboration) (Egger et al., 1997; Higgins et al., 2003).

Where subgroupings included less than five homogeneous studies, qualitative analysis was instead conducted. Findings were separated into experimental or clinical pain studies considering the three aspects of motoneuron behaviour evaluated (H-reflex, corticospinal excitability, motor unit behaviour) that fulfil the aims of this review. Due to the variability in both the measurement of outcomes and the tasks completed to elicit the outcomes, a vote-counting system of qualitative analysis was used for synthesis (McKenzie & Brennan, 2019). Thus, for analysis purposes, all measurement outcomes were distilled down to an 'Increase', 'No Change', or a 'Decrease' in comparison to a measured pain-free condition.

In order to collate results, a representative result each of an increase, no change or decrease per outcome was identified for each study. If this was not possible, for example, if the same study found increases in one muscle but decreases in a different muscle for the same outcome, the study was marked as Unclear/Mixed.

3 | RESULTS

3.1 | Study selection

The search identified 5,763 studies. After removal of duplicates, screening of titles and abstracts, 73 studies were eligible for full-text review (Figure 1). Of the 73 studies, 12 were excluded after full text review, and three additional studies were excluded at the data extraction stage, as no previously stated outcomes of interest were identified within the reported results. Therefore, 61 studies were included within the final review. In total, 28 studies considered experimental pain paradigms and 33 studies investigated clinical pain. Of these studies, five investigated more than one outcome measure, three in the clinical pain group and two in the experimental group. The results of these replicated studies have been included in each group independently; however, their reviewer scores were not included twice for risk of bias analysis.

3.2 | Methodological quality assessment

The quality assessment scores for each study and the outcomes of interest from the two reviewers are listed in Table 3. The percentage agreement between reviewers of the methodological quality assessment for the included studies (17 items for each of the 61 studies = 1,037 items) was 77.5% of agreement between individual reviewers. The κ Statistic (Cohen's Kappa) was 0.51, which is considered to be moderate.

The average score for methodological quality within eligible studies was 11.24 ± 1.9 out of a maximum score of 18, which equates to $62.8\% \pm 10.4\%$. Possible reasons for this low score include that only eight (R1) or zero (R2) of the 61 studies indicated that the subjects who participated were representative of the entire population from which they were recruited, and only seven (R1) or one (R2)/61 studies blinded the investigator during data collection and analysis.

3.3 | Participant characteristics

Of the included experimental pain studies, five (Le Pera et al., 2001; Matre et al., 1998; Park & Hopkins, 2013; Schabrun et al., 2013; Svensson et al., 2003) measured the H-reflex; 15 measured corticospinal excitability via MEP (Alhassani et al., 2019; Burns et al., 2016c; Del Santo et al., 2007; Larsen et al., 2018; Le Pera et al., 2001; Martin et al., 2008; Rice et al., 2015; Schabrun et al., 2013, 2016; Schabrun & Hodges, 2012; Seminowicz et al., 2019; Summers et al., 2019, 2020; Svensson et al., 2003; Tsao, Tucker, et al., 2011), and 11 recorded motor unit behaviour outcomes (Dideriksen et al., 2016; Farina et al., 2004, 2005, 2008; Hodges et al., 2008; Martinez-Valdes et al., 2020; Poortvliet et al., 2015; Tucker et al., 2009b, 2012; Tucker & Hodges, 2010; Yavuz et al., 2015). Within the clinical group, 12 measured the H-reflex (De Oliveira Silva et al., 2016; Dhand et al., 1991; Ginanneschi et al., 2007; Hoehler & Buerger, 1981; Humphreys et al., 1989; Kosik et al., 2017; Leroux et al., 1995; Mazzocchio et al., 2001; Pazzinatto et al., 2019; Salerno et al., 2000; Thompson et al., 2019; Wang et al., 2011); 18 recorded corticospinal excitability via the MEP (Burns et al., 2016a, 2017; Cardinal et al., 2019; Elgueta-Cancino et al., 2019; Kosik et al., 2017; Massé-Alarie et al., 2012, 2016, 2017; Mhalla et al., 2010; Ngomo et al., 2015; Rio et al., 2016; Salerno et al., 2000; Schabrun et al., 2015, 2017; Strutton et al., 2005; Te et al., 2017; Tsao et al., 2008; Tsao, Danneels, et al., 2011) and five investigated motor unit behaviour (Calder et al., 2008; Falla et al., 2010; Gallina et al., 2018; Kallenberg & Hermens, 2006; Yang et al., 2016). Full information on included studies can be found in Tables 4–9 and Figure 2a–c.

Hypertonic saline was the most frequent pain induction mechanism used in the experimental pain studies ($n = 29$),

TABLE 4 Characteristics and summary of the results of the included studies examining changes in the H-reflex following experimentally induced pain. R- or L- prior to the name of a muscle denotes laterality

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result |
|-------------|--------------------|-------------------------|-----------------|----------------|----------------------------|----------------------------|-----------|
| During pain | H/M reflex ratio | Park and Hopkins (2013) | 13 | HyperS 5% | Infrapatellar fat pad | Vastus medialis | Decreased |
| | | Matre et al. (1998) | 13 | HyperS 5% | Soleus | Soleus | No change |
| | H-reflex amplitude | Le Pera et al. (2001) | 11 | HyperS 5% | Tibialis anterior | Tibialis anterior | No change |
| | | Le Pera et al. (2001) | 11 | HyperS 5% | R-flexor carpi radialis | R-flexor carpi radialis | No change |
| Post pain | H-reflex latency | Le Pera et al. (2001) | 11 | HyperS 5% | R-flexor carpi radialis | R-flexor carpi radialis | No change |
| | H-reflex amplitude | Le Pera et al. (2001) | 11 | HyperS 5% | R-flexor carpi radialis | R-flexor carpi radialis | Decreased |
| | H-reflex latency | Le Pera et al. (2001) | 11 | HyperS 5% | R-flexor carpi radialis | R-flexor carpi radialis | No change |
| | M-wave amplitude | Schabrun et al. (2013) | 12 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | No change |
| | | Svensson et al. (2003) | 10 | HyperS 5% | R-flexor carpi radialis | R-flexor carpi radialis | No change |

Abbreviations: hyperS, hypertonic saline; NGF, nerve growth factor.

one used ascorbic acid (Del Santo et al., 2007) and three use nerve growth factor to create persistent pain (Schabrun et al., 2016; Seminowicz et al., 2019; Summers et al., 2019). Muscle was the most common site of injection ($n = 24$), with some studies injecting more than one muscle, followed by the infrapatellar fat pad ($n = 6$) and the interspinous ligament ($n = 1$). The muscles in which pain was induced were the first dorsal interosseous ($n = 7$), tibialis anterior ($n = 5$), extensor carpi radialis brevis ($n = 5$), abductor digiti minimi ($n = 3$), biceps brachii ($n = 2$), trapezius ($n = 1$), flexor carpi radialis ($n = 1$), soleus ($n = 1$), gastrocnemius ($n = 1$) and flexor pollicis longus ($n = 1$).

The clinical chronic musculoskeletal pain disorders investigated ($n = 33$) included low back pain ($n = 12$), patellofemoral dysfunction ($n = 5$), tendinopathy ($n = 3$), lateral epicondylitis ($n = 3$), fibromyalgia ($n = 3$), neck pain ($n = 3$), chronic ankle instability ($n = 2$), nonspecific arm pain ($n = 1$) and chronic pain ($n = 1$).

3.4 | Meta-analyses

Meta-analyses were not possible in most instances due to extreme heterogeneity between studies and within the reporting of results of the included studies. Five subgroups of between five and six studies each were identified for potential meta-analyses, two subgroups investigated outcomes in the experimental pain paradigms and three investigated clinical pain outcomes, specifically low back pain (LBP). However, one

study in two of these groupings was later excluded at the additional data extraction stage because participants with neuropathic pain were included which might have influenced the result. In both of these instances, the remaining four studies in the grouping did not reach the meta-analysis threshold. Therefore, three meta-analyses were performed, considering MEP amplitude in experimental pain, motor unit discharge rate in experimental pain and active motor threshold in clinical LBP.

