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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

Running head - Pain and motoneuron behaviour

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**Significance**: This is a comprehensive systematic review and meta-analysis which synthesises 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.

### 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 CINAHL, 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 has 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.

## 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 is unclear, with suggestions that it can be either be 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 and 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, Kosik et al., 2017, Le Pera et al., 2001, Knikou, 2008). 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 and 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, e.g. 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, Tucker et al., 2012, Tucker and 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., 2004, Sohn et al., 2000) 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 1) H reflex 2) corticospinal excitability or 3) motor unit firing and peripheral properties during voluntary contractions.

# **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) (Moher et al., 2009, Liberati et al., 2009).

# Eligibility criteria

The selection criteria for study inclusion was informed by the PICO framework (Smith et al., 2011, Shamseer et al., 2015).

# 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 softtissue. 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; non-specific neck pain, non-specific back pain, tendinopathy, fibromyalgia or myofascial pain.

# Comparator (C)

- In experimental pain studies, a comparator of either a sham or non-noxious 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.

### 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, EEG, 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. Stretch reflexes were also not included due to the measurement of sensory afferent activity and peripheral receptor involvement during the evoked stretch reflexes (Kandel et al., 2000).

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non-primary literature (e.g., systematic and narrative reviews), letters, editorials, commentaries, case studies, unpublished manuscripts, books and book chapters, conference proceedings, cost analyses, clinical practice guidelines were excluded.

### 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: CINAHL (EBSCO interface), 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<sup>st</sup> of March 2019 were searched initially, and the search was updated up to the 13<sup>th</sup> 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.

### **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 (Fig. 1) (Moher et al., 2009, Liberati et al., 2009).

### **Data extraction**

Data extraction was completed by one reviewer per search (SFW/AS) and checked for accuracy by secondary reviewers (ESS/EEC). A standardised, pre-piloted 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.

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 and Black, 1998), was used to incorporate the specific needs of the objectives of this review into the quality assessment process. Among 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 SPSS statistics 24 and 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 and Koch, 1977).

#### 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, these groupings must contain a significant number of studies, in this instance grouping of 5 or more studies were 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 SD for each study were used to calculate an odds-ratio (OR) and indicate homogeneity in the form of an I<sup>2</sup> using Review Manager (RevMan 5.4; The Cochrane Collaboration) (Egger et al., 1997, Higgins et al., 2003).

Where subgroupings included less than five homogenous 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 and Brennan, 2019). Thus, for analysis purposes, all measurement outcomes were distilled down to either 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 either 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.

# RESULTS Study selection

The search identified 5763 studies. After removal of duplicates, screening of titles and abstracts, 73 studies were eligible for full-text review (Fig. 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.

### 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 = 1037 items) was 77.5% of agreement between individual reviewers. The k Statistic (Cohen's Kappa) was 0.51, which is considered to be moderate.

The average score for methodological quality within eligible studies was  $11.24 \pm 1.9$  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.

### **Participant characteristics**

Of the included experimental pain studies, five (Le Pera et al., 2001, Matre et al., 1998, Park and Hopkins, 2013, Schabrun et al., 2013, Svensson et al., 2003) measured the H reflex; 15 measured corticospinal excitability via MEP (Burns et al., 2016c, Del Santo et al., 2007, Le Pera et al., 2001, Martin et al., 2008, Rice et al., 2015, Schabrun et al., 2016, Schabrun and Hodges, 2012, Schabrun et al., 2013, Svensson et al., 2003, Tsao et al., 2011b, Alhassani et al., 2019, Larsen et al., 2018, Seminowicz et al., 2019, Summers et al., 2020, Summers et al., 2019), and

11 recorded motor unit behaviour outcomes (Dideriksen et al., 2016, Farina et al., 2005, Farina et al., 2004, Farina et al., 2008, Hodges et al., 2008, Poortvliet et al., 2015, Tucker et al., 2009b, Tucker et al., 2012, Tucker and Hodges, 2010, Yavuz et al., 2015, Martinez-Valdes et al., 2020). Within the clinical group, 12 measured the H reflex (De Oliveira Silva et al., 2016, Dhand et al., 1991, Ginanneschi et al., 2007, Hoehler and Buerger, 1981, Humphreys et al., 1989, Kosik et al., 2017, Leroux et al., 1995, Mazzocchio et al., 2001, Salerno et al., 2000, Wang et al., 2011, Pazzinatto et al., 2019, Thompson et al., 2017, Kosik et al., 2017, Massé-Alarie et al., 2016, Burns et al., 2017, Kosik et al., 2017, Massé-Alarie et al., 2016, Massé-Alarie et al., 2017, Massé-Alarie et al., 2016, Salerno et al., 2000, Schabrun et al., 2017, Schabrun et al., 2019, Elgueta-Cancino et al., 2019), and five investigated motor unit behaviour (Calder et al., 2008, Falla et al., 2010, Gallina et al., 2018, Kallenberg and Hermens, 2006, Yang et al., 2016). Full information on included studies can be found in Tables 4-1 to 4-6 and Fig 2A-C.

Hypertonic saline was the most frequent pain induction mechanism used in the experimental pain studies (n=29), 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 inter-spinal 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 (2), non-specific arm pain (n=1), chronic pain (n=1).

### **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 5-6 studies each were identified for potential meta-analyses, two subgroups investigated outcomes in the experimental pain paradigms and three investigated clinical pain outcomes, specifically 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. **Experimental pain** *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

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 and 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 post-pain phase (Svensson et al., 2003, Schabrun et al., 2013), however this studies did not identify any differences in this outcome (Tables 4-1 and 5-1; Fig. 2A).

# 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 pre-treatment of the muscle with nerve growth factor prior to an experimental pain injection (Schabrun et al., 2016). Two other studies also used 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 non-target 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 et al., 2011b); in contrast to the muscular injection sites of the other studies considered. There was a similar range of results in the post-pain 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 MEPamplitude in the post-pain period after inducing pain with hypertonic saline in the 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 (Fig. 3) (Alhassani et al., 2019, Larsen et al., 2018, Schabrun and 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 standardised 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 et al., 2011b). One study measured the MEP-area, in an experimental pain condition and reported an increase in biceps brachii and abductor digiti minimi muscles, however this result was not sustained in the post-pain 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 post-pain 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 4-2 and 5-2, Fig. 2B).