3.5 | Experimental pain

3.5.1 | H-reflex

Measures of the H-reflex identified included amplitude and latency of the H-reflex, amplitude and latency of the M-wave and the H-reflex/M-wave (H/M) ratio. These five studies demonstrated no change in the measures of H-amplitude or H-latency during the pain induction period; however, following this period, one study supported a reduction in H-amplitude (Le Pera et al., 2001). Conflicting evidence was reported for the H/M ratio; one study identified a decrease in the H/M ratio following the injection of hypertonic saline into the infrapatellar fat pad (Park & Hopkins, 2013), whereas no changes were identified in other studies that measured this outcome following hypertonic saline injections into the soleus and tibialis anterior muscles (Matre et al., 1998). Two studies considered the M-amplitude during the postpain

TABLE 5 Characteristics and summary of the results of the included studies examining changes in corticospinal excitability following experimentally induced pain. R- or L- prior to the name of a muscle denotes laterality, and –C and –I denote if the muscle considered is ipsilateral or contralateral to the stimulus

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|-------------|------------------------|--------------------------|-----------------|----------------------------|----------------------------------|----------------------------------|-----------|------------------------------------|
| During pain | Active motor threshold | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 1, 2) |
| | Cortical peaks | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Increased | Sustained pain (day 4) |
| | | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 1, 2) |
| | Map volume | Seminowicz et al. (2019) | 20 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Increased | Sustained pain (day 4) |
| | | Summers et al. (2019) | 28 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 2, 4, 6) |
| | | Summers et al. (2019) | 28 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Reduced | Sustained pain (day 2, 4) |
| | MEP area (mV2) | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 1, 2) |
| | | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Increased | Sustained pain (day 4) |
| | MEP amplitude | Del Santo et al. (2007) | 8 | Ascorbic acid 40 mg/0.2 ml | Abductor Digiti Minimi | Abductor Digiti Minimi | Increased | Abductor Digiti Minimi contraction |
| | | Del Santo et al. (2007) | 8 | Ascorbic acid 90 mg/0.5 ml | Biceps brachii | Biceps brachii | Increased | Biceps brachii contraction |
| | | Summers et al. (2020) | 42 | HyperS 5.8% | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Decreased | |
| | | Summers et al. (2020) | 42 | HyperS 5.8% | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Decreased | |
| | | Alhassani et al. (2019) | 20 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | Alhassani et al. (2019) | 20 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | Seminowicz et al. (2019) | 20 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 2, 4, 6) |
| | | Seminowicz et al. (2019) | 20 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Decreased | Sustained pain (day 2, 4) |
| | | Summers et al. (2019) | 28 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | |
| | | Summers et al. (2019) | 28 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | |
| | | Larsen et al. (2018) | 13 | HyperS 5.8% | Extensor carpi radialis | Extensor Carpi Radialis | No change | |
| | | Larsen et al. (2018) | 13 | HyperS 5.8% | Extensor carpi radialis | Extensor Carpi Radialis | No change | |
| | | | | | | First dorsal interosseus | No change | |
| | | | | | | First dorsal interosseus | Decreased | |
| | | | | | | First dorsal interosseus | No change | |
| | | | | | | First dorsal interosseus | Decreased | |

(Continues)

TABLE 5 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (<i>n</i>) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|------------|-------------------|------------------------|--------------------------|-------------------|----------------------------|--|------------------------|-------------------------------------|
| | | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 1, 2, 4) |
| | | Burns et al. (2016) | 22 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | Decreased | |
| | | Rice et al. (2015) | 18 | HyperS 5.8% | R-Infrapatellar Fat Pad | R-Vastus Lateralis R-Vastus Medialis R-Biceps Femoris R-Tibialis Anterior | Increased No change | |
| | | Schabrun et al. (2013) | 12 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | Martin et al. (2008) | 6 | HyperS 5% | Biceps brachii | Biceps brachii Trapezius | No change | |
| | | | 7 | | | Biceps brachii Trapezius | Decreased | Biceps brachii contraction |
| | | | 6 | | | Biceps brachii Trapezius | No change | Biceps brachii constant contraction |
| | | | | | | Biceps brachii Trapezius | Decreased | Trapezius constant contraction |
| | | Le Pera et al. (2001) | 10 | HyperS 5% | R-Abductor Digiti Minimi | R-abductor digiti minimi R-abductor digiti minimi (NP) | Decreased Decreased | |
| | | | 12 | | L-Abductor Digiti Minimi | R-abductor digiti minimi (NP) | No change | |
| | | | | | R-Abductor Digiti Minimi | R-abductor digiti minimi | No change | |
| | | | 11 | | R-Flexor Carpi Radialis | R-flexor carpi radialis | Decreased | |

(Continues)

TABLE 5 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (<i>n</i>) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|------------|-----------------------------|--------------------------|--------------------------|---|--|--|-----------|--|
| | MEP latency | Le Pera et al. (2001) | 12 | HyperS 5% | R-Abductor Digiti Minimi | R-abductor digiti minimi | No change | |
| | | | 10 | HyperS 5% | R-Abductor Digiti Minimi | R-abductor digiti minimi | No change | |
| | | | 12 | | L-Abductor Digiti Minimi | R-abductor digiti minimi (NP) | | |
| | | | 11 | | R-Flexor Carpi Radialis | R-flexor carpi radialis | | |
| | | Seminowicz et al. (2019) | 20 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | |
| | Resting motor threshold | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 1, 2, 4) |
| Post pain | Active motor threshold | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | Cortical peaks | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | Map volume | Seminowicz et al. (2019) | 20 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | | Summers et al. (2019) | 28 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | MEP area (mV ²) | Del Santo et al. (2007) | 8 | Ascorbic Acid 40 mg/0.2 ml Ascorbic Acid 90 mg/0.5 ml HyperS 5.8% | Abductor Digiti Minimi Biceps brachii | Abductor digiti minimi Biceps brachii | No change | Abductor Digiti Minimi contraction Biceps brachii contraction |
| | MEP amplitude | Summers et al. (2020) | 42 | HyperS 5.8% | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | Decreased | |
| | | Alhassani et al. (2019) | 20 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | Decreased | |
| | | | | | L-first dorsal interosseus | L-first dorsal interosseus | No change | |
| | | | | | | | | |

(Continues)

TABLE 5 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|------------|-------------------|-----------------------------|-----------------|--------------------------------|----------------------------------|--|---|--|
| | | Seminowicz et al. (2019) | 20 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | | Summers et al. (2019) | 28 | NGF | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | Sustained pain (day 14) |
| | | Larsen et al. (2018) | 13 | HyperS 5.8% | Extensor carpi radialis | Extensor carpi radialis | No change | |
| | | | | | | First dorsal interosseus | No change | |
| | | | | | First dorsal interosseus | First dorsal interosseus | No change | |
| | | | | | | Extensor carpi radialis | No change | |
| | | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) HyperS 5% | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change Increased | Sustained pain (day 14) Following sustained pain from NGF |
| | | Rice et al. (2015) | 18 | HyperS 5.8% | R-infrapatellar fat pad | R-Vastus Lateralis R-Vastus Medialis R-Biceps Femoris R-Tibialis Anterior | No change | |
| | | Schabrun et al. (2013) | 12 | HyperS 5% | R-first dorsal interosseus | First dorsal interosseus | Decreased | |
| | | Schabrun and Hodges (2012) | 11 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | Decreased | |
| | | | | | | R-Abductor Digiti Minimi (NP) | | |
| | | Tsao, Tucker, et al. (2011) | 9 | HyperS 5% | ISL | Transversus Abdominus-C Transversus Abdominus-I External oblique-C External oblique-I Internal oblique-C Internal oblique-I Rectus abdominus-C | Decreased No change Increased No change Decreased | Transversus Abdominus rest |

(Continues)

TABLE 5 (Continued)

TABLE 5 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (<i>n</i>) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|-------------|-------------------|-----------------------------|--------------------------|----------------|----------------------------|-------------------------------|-----------|------------------------------|
| MEP latency | | Svensson et al. (2003) | 10 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | Decreased | Descending tract stimulation |
| | | | | | | R-flexor carpi ulnaris (NP) | No change | |
| | | Le Pera et al. (2001) | 2 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | Decreased | |
| | | | | | | R-abductor digiti minimi | Decreased | |
| | | | | | | R-abductor digiti minimi (NP) | No change | |
| | | | | | | R-abductor digiti minimi (NP) | No change | |
| | | | 12 | | L-Abductor Digiti Minimi | R-abductor digiti minimi | No change | |
| | | | | | | R-abductor digiti minimi | No change | |
| | | | | | | R-flexor carpi radialis | Decreased | |
| | | Tsao, Tucker, et al. (2011) | 9 | HyperS 5% | ISL | Transversus abdominus-C | No change | Transversus Abdominus rest |
| | | | | | | Transversus abdominus-I | | |
| | | | | | | External oblique-C | | |
| | | | | | | External oblique-I | | |
| | | | | | | Internal oblique-C | | |
| | | | | | | Internal oblique-I | | |
| | | | 11 | | | Rectus abdominus-C | | |
| | | | | | | Rectus abdominus-I | | |
| | | | | | | Lumbar erector spinae-C | | |
| | | | | | | Lumbar erector spinae-I | | |
| | | | | | | Transversus abdominus-C | No change | |
| | | | | | | | | |

(Continues)

TABLE 5 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|------------|-------------------------|----------------------------|-----------------|-------------------|----------------------------------|----------------------------------|-----------|----------------------------------|
| | | | | | | Transversus abdominus-I | | |
| | | | | | | External oblique-C | | |
| | | | | | | External oblique-I | | |
| | | | | | | Internal oblique-C | | |
| | | | | | | Internal oblique-I | | |
| | | | | | | Rectus abdominus-C | | |
| | | | | | | Rectus abdominus-I | | |
| | | | | | | Lumbar erector spinae-C | | |
| | | | | | | Lumbar erector spinae-I | | |
| | | Svensson et al. (2003) | 10 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | | | | | R-flexor carpi ulnaris (NP) | | |
| | | Le Pera et al. (2001) | 12 | HyperS 5% | R-Abductor Digiti Minimi | R-abductor digiti minimi | No change | |
| | | | 10 | | R-Abductor Digiti Minimi | R-abductor digiti minimi | | |
| | | | 12 | | L-Abductor Digiti Minimi | R-abductor digiti minimi (NP) | | |
| | | | 11 | | R-Flexor Carpi Radialis | R-flexor carpi radialis | | |
| | Resting motor threshold | Schabrun et al. (2016) | 12 | NGF 5 µg (0.2 ml) | R-extensor carpi radialis brevis | R-extensor carpi radialis brevis | No change | 14 days following sustained pain |
| | | Schabrun and Hodges (2012) | 11 | HyperS 5% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | Svensson et al. (2003) | 10 | HyperS 5.8% | R-first dorsal interosseus | R-first dorsal interosseus | No change | |
| | | | | | | R-flexor carpi ulnaris (NP) | | |

Abbreviations: hyperS, hypertonic saline; NGF, nerve growth factor.

TABLE 6 Characteristics and summary of the results of the included studies examining changes in motor unit behaviour following experimentally induced pain

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|--------------------------|---------------------|-------------------------------|-----------------|----------------|-------------------------|------------------------------|-----------|-----------------------|
| During pain | Amplitude | Martinez-Valdes et al. (2020) | 15 | HyperS 5.8% | Tibialis anterior | Tibialis anterior | No change | |
| | | Farina et al. (2008) | 16 | HyperS 5.8% | Tibialis anterior | Tibialis anterior | No change | |
| Coherence | Coherence | Dideriksen et al. (2016) | 12 | HyperS 5.8% | Trapezius | Trapezius | No change | Delta alpha beta band |
| | | Yavuz et al. (2015) | 23 | HyperS 5.8% | Abductor digiti minimi | Abductor Digiti Minimi | Decreased | Alpha and beta |
| Conduction Velocity | Conduction Velocity | Farina et al. (2008) | 16 | HyperS 5.8% | Tibialis anterior | Abductor Digiti Minimi | No change | Alpha band |
| | | Farina et al. (2005) | 11 | HyperS 5.8% | Tibialis anterior right | Tibialis anterior | No change | |
| Discharge rate (Hz) | Discharge rate (Hz) | Farina et al. (2004) | 12 | HyperS 5.8% | Tibialis anterior | Tibialis anterior right (NP) | No change | |
| | | Martinez-Valdes et al. (2020) | 15 | HyperS 5.8% | Tibialis anterior | Tibialis anterior | Decreased | 20% MVC |
| | | Dideriksen et al. (2016) | 12 | HyperS 5.8% | Trapezius | Trapezius | Increased | 70% MVC |
| | | Poortvliet et al. (2015) | 13 | HyperS 5% | Infrapatellar fat pad | Trapezius | Decreased | Cranial region |
| | | | | | | Vastus Medialis | No change | Caudal region |
| Tucker et al. (2012) | | | | | | Vastus Lateralis | Decreased | |
| | | | | | | Biceps Femoris | | |
| Tucker and Hodges (2010) | | | | | | Semitendinosus | | |
| | | | | | | Tensor Fasciae Latae | | |
| | | | | | | Vastus Medialis | Decreased | |
| | | | | | | Vastus Lateralis | | |
| | | | | | | Vastus Medialis | Decreased | |
| | | | | | | Vastus Lateralis | | |

(Continues)

TABLE 6 (Continued)

| Pain stage | Outcome parameter | Author and year | Sample size (n) | Pain mechanism | Pain induction location | Outcome muscle | Result | Notes |
|------------|-------------------|----------------------|-----------------|----------------|-------------------------|-----------------------------|-----------|-------|
| | | Tucker et al. (2009) | 8 | HyperS 5% | Infrapatellar fat pad | Vastus Medialis | Decreased | |
| | | | 7 | | Flexor pollicus longus | Vastus Lateralis | Decreased | |
| | | Hodges et al. (2008) | 10 | HyperS 5% | Gastrocnemius lateral | Flexor pollicus longus | Decreased | |
| | | | | | | Gastrocnemius | Decreased | |
| | | Farina et al. (2008) | 16 | HyperS 5.8% | Tibialis anterior | Soleus | Decreased | |
| | | | | | | Tibialis anterior | Decreased | |
| | | Farina et al. (2005) | 11 | HyperS 5.8% | Tibialis anterior right | Tibialis anterior right | Decreased | |
| | | | | | | Tibialis anterior Left (NP) | No change | |
| | | Farina et al. (2004) | 12 | HyperS 5.8% | Tibialis anterior | Tibialis anterior right | Decreased | |

phase (Schabrun et al., 2013; Svensson et al., 2003); however, these studies did not identify any differences in this outcome (Tables 4 and 10 and Figure 2a).

3.5.2 | Corticospinal excitability

The outcomes derived from studies investigating corticospinal excitability included the resting motor threshold, MEP amplitude and MEP latency. Twelve studies measured the MEP amplitude following pain induction through injections to muscle; however, there was no clear result for the effect of experimental pain on MEP amplitude across all muscles considered. Only one study reported an increase of the absolute MEP amplitude compared to the value before experimental pain was induced; however, this study involved the pretreatment of the muscle with nerve growth factor prior to an experimental pain injection (Schabrun et al., 2016). Two other studies also used nerve growth factor (NGF) as a sustained pain mechanism and reported MEP amplitudes which were the same (Seminowicz et al., 2019) or indeed showed a decrease (Summers et al., 2019) in this measure compared to baseline measurements. The majority of studies reported mixed results both in the target muscle and the nontarget muscles, with three results indicating 'No Change', four supporting a decrease and four with unclear or mixed results in the target muscle. Two of these unclear studies reported an increase in MEP amplitude; however, these studies involved the injection of hypertonic saline into the infrapatellar fat pad (Rice et al., 2015) or the interspinous ligament (Tsao, Tucker, et al., 2011), in contrast to the muscular injection sites of the other studies considered. There was a similar range of results in the postpain condition for the target muscle; however, the control muscle appeared to show a majority of changes in studies which assessed this outcome. A meta-analysis was performed on studies which measured MEP amplitude in the postpain period after inducing pain with hypertonic saline in the Foreign Direct Investment (FDI). Seven studies were included in this grouping, but data could not be extracted from two studies, so the resulting analysis is of five studies (Figure 3) (Alhassani et al., 2019; Larsen et al., 2018; Schabrun & Hodges, 2012; Schabrun et al., 2013; Svensson et al., 2003). The results of this analysis indicated significant heterogeneity in the sample ($I^2 = 0\%$) so a standardized mean difference model was used which indicated that MEP amplitude significantly decreased in this muscle ($p = 0.003$).