#### 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 non-muscular tissue in four (pain was induced in more than one location for one study). Among 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. Among the four studies that injected non-muscular tissue to induce pain (Poortvliet et al., 2015, Tucker et al., 2009b, Tucker et al., 2012, Tucker and Hodges, 2010), outcomes recorded for five muscles demonstrated a decrease in discharge rate (3 studies), and one muscle showed no change in discharge rate (1 study). Within these results, one study induced pain within both muscular tissue and non-muscular 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 Fig. 4 (Farina et al., 2004, Farina et al., 2005, Farina et al., 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 4-3 and 5-3, Fig. 2C).

### 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 6). 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 post-pain 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).

### **Clinical pain**

### 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) 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 4-4 and 5-1, Fig. 2A).

### 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 et al., 2011a, 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

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<sup>2</sup> score of 74% (Massé-Alarie et al., 2016, Massé-Alarie et al., 2017, Massé-Alarie et al., 2012, Strutton et al., 2005, Tsao et al., 2008). The resultant OR is shown in Fig. 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 4-5 and 5-2, Fig. 2B).

### 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 4-6 and 5-3, Fig. 2C).

### DISCUSSION

This is a wide-ranging systematic review, which is the first to synthesise 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 appear 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 and 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 (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 sensitised by treatment with nerve growth factor two and four 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 he 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), post-pain (Svensson et al., 1998), and after recovery from pain (Le Pera et al., 2001, Schabrun and 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., 2017, Schabrun et al., 2015, Te et al., 2017, Tsao et al., 2011a, 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 (Te et al., 2017, Kosik 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, Schabrun and Hodges, 2012, Svensson et al., 2003, Le Pera et al., 2001, Martin et al., 2008). 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 and Tucker, 2011, Lund et al., 1991). However, this finding is speculative, and while a reduction in excitability was identified, the underlying reasons for this reduction remain unknown. When pain was induced in non-contractile 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 non-contractile tissue. This argument is supported by studies within the clinical pain cohort (Schabrun et al., 2015, Tsao et al., 2011a, Tsao et al., 2008).

The largest disparity in results was found for the effects of experimental and clinical pain on motor unit behaviour. While 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 eight 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) 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 submaximal 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 non-specific 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 indicate 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). While 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.

### 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 and 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 and Black, 1998). Most included studies were cross-sectional in design, however standardised measurement methods, such as H-reflex and motor unit decomposition from intramuscular and surface EMG signals have well established validity and reliability (Martinez-Valdes et al., 2016, Chen et al., 2010), 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, while hypertonic saline injection was the most common mechanism for pain induction, the methodologies surrounding the tasks and the duration of monitoring was not fully standardised 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, while 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 localisation 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 non-reporting 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.

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### **Figure Captions**

Fig. 1 Study selection process

**Fig. 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 post-pain 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)

**Fig. 3** – MEP amplitude reported in the first dorsal interosseus in studies which induced pain in this muscle using hypertonic saline.

**Fig. 4** – Motor unit discharge rate in muscles of the lower limb following pain induction with hypertonic saline.

**Fig. 5** – Active Motor Threshold (AMP) in the muscles of the trunk in individuals with chronic LBP.

#### **Table Captions**

**Table 1**: Key words used to inform the search strategy.

**Table 2** Outcomes of interest for studies included in the systematic review, arranged by the type of measurement. (MEP – Motor Evoked Potential).

**Table 3** – Risk of Bias scores and key outcomes for each included studyReviewer 1 (R1), Reviewer 2 (R2), Motor evoked potential (MEP), Motor unit firing rate (MU)

**Table 4-1** 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.

hyperS (Hypertonic saline)

**Table 4-2** 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.

hyperS (Hypertonic saline), NGF (Nerve Growth Factor)

**Table 4-3** Characteristics and summary of the results of the included studies examining changes

 in motor unit behaviour following experimentally induced pain.

**Table 4-4** Characteristics and summary of the results of the included studies examining changes in the H Reflex in clinical pain conditions.

CAI (Chronic Ankle Instability), LBP (Low Back Pain), PFD (Patella-Femoral Dysfunction), TEND (Tendinopathy)

**Table 4-5** Characteristics and summary of the results of the included studies examining changes

 in corticospinal excitability in clinical pain conditions.

cLBP (Chronic Low Back Pain), LBP (Low Back Pain), LE (lateral Epicondylitis), PFP (Patellofemoral Pain), Ptend (Patella Tendinopathy), RCT (Rotator Cuff Tendinopathy)

**Table 4-6** Characteristics and summary of the results of the included studies examining changes

 in motor unit behaviour in clinical pain conditions.

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 5-1.** Summary of the compiled results for outcomes related to the H reflex in both experimental and clinical pain conditions. Grey shading indicates that the variable was not measured in that condition.

H/M (H-reflex/M-wave Ratio), HT (Threshold of H reflex), MA (Amplitude of M-wave)

**Table 5-2** - Summary of compiled results for changes in corticospinal excitability in both experimental and clinical pain conditions. Grey shading indicates that the variable was not measured in that condition.

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 5-3** - Summary of compiled results for changes in motor unit behaviour in bothexperimental and clinical pain conditions. Grey shading indicates that the variable was notmeasured in that condition.