No consistent changes from baseline/control conditions were reported in studies examining the MEP latency or Resting Motor Threshold. One study reported mixed results for the MEP latency; however, this study measured a variety of muscles and had many more outcomes than other included studies (Tsao, Tucker, et al., 2011). One study measured the MEP area, in an experimental pain condition, and reported

TABLE 7 Characteristics and summary of the results of the included studies examining changes in the H-reflex in clinical pain conditions

| Outcome parameter | Author and year | Sample size (<i>n</i>) | | Pain condition | Outcome muscle | Result |
|-------------------------|---------------------------------|--------------------------|---------|----------------|-----------------------|-----------|
| | | Patients | Control | | | |
| H/M ratio (%) | Thompson et al. (2019) | 12 | 12 | CAI | Soleus | No change |
| | Kosik et al. (2017) | 18 | 16 | CAI | Fibularis longus | No change |
| | De Oliveira Silva et al. (2016) | 15 | 15 | PFP | Vastus medialis | Decreased |
| | Wang et al. (2011) | 14 | 14 | TEND | Soleus | No change |
| | Ginanneschi et al. (2007) | 14 | 14 | LBP | Soleus | No change |
| | Mazzocchio et al. (2001) | 26 | 40 | LBP | Soleus | No change |
| | Salerno et al. (2000) | 13 | 13 | Fibromyalgia | Soleus | No change |
| | | 9 | 13 | | Flexor carpi radialis | |
| | Dhand et al. (1991) | 23 | 20 | LBP | Soleus | No change |
| | Humphreys et al. (1989) | 12 | 30 | LBP | Soleus | Increased |
| | Hoehler and Buerger (1981) | 7 | 7 | LBP | Soleus | Increased |
| H-reflex amplitude (mA) | Pazzinatto et al. (2019) | 30 | 30 | PFP | Vastus medialis | Decreased |
| | Ginanneschi et al. (2007) | 14 | 14 | LBP | Soleus | Increased |
| | Leroux et al. (1995) | 6 | 6 | PFD | Rectus femoris | No change |
| | | 6 | 6 | | Vastus lateralis | |
| | | 6 | 6 | | Vastus medialis | |
| H-reflex latency (ms) | Ginanneschi et al. (2007) | 14 | 14 | LBP | Soleus | No change |
| | Mazzocchio et al. (2001) | 26 | 40 | LBP | Soleus | No change |
| | Salerno et al. (2000) | 13 | 13 | Fibromyalgia | Soleus | No change |
| | | 9 | 13 | | Flexor carpi radialis | |
| | Leroux et al. (1995) | 6 | 6 | PFD | Rectus femoris | No change |
| | | | | | Vastus lateralis | |
| | | | | | Vastus medialis | |
| | Dhand et al. (1991) | 23 | 20 | LBP | Soleus | No change |
| | Humphreys et al. (1989) | 12 | 30 | LBP | Soleus | No change |
| | Hoehler and Buerger (1981) | 7 | 7 | LBP | Soleus | No change |
| H-reflex threshold (mV) | Ginanneschi et al. (2007) | 14 | 14 | LBP | Soleus | Increased |
| | Mazzocchio et al. (2001) | 26 | 40 | LBP | Soleus | Increased |

Abbreviations: CAI, chronic ankle instability; LBP, low back pain; PFD, patella-femoral dysfunction; TEND, tendinopathy.

TABLE 8 Characteristics and summary of the results of the included studies examining changes in corticospinal excitability in clinical pain conditions

| Outcome parameter | Author and year | Sample size (<i>n</i>) | | Pain condition | Outcome muscle | Result |
|-----------------------------|-------------------------------|--------------------------|---------|----------------|-----------------------------------|-----------|
| | | Patients | Control | | | |
| Active motor threshold (%) | Massé-Alarie et al. (2017) | 19 | 13 | cLBP (right) | Multifidus | Decreased |
| | | 16 | 13 | cLBP (left) | Multifidus | No change |
| | Kosik et al. (2017.) | 18 | 16 | CAI | Fibularis longus | No change |
| | Rio et al. (2016) | 11 | 8 | Ptend | Rectus femoris | No change |
| | Massé-Alarie et al. (2016) | 11 | 13 | LBP | Multifidus (bilateral) | No change |
| | Burns et al. (2016) | 14 | 14 | LE | Extensor carpi radialis brevis | No change |
| | Ngomo et al. (2015) | 39 | 39 | RCT | Infraspinatus | Increased |
| | Massé-Alarie et al. (2012) | 9 | 9 | LBP | Transversus abdominus | No change |
| | | | | | Internal oblique | |
| | Tsao et al. (2008) | 11 | 11 | LBP | Transversus abdominus | Decreased |
| Cortical peaks (<i>n</i>) | Strutton et al. (2005) | 24 | 11 | cLBP | Erector spinae | Increased |
| | Elgueta-Cancino et al. (2019) | 10 | 10 | cNP | Superficial neck flexors | Decreased |
| | Te et al. (2017) | 11 | 11 | PFP | Deep neck flexors | Decreased |
| | | | | | Rectus femoris | Decreased |
| | | | | | Vastus lateralis | |
| | | | | | Vastus medialis | |
| | Schabrun et al. (2017) | 27 | 23 | LBP | Erector spinae-L3 | Decreased |
| | | | | | Erector spinae-L6 | No change |
| | Schabrun et al. (2015) | 11 | 11 | LE | Extensor Digitorum | Decreased |
| | | | | | Extensor carpi radialis brevis | |
| Map volume | Elgueta-Cancino et al. (2019) | 10 | 10 | cNP | Superficial neck flexors | No change |
| | | | | | Deep neck flexors | |
| | Te et al. (2017) | 11 | 11 | PFP | Rectus femoris | Decreased |
| | | | | | Vastus lateralis | |
| | | | | | Vastus medialis | |
| | Burns et al. (2017) | 11 | 11 | LBP | Paraspinal muscles | No change |
| | Kosik et al. (2017) | 18 | 16 | CAI | Fibularis longus | Decreased |
| | Schabrun et al. (2017) | 27 | 23 | LBP | Erector spinae-L3 | No change |
| | | | | | Erector spinae-L5 | |
| | | | | | | |

(Continues)

TABLE 8 (Continued)

| Outcome parameter | Author and year | Sample size (<i>n</i>) | | Pain condition | Outcome muscle | Result |
|-------------------|-------------------------------|--------------------------|---------|----------------|---|-----------|
| | | Patients | Control | | | |
| Map area | Schabrun et al. (2015) | 11 | 11 | LE | Extensor digitorum Extensor carpi radialis brevis | Increased |
| | Tsao, Tucker, et al. (2011) | 9 | 11 | LBP | Multifidus Lumbar erector spinae | Decreased |
| | Tsao et al. (2008) | 11 | 11 | LBP | Transversus abdominus | Increased |
| | Elgueta-Cancino et al. (2019) | 10 | 10 | cNP | Superficial neck flexors Deep neck flexors | No change |
| | Kosik et al. (2017) | 18 | 16 | CAI | Fibularis longus | Decreased |
| MEP amplitude | Cardinal et al. (2019) | 17 | 41 | Fibromyalgia | First dorsal interosseus | No change |
| | Massé-Alarie et al. (2017) | 19 | 13 | cLBP (right) | Multifidus | No change |
| | | 16 | 13 | cLBP (left) | | |
| | Burns et al. (2017) | 11 | 11 | LBP | Paraspinal muscles | Decreased |
| | Massé-Alarie et al. (2016) | 11 | 13 | LBP | Multifidus (bilateral) | No change |
| | Burns et al. (2016) | 14 | 14 | LE | Extensor carpi radialis brevis | No change |
| | Schabrun et al. (2015) | 11 | 11 | LE | Extensor digitorum Extensor carpi radialis brevis | Increased |
| | | | | | Infraapinatus | No change |
| | Ngomo et al. (2015) | 39 | 39 | RCT | First dorsal interosseus | Decreased |
| | Mhalla et al. (2010) | 46 | 21 | Fibromyalgia | First dorsal interosseus | No change |
| | Salerno et al. (2000) | 13 | 13 | Fibromyalgia | Tibialis anterior | |
| MEP area | Strutton et al. (2005) | 24 | 11 | cLBP | Erector spinae | No change |
| MEP latency (ms) | Tsao, Tucker, et al. (2011) | 9 | 11 | LBP | Multifidus Lumbar erector spinae | No change |
| | Tsao et al. (2008) | 11 | 11 | LBP | Transversus abdominus | No change |
| | Strutton et al. (2005) | 24 | 11 | cLBP | Erector spinae | No change |
| | Salerno et al. (2000) | 13 | 13 | Fibromyalgia | First dorsal interosseus Tibialis anterior | No change |
| | | | | | | |
| | | | | | | |

(Continues)

TABLE 8 (Continued)

| Outcome parameter | Author and year | Sample size (<i>n</i>) | | Pain condition | Outcome muscle | Result |
|-----------------------------|----------------------------|--------------------------|---------|----------------|-----------------------------------|-----------|
| | | Patients | Control | | | |
| Resting motor threshold (%) | Burns et al. (2016) | 14 | 14 | LE | Extensor carpi radialis brevis | No change |
| | Mhalla et al. (2010) | 46 | 21 | Fibromyalgia | First dorsal interosseus | Increased |
| | Tsao et al. (2008) | 11 | 11 | LBP | Transversus abdominus | No change |
| | Salerno et al. (2000) | 13 | 13 | Fibromyalgia | First Dorsal Interosseus | Increased |
| SP duration (ms) | Cardinal et al. (2019) | 17 | 41 | Fibromyalgia | Tibialis anterior | Decreased |
| | Massé-Alarie et al. (2017) | 19 | 13 | cLBP (right) | First dorsal interosseus | No change |
| | | 16 | 13 | cLBP (left) | Multifidus | No change |
| | Burns et al. (2017) | 11 | 11 | LBP | Multifidus | No change |
| | Massé-Alarie et al. (2016) | 11 | 13 | LBP | Paraspinal muscles | No change |
| | Strutton et al. (2005) | 24 | 11 | LBP | Multifidus (bilateral) | No change |
| | Salerno et al. (2000) | 13 | 13 | cLBP | Erector spinae | No change |
| | | | | Fibromyalgia | First dorsal interosseus | Decreased |
| | | | | | Tibialis anterior | |
| | | | | | | |

Abbreviations: cLBP, chronic low back pain; LBP, low back pain; LE, lateral epicondylitis; PFP, patellofemoral pain; Prend, patella tendinopathy; RCT, rotator cuff tendinopathy.

an increase in biceps brachii and abductor digiti minimi muscles; however, this result was not sustained in the postpain period (Del Santo et al., 2007). A range of results were identified for the map volume in the three studies which identified this outcome in experimental pain with results during pain showing a decrease no change and mixed results. However, in the postpain period, all studies consistently identified a return to the baseline value for map volume (Schabrun et al., 2016; Seminowicz et al., 2019; Summers et al., 2019), (Tables 5 and 11 and Figure 2b).

3.5.3 | Motor unit properties

The outcome measures of motor unit behaviour included discharge rate, conduction velocity, coherence of cumulative spike trains and the action potential amplitude. Of the 10 studies that measured motor unit discharge rate, pain was induced in muscle in seven and in nonmuscular tissue in four (pain was induced in more than one location for one study). Amongst the studies that induced pain into muscle, six reported a decrease in motor unit firing rate and the remaining study recorded regional differences in the firing rate within the muscle. Amongst the four studies that injected nonmuscular tissue to induce pain (Poortvliet et al., 2015; Tucker et al., 2009b, 2012; Tucker & Hodges, 2010), outcomes recorded for five muscles demonstrated a decrease in discharge rate (three studies), and one muscle showed no change in discharge rate (one study). Within these results, one study induced pain within both muscular tissue and nonmuscular tissue; therefore, in total, eight studies showed a decrease in the discharge rate and two showed unclear/mixed results. A meta-analysis was performed considering studies which induced pain and measured discharge rate in muscles of the lower limb. Five studies considered this outcome, and the resultant OR plot is shown in Figure 4 (Farina et al., 2004, 2005, 2008; Hodges et al., 2008; Martinez-Valdes et al., 2020). There was some significant heterogeneity between studies with an I^2 value of 49%; however, the pooled evidence indicates that experimental pain causes a significant decrease in discharge rate when low-force contractions were examined ($p = 0.0001$).

Variable results were also demonstrated for changes in coherence between groups of motor unit spike trains, with one study reporting a reduction in coherence in the painful condition (alpha [5–13 Hz] and beta [15–30 Hz] bands for the abductor digiti minimi muscle) and in the other study no changes were identified compared to pre pain condition in all assessed bandwidths. No changes of motor unit action potential amplitude ($n = 2$) or conduction velocity ($n = 3$) was described (Tables 6 and 12 and Figure 2c).

TABLE 9 Characteristics and summary of the results of the included studies examining changes in motor unit behaviour in clinical pain conditions

| Outcome parameter | Author and year | Sample size (<i>n</i>) | | Pain condition | Outcome muscle | Result | Notes |
|-------------------|-------------------------------|--------------------------|----------|----------------|--------------------------------|-----------|-----------------------------|
| | | Patients | Controls | | | | |
| Amplitude | Calder et al. (2008) | 16 | 37 | NSAP | Extensor Carpi Radialis Brevis | Decreased | |
| | | 11 | 37 | LE | Extensor Carpi Radialis Brevis | No change | |
| | Falla et al. (2010) | 9 | 9 | cNP | Sternocleidomastoid | Increased | 15N (circular contractions) |
| Discharge rate | | | | | | No change | 30N (circular contractions) |
| | | | | | | No change | constant force directions |
| | Calder et al. (2008) | 16 | 37 | NSAP | Extensor Carpi Radialis Brevis | Decreased | |
| | | 11 | 37 | LE | Extensor Carpi Radialis Brevis | Decreased | |
| | Falla et al. (2010) | 9 | 9 | cNP | Sternocleidomastoid | No change | Mean |
| | Gallina et al. (2018) | 36 | 20 | PFD | Vastus Lateralis | Increased | Initial |
| | | | | | | Increased | 5–35 s |
| | | | | | Vastus Medialis | No change | Initial |
| | | | | | | No change | 5–35 s |
| | | | | | | Increased | Across several tasks |
| | Kallenberg and Hermens (2006) | 10 | 10 | Cpain | Trapezius | Increased | |
| | Yang et al. (2016) | 12 | 12 | MNP | Sternocleidomastoid | Increased | 0%–15% MVC |
| | | | | | | No change | 15%–20% MVC |
| | | | | | | Increased | 20%–25% MVC |

Abbreviations: CNP, chronic neck pain; Cpain, chronic pain; LE, lateral epicondylitis; MNP, mechanical neck pain; MVC, maximum voluntary contraction; NSAP, non-specific arm pain; PFD, patellofemoral disorder.

TABLE 10 Summary of the compiled results for outcomes related to the H-reflex in both experimental and clinical pain conditions

| Experimental pain | | Clinical pain | | | | | | | | | |
|--------------------------------|-----------------------------|-----------------------------|----------|-----------|----------|--------------------|-----------------------------|----------|-----------|----------|-------------------|
| Outcome | Conditions | Number of studies (muscles) | Increase | No change | Decrease | Outcome | Number of studies (muscles) | Increase | No change | Decrease | Unclear/ mixed |
| H-reflex amplitude | Injected muscle | 1 (1) | – | 1 | – | H-reflex amplitude | 3 (5) | 1 | 1 | 1 | – |
| | Injected muscle (post pain) | 1 (1) | – | – | 1 | | | | | | |
| H-reflex latency | Injected muscle | 1 (1) | – | 1 | – | H-reflex latency | 7 (10) | – | 7 | – | – |
| | Injected muscle (post pain) | 1 (1) | – | 1 | – | | | | | | |
| H/M ratio | | 2 (3) | – | 1 | 1 | H/M | 10 (11) | 2 | 7 | 1 | – |
| H-reflex threshold | | – | – | – | – | HT | 2 (2) | 2 | – | – | – |
| M-reflex amplitude (post pain) | | 2 (2) | – | 2 | – | MA | – | – | – | – | – |

Note: Grey shading indicates that the variable was not measured in that condition.
Abbreviations: H/M, H-reflex/M-wave ratio; HT, threshold of H-reflex; MA, amplitude of M-wave.