CV (Conduction Velocity)

**Table 6** – 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.

RMT (Resting Motor Threshold); NGF (Nerve Growth Factor)

# SF. 1– Prisma Checklist

## SF. 2 – Search String

**SF. 3** – Modified Downs and Black (1998) checklist for assessment of methodological quality of observational trials

Pain Acute Pain, Chronic Pain Acute Chronic	Magnetic Stimulation Electrical stimulation Cranial	Motor neuron* Alpha Motoneuron* Motor unit*	EMG Electromyograph* MEP
Acute Pain, Chronic Pain Acute Chronic	Electrical stimulation Cranial	Alpha Motoneuron* Motor unit*	Electromyograph* MEP
Chronic Pain Acute Chronic	Cranial	Motoneuron* Motor unit*	MEP
Acute Chronic	Cranial	Motor unit*	
Chronic		infotor unit	Motor evoked potential
	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	Motor activity	Recruitment threshold
	Eccentric	hiotor activity	Conduction velocity
	Sustained	Movement strategy	IPSP
	Movement	his venient strategy	Inhibitory postsynantic potentials
	Wovement		Oscillation
			Coherence
			Force variability
			Force steadiness
			Coefficient of variation
			Synchronization
			Spatial resolution
			Motor unit recruitment
			Neurophysiological recruitment
			TMS recruitment curves
			TMS intensity
			MED amplitude
			MEP amplitude

## **Table 1:** Key words used to inform the search strategy.

**Table 2**: Outcomes of interest for studies included in the systematic review, arranged by the type of measurement. (MEP – Motor Evoked Potential).

Measurement Type	Outcome of Interest	Abbreviation
	H-Reflex Amplitude	HA
	Amplitude of the M-wave	MA
H Reflex	H-reflex /M-Wave Ratio	H/M
	Latency of the H-Reflex	HL
	Threshold of the H-Reflex	HT
	Amplitude of MEP	MEPA
	MEP Latency	MEPL
Corticospinal Excitability /	Resting Motor Threshold	RMT
Motor Evoked Potentials	Active Motor Threshold	AMT
(MEPs)	Duration of the Silent Period	SP
(1122 5)	Spatial Distribution of the MEP	MEP Area
	Spatial Volume of the MEP Map	Map Volume
	Number of Discrete Cortical Peaks	Cortical Peaks
	Discharge Rate	Discharge Rate
	Coherence of Cumulative Spike Trains	Coh
Motor Unit Behaviour	Conduction Velocity	CV
	Action Potential Amplitude	Amplitude

Table 3 – Risk of Bias scores and key outcomes for each included study Reviewer 1 (R1), Reviewer 2 (R2), Motor evoked potential (MEP), Motor unit decomposition (MU)

	Experimental	Pain		Clinical Pain				
	Author and Year	Outcom	Score	Author and Year	Outcom	Score		
		е	R1 R2		е	R1 R2		
	Schabrun et al., 2013	H-Reflex	11 10	Pazzinatto et al., 2019	H-Reflex	12 1		
						2		
	Park and Hopkins, 2013	H-Reflex	13 13	Thompson et al., 2019	H-Reflex	13 1		
	Svensson et al. 2003	H-Reflex	11 11	Kosik et al. 2017	H-Reflex	3 9 11		
			11 10			12 12		
					n-Reliex	12 12		
	Matre et al., 1998	H-Reflex	9 9	Wang et al., 2011	H-Reflex	13 11		
0	Summers et al., 2020	MEP	13 1 3	Ginanneschi et al., 2007	H-Reflex	8 11		
	Alhassani et al., 2019	MEP	13 1	Mazzocchio et al., 2001	H-Reflex	12 11		
			11 1					
	Seminowicz et al., 2019	MEP	4	Salerno et al., 2000	H-Reflex	9 11		
	Summers et al., 2019	MEP	14 1 3	Leroux et al., 1995	H-Reflex	10 12		
	Larsen et al., 2018	MEP	15 1 4	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 1 5		
	Schabrun et al., 2013	MEP	11 10	Elgueta-Cancino et al., 2019	MEP	12 1 4		
	Schabrun and Hodges, 2012	MEP	13 10	Te et al., 2017	MEP	11 11		
	Tsao 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., 2007	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 1 4	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 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

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T: inc	able 4-1 Characteristics duced pain. R- or L- pr	and summary of the results of the results of the results of a muscle d	of the inclue enotes later	ded studies examini ality. hyperS (Hype	ng changes in the H Reflex rtonic saline), NGF (Nerve	x following experimentall	у
Pain Stage	Outcome Parameter	Author and Year	Sample Size (n)	Pain Mechanism	Pain Induction Location	Outcome Muscle	Resu
		Park and Hopkins, 2013	13	HyperS 5%	Infrapatellar Fat Pad	Vastus Medialis	Decrea
During	H/M Reflex Ratio	Matre et al., 1998	13	HyperS 5%	Soleus Tibialis Anterior	Soleus Tibialis Anterior	No Cha No Cha
1 din	H-Reflex Amplitude	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Cha
	H-Reflex Latency	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Cha
	H-Reflex Amplitude	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	Decrea
Dect	H-Reflex Latency	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Cha
Post Pain	M-Wave Amplitude	Schabrun et al., 2013	12	HyperS 5%	R-First Dorsal Interosseus	R-First Dorsal Interosseus	No Cha
		Svensson et al., 2003	10	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Cha

hyperS (Hypertonic saline)

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**Table 4-2** 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
	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 Increased	Sustained Pain (Day 1, 2) Sustained Pain (Day 4)
-	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 Increased	Sustained Pain (Day 1, 2) Sustained Pain (Day 4)
	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 2, 4, 6)
During Pain		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)
i uni		Schabrun et al., 2016	12	NGF 5 μg (0.2 mL)	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change Increased	Sustained Pain (Day 1, 2) Sustained Pain (Day 4)
	MEP area (mV2)	Del Santo et	8	Ascorbic Acid 40mg/0.2 ml	Abductor Digiti Minimi	Abductor Digiti Minimi	Increased	Abductor Digiti Minimi Contraction
		ui., 2007		Ascorbic Acid	Biceps Brachii	Biceps Brachii	Increased	Biceps Brachii Contraction