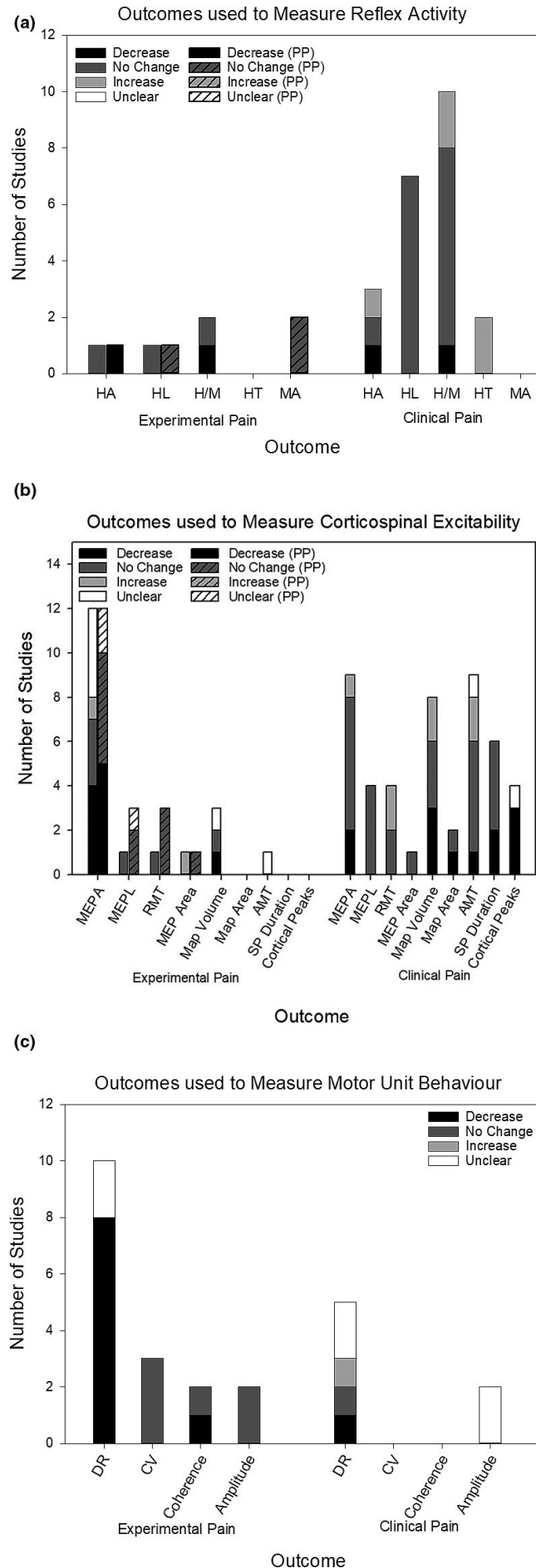


FIGURE 2 The various different outcomes used to measure (a) reflex activity, (b) corticospinal excitability and (c) motor unit behaviour with an indication of whether the measure was decreased, unchanged, increased or had inconsistent results in the experimental pain and clinical pain conditions. Results from control groups and muscles have been excluded for clarity, and results from pain studies in the recovery or postpain period are denoted by dashed columns. (a) HA, Amplitude of the H-Reflex; HL, Latency of the H-Reflex; H/M, H-Reflex/M-Wave Ratio; HT, H-Reflex Threshold; MA, Amplitude of the M-Wave; PP, Post Pain. (b) MEP, Motor Evoked Potential; MEPA, MEP Amplitude; MEPL, MEP Latency; RMT, Resting Motor Threshold; AMT, Active Motor Threshold; SP, Duration of the Silent Period; PP, Post Pain. (c) DR, Discharge Rate; CV, Conduction Velocity; PP, Post Pain

3.5.4 | Pain mechanisms

The majority of studies used hypertonic saline as the experimental pain mechanism, with the exception of four studies which used other pain paradigms to assess MEP outcomes. One study used ascorbic acid (Del Santo et al., 2007); however, this study shared no outcomes with other studies, so it is not clear if these results differ to those induced with hypertonic saline. Two studies used NGF over a sustained period as the primary pain mechanism (Seminowicz et al., 2019; Summers et al., 2019), and one study used a combination of NGF over a sustained period and then hypertonic saline (Schabrun et al., 2016). Results from MEP amplitude during and following the painful period, and the resting motor threshold following the painful period, could all be compared against results from hypertonic saline (Table 13). All results from studies which induced sustained pain using NGF tended to report 'No Change' in MEP amplitude and the resting motor threshold in both painful and postpain conditions. Conversely, studies which induced pain using hypertonic saline tended to report a decrease in MEP amplitude in a majority of cases but was consistent with NGF in reporting no change in the resting motor threshold. Only one study which used hypertonic saline reported an increase in MEP amplitude; however, this study used hypertonic saline after 14 days of NGF infusions (Schabrun et al., 2016).

3.6 | Clinical pain

3.6.1 | H-reflex

Seven out of 10 studies reported no change in the H-reflex/M-wave (H/M) ratio in people with painful musculoskeletal disorders compared to healthy controls. Two studies reported an increase in the H/M ratio, and the remaining study reported a decrease in this value. Studies reporting H-latency ($n = 7$)

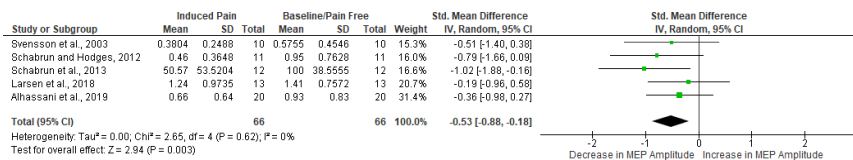
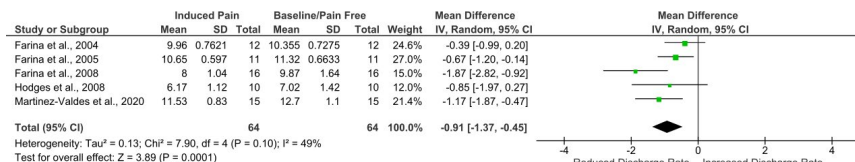


FIGURE 3 Motor evoked potential (MEP) amplitude reported in the first dorsal interosseus in studies which induced pain in this muscle using hypertonic saline

FIGURE 4 Motor unit discharge rate in muscles of the lower limb following pain induction with hypertonic saline



showed unchanged outcomes in people with musculoskeletal pain compared to the control group. Two studies examined the threshold of the H-reflex, and both reported an increase in the presence of pain. Measures of H-amplitude in three studies showed inconsistent results, with one study describing an increase, one a decrease and the other reporting no change (Tables 7 and 10 and Figure 2a).

3.6.2 | Corticospinal excitability

Parameters recorded included the MEP amplitude, MEP latency, resting motor threshold, active motor threshold, silent period duration, MEP area, volume of cortical map and number of cortical discrete peaks. The MEP latency showed no change compared to the value of the control group across the four studies which measured this outcome (Salerno et al., 2000; Strutton et al., 2005; Tsao, Danneels, et al., 2011; Tsao et al., 2008). No change in MEP amplitude was demonstrated in six studies; however, one study showed an increase and two reported a decrease of the MEP amplitude. One study investigated MEP area and identified no changes in the presence of pain (Strutton et al., 2005). Resting motor threshold was measured in four studies and the results indicated an increase in two studies (Mhalla et al., 2010; Salerno et al., 2000), and no changes in a further two studies. Map area was considered in only two studies; one found no change from a pain-free condition (Elgueta-Cancino et al., 2019), and the other identified a decrease (Kosik et al., 2017).

Variable results were identified across studies which measured MEP active motor threshold. Nine studies reported this outcome with the majority ($n = 5$) supporting no change; however, two studies showed an increase in this value, one showed a decrease, and the final study reported unclear/mixed results. Five studies assessed this outcome in the muscles of the trunk in individuals with LBP allowing a

meta-analysis to be performed; these studies were shown to be homogenous with an I^2 score of 74% (Massé-Alarie et al., 2012, 2016, 2017; Strutton et al., 2005; Tsao et al., 2008). The resultant OR is shown in Figure 5. In this instance, the cumulative evidence indicated that LBP appeared to have no influence on the active motor threshold in the muscles of the trunk ($p = 0.75$). This effect was sustained if the studies which investigated trunk flexors were excluded ($p = 0.99$) or the muscles which considered the extensors were excluded ($p = 0.64$).

The silent period duration was not altered in the presence of pain in four studies but was reported to decrease in two studies. There was no clear response to pain in studies investigating the cortical map volume, with two studies reporting an increase, three reporting no change and three, a decrease. There was, however, three studies which provided evidence for a decreased number of discrete cortical peaks; however, a further study reported unclear/mixed results for this outcome in people with musculoskeletal pain (Schabrun et al., 2017) (Tables 8 and 11 and Figure 2b).

3.6.3 | Motor unit properties

There were fewer consistent variables across the studies investigating motor unit activity in clinical pain populations. Thus, despite identifying five relevant studies, it was only possible to collect data on the discharge rate and the motor unit action potential amplitude outcomes. There was no consistent evidence for a change in motor unit discharge rate; all five studies investigated this outcome and one reported an increase, one identified no change, one a decrease and the final two studies reported unclear/mixed results. Two studies investigated motor unit action potential amplitude and both studies reported unclear results, with increases, decreases and no changes identified within the individual muscles and conditions (Tables 9 and 12 and Figure 2c).

TABLE 11 Summary of compiled results for changes in corticospinal excitability in both experimental and clinical pain conditions

| Experimental pain | | Clinical pain | | | | | | |
|-------------------------|------------------------|-----------------------------|----------|-----------|----------|---------------|------------------|-----------------------------|
| Outcome | Conditions | Number of studies (muscles) | Increase | No change | Decrease | Unclear/mixed | Outcome | Number of studies (muscles) |
| MEP amplitude | Painful muscle | 12 (18) | 1 | 3 | 4 | 4 | MEPA | 9 (12) |
| | Painful muscle (PP) | 12 (18) | – | 5 | 5 | 2 | | |
| | Control muscle (DP) | 4 (6) | – | 2 | – | 2 | | |
| | Control muscle (PP) | 6 (8) | – | 4 | 1 | 1 | | |
| MEP latency | Painful muscle | 1 (3) | – | 1 | – | – | MEPL | 4 (6) |
| | Painful muscle (PP) | 3 (14) | – | 2 | – | 1 | | |
| | Control muscle (DP) | 1 (1) | – | 1 | – | – | | |
| | Control muscle (PP) | 2 (2) | – | 2 | – | – | | |
| Resting motor threshold | Painful muscle | 1 (1) | – | 1 | – | – | RMT | 4 (6) |
| | Painful muscle (PP) | 3 (3) | – | 3 | – | – | | |
| | Control muscle (PP) | 1 (1) | – | 1 | – | – | | |
| | | | | | | | | |
| MEP area | During pain | 1 (2) | 1 | – | – | – | MEP area | 1 (1) |
| | Post pain | 1 (2) | – | 1 | – | – | | |
| | During pain | 3 (3) | – | 1 | 1 | 1 | Map volume | 8 (14) |
| | Post pain | 3 (3) | – | 3 | – | – | | |
| Map area | – | – | – | – | – | – | Map area | 2 (3) |
| | Active motor threshold | 1 (1) | – | – | – | – | 1 AMT | 9 (13) |
| | Silent period duration | – | – | – | – | – | – SP duration | 6 (8) |
| | Cortical peaks | 1 (1) | – | – | – | – | 1 Cortical peaks | 4 (9) |

Note: Grey shading indicates that the variable was not measured in that condition.

Abbreviations: AMT, active motor threshold; DP, during painful period; MEP, magnetic evoked potential; MEPA, amplitude of MEP; MEPL, latency of MEP; PP, post painful period; RMT, resting motor threshold; SP, silent period.

TABLE 12 Summary of compiled results for changes in motor unit behaviour in both experimental and clinical pain conditions

| Experimental pain | | | Clinical pain | | | | | | | | | |
|-------------------|----------------|-----------------------------|---------------|-----------|----------|-------------------|----------------|-----------------------------|----------|-----------|----------|-------------------|
| Outcome | Conditions | Number of studies (muscles) | Increase | No change | Decrease | Unclear/ mixed | Outcome | Number of studies (muscles) | Increase | No change | Decrease | Unclear/ mixed |
| Discharge rate | Painful muscle | 10 (19) | – | – | 8 | 2 | Discharge rate | 5 (5) | 1 | 1 | 1 | 2 |
| | Control muscle | 1 (1) | – | 1 | – | – | | | | | | |
| CV | Painful muscle | 3 (3) | – | 3 | – | – | CV | – | – | – | – | – |
| | Control muscle | 1 (1) | – | 1 | – | – | | | | | | |
| Coherence | | 2 (2) | – | 1 | 1 | – | Coherence | – | – | – | – | – |
| Amplitude | | 2 (2) | – | 2 | – | – | Amplitude | 2 (2) | – | – | – | 2 |

Note: Grey shading indicates that the variable was not measured in that condition.

Abbreviation: CV, conduction velocity.

4 | DISCUSSION

This is a wide-ranging systematic review, which is the first to synthesize the effects of both experimental and clinical pain on spinal and supraspinal projections to motoneurons and motor unit properties. The results indicate that both experimental and clinical pain appear to have no major influence on measures of the H-reflex. Secondly, experimental and chronic, clinical pain appeared to have differing effects on corticospinal excitability. Finally, experimental pain consistently reduced motor unit discharge rate, a finding which was not consistent with data obtained from patients with musculoskeletal pain. The results of this review indicate that clinical and experimentally induced pain appears to induce differing effects on motoneurons, highlighting the need for the development of new experimental pain paradigms to simulate clinical pain.

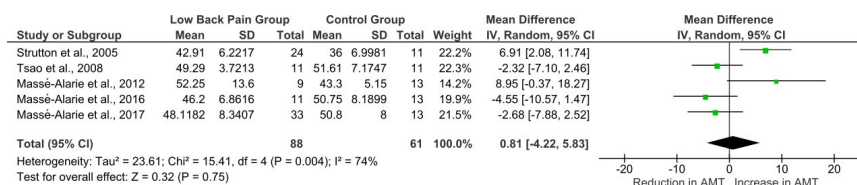
The majority of studies reported no change in H-reflex outcomes following experimentally induced pain. This finding indicates that experimental pain appears to cause no changes in the monosynaptic reflex pathway in the spinal cord and that changes are induced through other means. These results were slightly more varied in the clinical population, with both increases and decreases identified for the H/M ratio. However, one study which reported a significant change in the H/M ratio was potentially influenced by the likely inclusion of patients with neuropathic pain as these participants were not specifically excluded, potentially accounting for this result and precluding a meta-analysis on this outcome (Hoehler & Buerger, 1981). The measures of H-threshold increased in both studies which measured this outcome in a clinical population. However, both studies considered the same muscle and the same clinical condition so it is unknown if this result would be observed in other clinical conditions or other muscles (Mazzocchio et al., 2001; Salerno et al., 2000). Nevertheless, the majority of studies provided evidence indicating that the H-reflex is not modified in clinical pain conditions.

For measures of corticospinal excitability, across the majority of outcomes examined, studies considering clinical pain conditions reported conflicting results, whereas more consistent findings were reported under experimental pain conditions (Rohel et al., 2021). This result was however reversed for the measurement of MEP amplitude, where experimental pain led to mixed and unclear results and the majority of clinical pain studies demonstrated no change in this outcome. Previous reviews have individually assessed corticospinal excitability in response to acute and chronic clinical pain conditions (Burns et al., 2016b; Chang et al., 2018; Parker et al., 2016). In the experimental pain condition, meta-analyses indicated moderate evidence to support a reduction in MEP amplitude during rest, which concurs with effects of tonic pain (Rohel et al., 2021), but not during a contraction

TABLE 13 A comparison of pain induction methodologies on the individual MEP outcomes where possible. Studies which induced pain in the muscles of the wrist have also been included in 'pain induced in target muscle' grouping

| Condition | Outcome | Number of studies | Combined sample size (n) | Pain mechanism | Pain induction location and outcome muscle | Increase | No change | Decrease | Mixed |
|-------------|---------------|-------------------|--------------------------|-------------------|--|----------|-----------|----------|-------|
| During pain | MEP amplitude | 3 | 60 | NGF 5 µg (0.2 ml) | Muscles of the wrist | – | 2 | 1 | – |
| | | 3 | 66 | HyperS 5%–5.8% | Muscles of the wrist | – | 1 | 2 | – |
| | | 7 | 161 | HyperS 5%–5.8% | Pain induced in target muscle tissue | – | 1 | 3 | 3 |
| Post pain | MEP amplitude | 3 | 60 | NGF 5 µg (0.2 ml) | Muscles of the wrist | – | 3 | – | – |
| | | 4 | 78 | HyperS 5%–5.8% | Muscles of the wrist | 1 | 1 | 2 | – |
| | | 9 | 174 | HyperS 5%–5.8% | Pain induced in target muscle tissue | 1 | 1 | 5 | 2 |
| | RMT | 1 | 12 | NGF 5 µg (0.2 ml) | Muscles of the wrist | – | 1 | – | – |
| | | 2 | 21 | HyperS 5%–5.8% | Pain induced in target muscle tissue | – | 2 | – | – |

Abbreviations: NGF, nerve growth factor; RMT, resting motor threshold.


FIGURE 5 Active motor threshold (AMP) in the muscles of the trunk in individuals with chronic low back pain (LBP)

(Burns et al., 2016b); the results from clinical populations were found to be inconclusive for this outcome following meta-analyses in two reviews (Chang et al., 2018; Parker et al., 2016). In this review, experimental pain appeared to induce a decrease of corticospinal excitability; however, different methodologies for pain induction did produce some contrasting results. For example, in the study by Schabrun and colleagues (Schabrun et al., 2016), the target muscle was sensitized by treatment with nerve growth factor 2 and 4 days before a hypertonic saline injection was used to induce

experimental muscle pain. In this study, the results obtained on days where pain was sustained with the nerve growth factor supported no changes in most outcomes, including MEP amplitude, a result mirrored in one of two other studies which used this pain mechanism (Seminowicz et al., 2019). In clinical pain conditions, no significant changes were identified in measures of the MEP amplitude or latency, indicating that the NGF model may potentially more closely emulate these sustained clinical pain conditions; however, as these studies represented just three of the included studies, further studies

are required to confirm this effect. The experimental methodology presented significant heterogeneity in these studies, and the point at which measurements were taken may explain some of the variability between studies measuring corticospinal excitability since some measurements were taken during the transition to pain (Schabrun et al., 2016), during pain (Del Santo et al., 2007), postpain (Svensson et al., 1998) and after recovery from pain (Le Pera et al., 2001; Schabrun & Hodges, 2012).