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			90mg/0.5 ml				
	Summers et al., 2020	42	HyperS 5.8%	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	Decreased	
	Alhassani et	20	HyperS 5.8%	R-First Dorsal	R-First Dorsal Interosseus	Decreased	
	al., 2019	20		Interosseus	L-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)
MEP	Summers et al., 2019	28	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	Decreased	Sustained Pain (Day 2, 4)
Amplitude		12		Extensor Carpi Radialis	Extensor Carpi Radialis	No Change	
	Larsen et al.,		HyperS 5.8%		First Dorsal Interosseus	No Change	
	2018	15		First Dorsal	First Dorsal Interosseus	Decreased	
				Interosseus	Extensor Carpi Radialis	No Change	
	Schabrun et	12	NGF 5 µg	R-Extensor Carpi	R-Extensor Carpi	No Change	Sustained Pain (Day 1, 2,
	al., 2016		(0.2 mL)	Radialis Brevis	Radialis Brevis		4)

Burns et al.,	22	Have over 50/	<b>R-First Dorsal</b>	<b>R-First Dorsal</b>	Deerseed	
2016	22	Hypers 5%	Interosseus	Interosseus	Decreased	
				R-Vastus Lateralis	Increased	
Rice et al.,	10	HyperS 5.8%	R-Infrapatellar	R-Vastus Medialis	mereaseu	
2015	10		Fat Pad	<b>R-Biceps Femoris</b>	No Change	
				<b>R</b> -Tibialis Anterior	No Change	
Schabrun et	12	Humars 50/	R-First Dorsal	R-First Dorsal	No Change	
al., 2013	12	nypers 5%	Interosseus	Interosseus	No Change	
	6			Biceps Brachii	No Changa	
	0			Trapezius	No Change	
	7			Biceps Brachii	Decreased	Biceps Brachii
Martin et al.,	1	HyperS 5%	Bicens Brachii	Trapezius	Decreased	contraction
2007			Diceps Diacini	Biceps Brachii		Biceps Brachii constant
	6			Trapezius	No Change	contraction
	0			Biceps Brachii		Trapezius constant
				Trapezius	Decreased	contraction
			R-Abductor Digiti	R-Abductor Digiti	Decreased	
Le Pera et al.,	10	HyperS 5%	Minimi	Minimi	Decleased	
2001	10	11,1010 570	R-First Dorsal	R-Abductor Digiti	Decreased	
			Interosseus	Minimi (NP)	DUICASEU	

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					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	
			12	HyperS 5%	R-Abductor Digiti Minimi	R-Abductor Digiti Minimi	No Change	
	MEP Latency	Le Pera et al., 2001	10		R-Abductor Digiti Minimi	R-Abductor Digiti Minimi		
	Latency		12	HyperS 5%	L-Abductor Digiti Minimi	R-Abductor Digiti Minimi (NP)	No Change	
			11		R-Flexor Carpi Radialis	R-Flexor Carpi Radialis		
	Resting Motor	Seminowicz et al., 2019	20	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	
	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)
- 1111	Cortical	Schabrun et	12	NGF 5 µg	R-Extensor Carpi	R-Extensor Carpi	No Change	Sustained Pain (Day 14)

Peaks	al., 2016		(0.2 mL)	Radialis Brevis	Radialis Brevis		
	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)
Map Volume	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 (mV2)	Del Santo et al., 2007	8	Ascorbic Acid 40mg/0.2 ml Ascorbic	Abductor Digiti Minimi	Abductor Digiti Minimi	No Change	Abductor Digiti Minimi Contraction Bicens Brachii
			Acid 90mg/0.5 ml	Biceps Brachii	Biceps Brachii		Contraction
	Summers et al., 2020	42	HyperS 5.8%	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	Decreased	
MEP	Alhassani et	20	HyperS 5.8%	R-First Dorsal	R-First Dorsal Interosseus	Decreased	
Amplitude	al., 2019	-		Interosseus	L-First Dorsal	No Change	
	Seminowicz et al., 2019	20	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	Sustained Pain (Day 14)

Summers e al., 2019	et	28	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	Sustained Pain (Day 14)
				Extensor Carpi	Extensor Carpi Radialis	No Change	
Larsen et a	1.,	13	HyperS 5.8%	Radialis	First Dorsal Interosseus	No Change	
2018			51	First Dorsal	First Dorsal Interosseus	No Change	
				Interosseus	Extensor Carpi Radialis	No Change	
Schabrun	et	12	NGF 5 μg (0.2 mL)	R-Extensor Carpi	R-Extensor Carpi	No Change	Sustained Pain (Day 14)
al., 2016		12	HyperS 5%	Radialis Brevis	Radialis Brevis	Increased	Following sustained pain from NGF
Rice et al. 2015	Rice et al., 2015		HyperS 5.8%	R-Infrapatellar Fat Pad	R-Vastus Lateralis R-Vastus Medialis R-Biceps Femoris R-Tibialis Anterior	No Change	
Schabrun e al., 2013	et	12	HyperS 5%	R-First Dorsal Interosseus	First Dorsal Interosseus	Decreased	
Schabrun an	nd	11	HyperS 5%	R-First Dorsal	R-First Dorsal	Decreased	

	Hodges, 2012			Interosseus	Interosseus		
					R-Abductor Digiti		
					Minimi (NP)		
					Transversus	Deerseed	
					Abdominus -C	Decreased	
					Transversus	No Change	
					Abdominus-I	No Change	
					External Oblique-C	To any set of	
					External Oblique-I	Increased	
					Internal Oblique-C	No Change	
					Internal Oblique-I	No Change	Transversus Abdominus
	Tsao et al.,	0	HyperS 5%	151	Rectus	Decreased	rest
	2011		11ype15 570	ISL	Abdominus-C	Decleased	
					Rectus	No Change	
					Abdominus-I	No Change	
					Lumbar Erector		
					Spinae-C	Increased	
					Lumbar Erector	mereuseu	
					Spinae-I		
					Transversus	No Change	Transversus Abdominus
					Abdominus -C	rto chunge	contraction

				Transversus Abdominus-I		
				External Oblique-C	Increased	
				External Oblique-I		
				Internal Oblique-C		
				Internal Oblique-I		
				Rectus		
				Abdominus-C		
				Rectus	No Change	
				Abdominus-I		
				Lumbar Erector		
				Spinae-C		
				Lumbar Erector		
				Spinae-I		
	6			Biceps Brachii	No Change	
	0			Trapezius	No Change	
Martin et al.,	7	HyperS 5%	Bicens Brachii	Biceps Brachii	Decreased	Biceps Brachii
2007	1	Trypers 570	Diceps Drachin	Trapezius	Decreased	contraction
	6	1		Biceps Brachii	No Change	Biceps Brachii consta
	0			Trapezius	The Change	contraction

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					Biceps Brachii	No Change	Trapezius constant
					Trapezius	Decreased	contraction
		10		R-First Dorsal	R-First Dorsal Interosseus	Decreased	
	Svensson et al., 2003		HyperS 5.8%	Interosseus	R-Flexor Carpi Ulnaris (NP)	No Change	
		2		R-First Dorsal Interosseus	R-First Dorsal Interosseus	Decreased	Descending tract stimulation
				R-Abductor Digiti Minimi	R-Abductor Digiti Minimi	Decreased	
	Le Pera et al., 2001	10		R-First Dorsal Interosseus	R-Abductor Digiti Minimi (NP)	No Change	
		.,	HyperS 5%	L- Abductor Digiti Minimi	R- Abductor Digiti Minimi (NP)	No Change	
		12		R- Abductor Digiti Minimi	R- Abductor Digiti Minimi	No Change	
		11		R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	Decreased	
MEP Latency	Tsao 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		
				Rectus		
				Abdominus-C		
				Rectus		
				Abdominus-I		
				Lumbar Erector		
				Spinae-C		
				Lumbar Erector		
				Spinae-I		
				Transversus		
				Abdominus -C		
				Transversus		Transversus Abdominus
				Abdominus-I	No Change	
$\mathbf{C}$				External Oblique-C		contraction
				External Oblique-I		
				Internal Oblique-C		
	L	1				

						Internal Oblique-I		
						Rectus		
$\mathbf{O}$						Abdominus-C		
						Rectus		
						Abdominus-I		
						Lumbar Erector		
						Spinae-C		
						Lumbar Erector		
						Spinae-I		
					R-First Dorsal	R-First Dorsal		
$\bigcirc$		Svensson et	10	HyperS 5.8%	Interosseus	Interosseus	No Change	
		al., 2003	10		R-First Dorsal	R-Flexor Carpi	rto enunge	
					Interosseus	Ulnaris (NP)		
			12		R-Abductor Digiti	R-Abductor Digiti		
					Minimi	Minimi		
			10		R-Abductor Digiti	R-Abductor Digiti		
		Le Pera et al.,		HyperS 5%	Minimi	Minimi	No Change	
		2001	12		L-Abductor Digiti	R-Abductor Digiti	_	
$\mathbf{C}$					Minimi	Minimi (NP)		
			11		R-Flexor Carpi	R-Flexor Carpi		
					Radialis	Radialis		

	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
Resting	Schabrun and Hodges, 2012	11	HyperS 5%	R-First Dorsal Interosseus	R-First Dorsal Interosseus	No Change	
Threshold	Svensson et al., 2003	10	HyperS 5.8%	R-First Dorsal Interosseus	R-First Dorsal Interosseus R-Flexor Carpi Ulnaris (NP)	No Change	

hyperS (Hypertonic saline), NGF (Nerve Growth Factor)

**Table 4-3** Characteristics and summary of the results of the included studies examining changes in motor unit behaviour following experimentally induced pain.

Pain	Outcome	Author and Voor	Sample	Pain	Pain Induction	Outcomo Muselo	Docult	Notoc
Stage	Parameter	Author and rear	Size (n)	Mechanism	Location	Outcome Muscle	Result	notes
	Amplitude	Martinez-Valdes et al., 2020	15	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	No Change	
	, inpittude	Farina et al., 2008	16	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	No Change	
	Coherence	Dideriksen et al., 2016	12	HyperS 5.8%	Trapezius	Trapezius	No Change	delta alpha beta band
During	During	Yavuz et al., 2015	23	HyperS 5 8%	Abductor Digiti	Abductor Digiti Minimi	Decreased	alpha and beta
Pain			23	Typelo 5.070	Minimi	Abductor Digiti Minimi	Decreased	alpha band
		Farina et al., 2008	16	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	No Change	
	Conduction	Farina et al.,			Tibialis Anterior	Tibialis Anterior Right		
Velocity	Velocity	2005	11	HyperS 5.8%	Right	Tibialis Anterior Left (NP)	No Change	
		Farina et al.,	12	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior right	No Change	
		2004				Survey and the second sec		