Changes could be seen in cortical maps in the presence of clinical pain (Burns et al., 2017; Kosik et al., 2017; Schabrun et al., 2015, 2017; Te et al., 2017; Tsao, Danneels, et al., 2011; Tsao et al., 2008), possibly indicating pain-induced cortical reorganization. Two studies (Schabrun et al., 2015; Tsao et al., 2008) reported an increase in the map volume and two, a decrease in map volume (Kosik et al., 2017; Te et al., 2017); thus, the results were conflicting. Three experimental pain studies examined the map volume (Schabrun et al., 2016; Seminowicz et al., 2019; Summers et al., 2019), and all used the same pain mechanism, muscle and similar measurement timepoints. Despite this, there were contrasting results presented with an increase, a decrease and no change in map volume all reported across the three studies. Additionally, further analysis within the pain group in the study by Seminowicz and colleagues identified two distinct patterns of pain adaptation within participants, terms 'facilitation' and 'depression' with diverging responses in map volume and resting motor threshold, presenting an important area for further investigation (Seminowicz et al., 2019).

The changes in corticospinal excitability as a result of experimental muscle pain appear to differ depending on the type of musculoskeletal tissues stimulated. For example, when pain was induced within a muscle, the majority of studies reported either a decrease or a combination of a decrease and no change in corticospinal excitability of the targeted muscles (Burns et al., 2016c; Le Pera et al., 2001; Martin et al., 2008; Schabrun & Hodges, 2012; Svensson et al., 2003). This effect may serve the purpose of protecting the painful muscle, whereby excitability is reduced in order to prevent movement which may exacerbate symptoms. Several pain theories have identified motor adaptations in response to pain, either as a form of protection to avoid moving the painful area or as an adaptation to function around the painful area (Hodges & Tucker, 2011; Lund et al., 1991). However, this finding is speculative, and whilst a reduction in excitability was identified, the underlying reasons for this reduction remain unknown. When pain was induced in noncontractile tissues, such as the infrapatellar fat pad and interspinal ligament, corticospinal excitability increased within local muscles. This phenomenon might be related to a compensatory increased excitability of the muscles to protect the painful noncontractile tissue. This argument is supported by studies

within the clinical pain cohort (Schabrun et al., 2015; Tsao, Danneels, et al., 2011; Tsao et al., 2008).

The largest disparity in results was found for the effects of experimental and clinical pain on motor unit behaviour. Whilst numerous outcomes were reported in the clinical pain studies, these outcomes were largely study specific, and very few variables were common between studies or across patient groups. Additionally, of the studies that did measure the same outcomes, there was no clear majority supporting the effect of clinical pain on any outcome. These results are in contrast to experimental pain studies in which common adaptations of motor unit behaviour were described. In general, the results from this systematic review and meta-analysis support the observation of an inhibition on motoneuron firing rate during tonic experimental pain since 8 out of 10 studies supported a decrease in motor unit discharge rate, with the remaining two studies showing a combination of no change and decrease. Nevertheless, it is important to mention that these studies mainly analysed the behaviour of low-threshold motor units during low-force contractions. Indeed, only one of the reviewed studies measured motor unit behaviour at forces higher than 20% of the maximum voluntary contraction. Martinez-Valdes et al. (2020) measured the influence of pain on motor unit behaviours at both low forces (20% MVC [maximum voluntary contraction]) and high forces (70% MVC). As expected, the motor unit discharge rate decreased at low forces during the painful condition; however, the discharge rate was either maintained or even increased at high forces during pain. Further future studies are needed to examine motor unit behaviour during experimentally induced pain at higher forces, as this study indicates that it is possible that high-threshold motor units adapt differently under painful conditions. Despite the clear inhibitory effects observed across studies, it is important to highlight that the firing behaviour of motoneurons can differ across the motor unit pool, with possible recruitment of new units and excitation of high threshold motor units, compensating for the inhibition of low-threshold units (Martinez-Valdes et al., 2020); this behaviour allows force to be maintained during painful sub-maximal contractions. In clinical pain conditions, reports of changes in motor unit discharge rate were less consistent. In some instances, the motor unit discharge rate was lower, for example, for the extensor carpi radialis brevis in people with nonspecific arm pain (Calder et al., 2008). In contrast, sternocleidomastoid motor unit discharge rate was unchanged (Falla et al., 2010) or was higher in people with in chronic neck pain (Yang et al., 2016).

This difference in responses in clinical and experimental pain indicates that current experimental pain models do not appear to emulate the motor adaptations to chronic pain. The disparity between experimental and chronic clinical pain results for all the techniques used to measure motoneuron excitability and motor unit properties can likely be

explained by a number of factors. Importantly, experimental pain models induce short-term pain, whereas clinical studies have been conducted in people with chronic symptoms which can impact on multiple systems with the potential to influence motor responses (e.g. cognition, tissue structure/morphology). Whilst it is not expected that the responses to tonic experimental pain would be identical to chronic clinical paradigms, as these experimental pain mechanisms are often used to emulate chronic conditions the disparate results in many outcomes may indicate that further research is required to identify how suitable these paradigms are for investigating responses to pain in chronic pain conditions. A small number of results from this review indicate that sustained pain caused by NGF may more closely emulate chronic pain; however, further research is required to confirm this. It is important to consider however that within clinical pain, different conditions are likely to produce differing effects on motor output (Chang et al., 2018; Parker et al., 2016). However, it can also be seen in these results that within clinical conditions, between study, and indeed between subject differences can be identified. For example, in two similar studies which assessed the MEP amplitude in the extensor carpi radialis brevis in individuals with Lateral Epicondylalgia, one study identified an increase in amplitude and one identified a decrease (Burns et al., 2016a; Schabrun et al., 2015). The current results indicate that current experimental pain approaches do not provide an optimal model of the adaptations associated with clinical chronic pain; however, further research is required in populations experiencing both clinical and experimental pain to identify novel approaches to emulating motor adaptations to clinical pain.

4.1 | Strengths and limitations

The agreement of the risk of bias assessment by the reviewers is over 75%, and as such is considered to be a moderate agreement with kappa value of 0.51 (Landis & Koch, 1977). The methodological quality for all studies included was approximately 63%. The items of the bias assessment demonstrating low scores included small sample sizes, no a priori sample size calculation, recruitment via convenience sampling and no experimenter blinding during data analysis (Downs & Black, 1998). Most included studies were cross-sectional in design; however, standardized measurement methods, such as H-reflex and motor unit decomposition from intramuscular and surface EMG signals, have well-established validity and reliability (Chen et al., 2010; Martinez-Valdes et al., 2016), which decreases measurement errors.

It is relevant to note that there are limitations within the studies which must be considered for a full interpretation of these results. As identified in Table 3, some studies showed significant risk of bias including in the sample size

and selection, such as incomplete reporting of recruitment means and pain characteristics. Furthermore, whilst hypertonic saline injection was the most common mechanism for pain induction, the methodologies surrounding the tasks and the duration of monitoring were not fully standardized and so this complicates direct comparison. It is relevant also to discuss the limitations of the neurophysiological techniques employed. The H-reflex is not the only measure of spinal excitability and has been shown to be influenced by external factors (Misiaszek, 2003). There are studies which use alternative techniques including F-Waves and V-Waves to assess this outcome. However, in scoping studies for this review, the H-Reflex was the most consistently reported outcome, so this metric was chosen for inclusion. It may therefore be beneficial for further research on other measures of spinal excitability to strengthen this evidence base.

Finally, whilst attempts were made to include meta-analysis of the results of individual studies, these efforts were affected by significant heterogeneity. The included studies reported a diverse range of outcomes; pain was induced in 12 locations and aligned with 9 clinical pain presentations, and outcomes were measured from the intrinsic muscles of the hand through to gross muscles of the trunk. Due to differences in function, it would not be appropriate to compare muscles which flex a finger to those which move the knee, and as such the localization of outcome measures is an important area to consider for further research. Where homogeneity was found between studies, meta-analyses were further obstructed by the nonreporting of data and inclusion of participants which could affect the study results. As a result, one of the primary recommendations of this review surrounds increasing consistency in measurements within individual methodologies.

In conclusion, this systematic review is the first to provide a wide synthesis of evidence describing the influence of pain on spinal and supraspinal projections to motoneurons and motor unit properties. In general, motoneuron inhibition was evident under experimentally induced pain conditions; however, the changes observed in clinical populations were much more variable, likely reflecting the complexity and variability of clinical pain disorders. Further research using more consistent and comparable methodologies is required to elucidate the influences of clinical and experimental pain on spinal and supraspinal projections to motoneurons.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

This review was conceived by DF and SW; searches, study selection, data extraction and data handling were conducted by AS, EE-C, SW, and ES-S. The manuscript was prepared by AS, DF, SW, EM-V and EE-C, all authors were involved in drafting and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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