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Martinez-Valdes	15	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	Decreased	20% MVC
et al., 2020		,pere erere			Increased	70% MVC
Dideriksen et al.,	17	Hupers 5.8%	Trapozius	Trapezius	Decreased	Cranial region
2016	12	1199615 5.8%	Παρεείας	Trapezius	No Change	Caudal region
				Vastus Medialis		
Poortvliet et al.			Infranatellar Fat	Vastus Lateralis		
2015	13	HyperS 5%	Pad	Biceps Femoris	Decreased	
2013				Semitendinosus		
				Tensor Fasciae Latae		
Tucker et al.,	0	HyperS 5%	Infrapatellar Fat	Vastus Medialis	Decreased	
2012	9	Typers 576	Pad	Vastus Lateralis	Decreased	
Tucker and	٩	HyperS 5%	Infrapatellar Fat	Vastus Medialis	Decreased	
Hodges, 2010	5	Typers 576	Pad	Vastus Lateralis	Decreased	
	8		Infrapatellar Fat	Vastus Medialis	Decreased	
Tucker et al.,	0	HyperS 5%	Pad	Vastus Lateralis	Decreased	
2009	7	,	Flexor Pollicus	Flexor Pollicus Longus	Decreased	
	-		Longus		200.00000	
Hodges et al.,	10	HyperS 5%	Gastrocnemius	Gastrocnemius	Decreased	
2008	10	1199013 370	lateral	Soleus		
Farina et al.,	16	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	Decreased	
	Martinez-Valdes et al., 2020 Dideriksen et al., 2016 Poortvliet et al., 2015 Tucker et al., 2012 Tucker and Hodges, 2010 Tucker et al., 2009 Hodges et al., 2008 Farina et al.,	Martinez-Valdes et al., 202015Dideriksen et al., 201612Poortvliet et al., 201513Tucker et al., 20129Tucker and Hodges, 20109Tucker et al., 20099Tucker et al., 20097Hodges et al., 200810Farina et al., 1616	Martinez-Valdes et al., 202015HyperS 5.8%Dideriksen et al., 201612HyperS 5.8%Poortvliet et al., 201513HyperS 5%Tucker et al., 20129HyperS 5%Tucker and Hodges, 20109HyperS 5%Tucker et al., 20129HyperS 5%Tucker et al., 20129HyperS 5%Tucker and Hodges, 20109HyperS 5%Tucker et al., 200978Hodges et al., 200810HyperS 5%Farina et al.,16HyperS 5.8%	Martinez-Valdes et al., 202015HyperS 5.8%Tibialis AnteriorDideriksen et al., 201612HyperS 5.8%TrapeziusPoortvliet et al., 201513HyperS 5%Infrapatellar Fat PadTucker et al., 20129HyperS 5%Infrapatellar Fat PadTucker et al., 20129HyperS 5%Infrapatellar Fat PadTucker et al., 20129HyperS 5%Infrapatellar Fat PadTucker et al., 20099HyperS 5%Infrapatellar Fat PadTucker et al., 20097Infrapatellar Fat PadHodges et al., 200810HyperS 5%Infrapatellar Fat Infrapatellar Fat Infrapatellar Fat Infrapatellar Fat PadHodges et al., 200810HyperS 5%Gastrocnemius IateralFarina et al.,16HyperS 5.8%Tibialis Anterior	Martinez-Valdes et al., 202015HyperS 5.8%Tibialis AnteriorTibialis AnteriorDideriksen et al., 201612HyperS 5.8%TrapeziusTrapeziusPoortvliet et al., 201513HyperS 5%Infrapatellar Fat PadVastus MedialisPoortvliet et al., 201513HyperS 5%Infrapatellar Fat PadVastus MedialisTucker et al., 20129HyperS 5%Infrapatellar Fat PadVastus MedialisTucker et al., 20129HyperS 5%Infrapatellar Fat PadVastus MedialisTucker et al., 20129HyperS 5%Infrapatellar Fat PadVastus MedialisTucker and Hodges, 20109HyperS 5%Infrapatellar Fat PadVastus MedialisTucker et al., 20099116Infrapatellar Fat HyperS 5%Vastus LateralisTucker et al., 20097Infrapatellar Fat PadVastus MedialisHodges et al., 200810HyperS 5%Flexor Pollicus LongusFlexor Pollicus SoleusHodges et al., 200810HyperS 5%Gastrocnemius IateralSoleus	Martinez-Valdes et al., 202015HyperS 5.8%Tibialis AnteriorTibialis AnteriorDecreasedDideriksen et al., 201612HyperS 5.8%TrapeziusTrapeziusDecreased201612HyperS 5.8%TrapeziusTrapeziusNo ChangePoortvliet et al., 201513HyperS 5.8%Infrapatellar Fat PadVastus MedialisMartinesPoortvliet et al., 20159HyperS 5%Infrapatellar Fat PadVastus LateralisDecreasedTucker et al., 20129HyperS 5%Infrapatellar Fat PadVastus MedialisDecreasedTucker and Hodges, 20109HyperS 5%Infrapatellar Fat PadVastus MedialisDecreasedTucker et al., 2009910Infrapatellar Fat PadVastus MedialisDecreasedTucker et al., 2009710Infrapatellar Fat PadVastus MedialisDecreasedFlexor Pollicus LongusFlexor Pollicus LongusPadVastus LateralisDecreasedHodges et al., 200810HyperS 5%Gastrocnemius IateralGastrocnemius SoleusDecreasedHodges et al., 200810HyperS 5.8%Tibialis AnteriorTibialis AnteriorDecreasedFarina et al.,16HyperS 5.8%Tibialis AnteriorTibialis AnteriorDecreased

2008						
Farina et al.,			Tibialis Anterior	Tibialis Anterior Right	Decreased	
2005	11	HyperS 5.8%	Right	Tibialis Anterior Left (NP)	No Change	
Farina et al., 2004	12	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior right	Decreased	

hyperS (Hypertonic saline)

Table 4-4 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 (n)		Pain	Outcome Muscle	Result
outcome r urumeter		Patients	Control	Condition	Outcome MuscleISoleusNoFibularis LongusNoVastus MedialisDeSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNoSoleusNo	nesur
	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.,	15	15	DED	Vastus Medialis	Decreased
	2016	15	15	FIF		Decreased
	Wang et al., 2011	14	14	TEND	Soleus	No Change
	Ginanneschi et al., 2007	14	14	LBP	Soleus	No Change
H/M Ratio (%)	Mazzocchio et al., 2001	26	40	LBP	Soleus	No Change
		13	13		Soleus	
	Salerno et al., 2000	9	13	Fibromyalgia	Flexor Carpi	No Change
		)	10		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	Pazzinatto et al., 2019	30	30	PFP	Vastus Medialis	Decreased
(mA)	Ginanneschi et al., 2007	14	14	LBP	Soleus	Increased
	Leroux et al., 1995	6	6	PFD	Rectus Femoris	No Change

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		6	6		Vastus Lateralis	
		6	6		Vastus Medialis	
	Ginanneschi et al., 2007	14	14	LBP	Soleus	No Change
	Mazzocchio et al., 2001	26	40	LBP	Soleus	No Change
		13	13		Soleus	
	Salerno et al., 2000	٩	13	Fibromyalgia	Flexor Carpi	No Change
		9	15		Radialis	
H-Reflex Latency (ms)					Rectus Femoris	
	Leroux et al., 1995	6	6	PFD	Vastus Lateralis	No Change
					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	Ginanneschi et al., 2007	14	14	LBP	Soleus	Increased
(mV)	Mazzocchio et al., 2001	26	40	LBP	Soleus	Increased
			•	-		

CAI (Chronic Ankle Instability), LBP (Low Back Pain), PFD (Patella-Femoral Dysfunction), TEND (Tendinopathy)

Table 4-5 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 (n)	Pain	Outcome Muscle	Result
Outcome Parameter		Patients	Control	Fize (n)Pain ConditionOutcome Muscle13CLBP (Right)MultifidusE13CLBP (Left)MultifidusE16CAIFibularis LongusF8PtendRectus FemorisF13LBPMultifidus (bilateral)F14LEExtensor Carpi Radialis BrevisF39RCTInfraspinatusI9LBPTransversus AbdominusI	Nesuit	
		19	13	cLBP (Right)	Multifidus	Decreased
	Massé-Alarie et al., 2017	16	13	cl BP (Left)	Multifidus	No
		10	10		mannado	Change
	Kosik et al. 2017.	18	16	CAI	Fibularis Longus	No
				<b>e</b> ,		Change
	Rio et al., 2016	11	8	Ptend	Rectus Femoris	No
			0	i tena		Change
Active Motor Threshold	Massé-Alarie et al., 2016	11	13	LBP	Multifidus (bilateral)	No
(%)						Change
	Burns et al., 2016	14	14	LF	Extensor Carpi Radialis	No
					Brevis	Change
	Ngomo et al., 2015	39	39	RCT	Infraspinatus	Increased
-	Massé-Alarie et al 2012	9	9	I RP	Transversus Abdominus	No
		5	5	201	Internal Oblique	Change
	Tsao et al., 2008	11	11	LBP	Transversus Abdominus	Decreased
	Strutton et al., 2005	24	11	cLBP	Erector Spinae	Increased

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	Elgueta-Cancino et al. 2019	10	10	cNIP	Superficial Neck Flexors	Decreased
Elgueta-Cancino et al., 20191010CNPSuperficial Nei Deep NeckTe et al., 2017111111PFPVastus LatCortical peaks (n)Te et al., 20172723LBPErector SpiSchabrun et al., 20172723LBPErector SpiSchabrun et al., 20151111LEExtensor DigSchabrun et al., 20151111LEExtensor CarpBurns et al., 2017111111LBPRectus FeiMap volumeBurns et al., 20171111LBPParaspinal Nei	Deep Neck Flexors	Decreased				
					Rectus Femoris	
	Te et al., 2017	11	11	PFP	Vastus Lateralis	Decreased
					Vastus Medialis	
Cortical peaks (n)					Erector Spinae-L3	Decreased
	Schabrun et al., 2017	27	23	LBP	Frector Spinae-L6	No
						Change
					Extensor Digitorum	
	Schabrun et al., 2015	11	11	LE	Extensor Carpi Radialis	Decreased
					Brevis	
	Elgueta-Cancino et al., 2019	10	10	cNP	Superficial Neck Flexors	No
					Deep Neck Flexors	Change
					Rectus Femoris	
	Te et al., 2017	11	11	PFP	Vastus Lateralis	Decreased
Map volume					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
	, -		_		Erector Spinae-L5	Change

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					Extensor Digitorum	
	Schabrun et al., 2015	11	11	LE	Extensor Carpi Radialis	Increased
					Brevis	
	Tsao et al 2011	٩	11	IRP	Multifidus	Decreased
	1300 et al., 2011	5	11	LDI	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	No
Map Area		10	10	CIVI	Deep Neck Flexors	Change
	Kosik et al. 2017.	18	16	CAI	Fibularis Longus	Decreased
	Cardinal et al. 2019	17	41	Fibromvalgia	First Dorsal Interosseus	No
				r isroniyaigia		Change
	Massé-Alarie et al 2017	19	13	cLBP (Right)	Multifidus	No
		16	13	cLBP (Left)	Wattindus	Change
	Burns et al., 2017	11	11	LBP	Paraspinal Muscles	Decreased
MFP Amplitude	Massé-Alarie et al 2016	11	12	I BP	Multifidus (bilateral)	No
			15	EDI	Materials (Shateraly	Change
	Burns et al., 2016	14	14	IF	Extensor Carpi Radialis	No
	20110 Ct 011) 2010		1.		Brevis	Change
					Extensor Digitorum	
	Schabrun et al., 2015	11	11	LE	Extensor Carpi Radialis	Increased
					Brevis	

	Ngomo et al. 2015	39	20	DCT	Infraction	No
	Ngomo et al., 2015	39	39	RCI	iniraspinatus	Change
	Mhalla et al., 2010	46	21	Fibromyalgia	First Dorsal Interosseus	Decreased
	Salerno et al 2000	13	13	Fibromvalgia	First Dorsal Interosseus	No
	Salerno et al., 2000	15	15	i ibi offiyalgia	Tibialis Anterior	Change
MFP Area	Strutton et al. 2005	24	11	cl BP	Frector Spinae	No
		21		CEDI		Change
	Tsao et al., 2011	9	11	LBP	Multifidus	No
MEP Latency (ms)		5			Lumbar Erector Spinae	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	Fibromvalgia	First Dorsal Interosseus	No
		-	_	,	Tibialis Anterior	Change
	Burns et al 2016	14	14	LE	Extensor Carpi Radialis	No
					Brevis	Change
Resting Motor Threshold	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

	Docroscod
Cardinal et al., 2019 17 41 Fibromyalgia First Dorsal Interosseus De	Jecieaseu
19 13 cLBP (Right) Multifidus	No
Massé-Alarie et al., 2017	Change
16 13 cLBP (Left) Multifidus	No
	Change
Burns et al., 2017 11 11 LBP Paraspinal Muscles	No
tion (ms)	Change
Massé-Alarie et al., 2016 11 13 LBP Multifidus (bilateral)	No
	Change
Strutton et al. 2005 24 11 CLBP Erector Spinae	No
	Change
Salerno et al. 2000 13 13 Eibromyalgia First Dorsal Interosseus	Decreased
Tibialis Anterior	

cLBP (Chronic Low Back Pain), cNP (Chronic Neck Pain), LBP (Low Back Pain), LE (Lateral Epicondylitis), PFP (Patellofemoral Pain), Ptend (Patella Tendinopathy), RCT (Rotator Cuff Tendinopathy)

Outcome	Author and Year	Samp	le Size (n)	Pain Condition	Outcome Muscle	Result	Notes
Parameter		Patients Controls					
	Calder et al 2008	16	37	NSAP	Extensor Carpi Radialis Brevis	Decreased	
Amplitude		11	37	LE	Extensor Carpi Radialis Brevis	No Change	
	Falla et al., 2010	9	9	CNP	Sternocleidomastoid	Increased No Change No Change	15N (circular contract 30N(circular contract constant force direct
	Calder et al 2008	16	37	NSAP	Extensor Carpi Radialis Brevis	Decreased	
Discharge		11	37	LE	Extensor Carpi Radialis Brevis	Decreased	
rate	Falla et al., 2010	9	9	cNP	Sternocleidomastoid	No Change	mean
	Gallina et al., 2018	36	20	PFD	Vastus Lateralis	Increased Increased	Initial 5-35 s

				Vastus Medialis	No Change	Initial
					No Change	5-35 s
Kallenberg and Hermens, 2006	10	10	Cpain	Trapezius	Increased	Across Several Tasks
					Increased	0-15% MVC
Yang et al., 2016	12	12	MNP	Sternocleidomastoid	No Change	15-20 % MVC
					Increased	20-25% MVC

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 5-1.** Summary of the compiled results for outcomes related to the H reflex in both experimental and clinical pain conditions. Grey shading indicates that the variable was not measured in that condition.

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					
	Injected Muscle (Post pain)	1 (1)	-	-	1	Amplitude	3 (5)	1	1	1	-
H- Reflex Latency	Injected Muscle Injected Muscle	1 (1)	-	1	-	H- Reflex Latency	7 (10)	_	7	-	-
	(Post pain)										
H/M	Ratio	2 (3)	-	1	1	H/M	10 (11)	2	7	1	-
H- Reflex	Threshold	-	-	-	-	HT	2 (2)	2	-	-	-
M-Reflex	Amplitude	2 (2)	-	2	-	MA	-	-	-	-	-

	-		-	_	
(Post Pain)					
		-			

H/M (H-reflex/M-wave Ratio), HT (Threshold of H reflex), MA (Amplitude of M-wave)

CIG	<b>Table 5-2</b> - Summary of compiled results for changes in corticospinal excitability in both experimental and clinical pain conditions. Grey shading indicates that the variable was not measured in that condition.											
		Experim	ental 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
MEP	Painful Muscle	12 (18)	1	3	4	4						
Amplitu	Painful Muscle (PP)	12 (18)	-	5	5	2	ΜΕΡΔ	9 (12)	1	6	2	-
de	Control Muscle (DP)	4 (6)	-	2	-	2						
de	Control Muscle (PP)	6 (8)	-	4	1	1						
	Painful Muscle	1 (3)	-	1	-	-						
MEP	Painful Muscle (PP)	3 (14)	-	2	-	1	MEDI	1 (6)		4		
Latency	Control Muscle (DP)	1 (1)	-	1	-	-	WIEFL	4 (0) -	4 -	-	-	
	Control Muscle (PP)	2 (2)	-	2	-	-						
Resting	Painful Muscle	1 (1)	-	1	-	-						
Motor	Painful Muscle (PP)	3 (3)	-	3	-	-	РМТ	4 (6)	2	2	_	_
Threshol d	Control Muscle (PP)	1 (1)	-	1	-	-	KIVI I	+ (0)	2	Z	-	-
MEP	During Pain	1 (2)	1	-	-	-	MEP Area	1 (1)		1	_	_
Area	Post Pain	1 (2)	-	1	-	-	MILI AICA	± (±)		Ŧ		
Мар	During Pain	3 (3)	-	1	1	1	Мар	8 (14)	2	3	З	_
------------------------	---------------	-------	---	---	---	---	-------------	--------	---	---	---	---
Volume	Post Pain	3 (3)	-	3	-	-	Volume	0(11)	-	3	3	
Map Area		-	-	-	-	-	Map Area	2 (3)	-	1	1	-
Active Motor Threshold		1 (1)	-	-	-	1	AMT	9 (13)	2	5	1	1
Silent Period Duration		-	-	-	-	-	SP Duration	6 (8)	-	4	2	-
Co	ortical Peaks	1 (1)	_	_	_	1	Cortical	4 (9)	_	_	3	1
		(-/					Peaks	( )				

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)

Accepted

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	Painful Muscle	10 (19)	-	-	8	2	Discharge	5 (5)	1	1	1		
Rate	Control Muscle	1 (1)	-	1	-	-	Rate	5 (5)	1	1	1	2	
CV	Painful Muscle	3 (3)	-	3	-	-	CV						
	Control Muscle	1 (1)	-	1	-	-		-	-	-	-	-	
Co	herence	2 (2)	-	1	1	-	Coherence	-	-	-	-	-	
Amplitude		2 (2)	-	2	-	-	Amplitude	2 (2)	-	-	-	2	
	CV (Conduction Vo	elocity)											

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Condition	Outcome	Number of	Combined	Pain	Pain Induction location	Increase	No	Decrease	Mixed
Condition		Studies	Sample Size (n)	Mechanism and Outcome Muscle		mcrease	Change	Decrease	wiixeu
	MEP Amplitude	3	60	NGF 5 μg (0.2 mL)	Muscles of the Wrist	-	2	1	-
During Pain		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	-	-

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