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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.

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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 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.

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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.,

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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.

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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 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; 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.

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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.

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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 1st of March 2019 were searched initially, and the search was updated up to the 13th 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

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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^2 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

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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.

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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 ± 1.9 out of a maximum score of 18, which equates to 62.8%±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

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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., 2019); 18 recorded corticospinal excitability via the MEP (Burns et al., 2016a, Burns et al., 2017, Kosik et al., 2017, Massé-Alarie et al., 2016, Massé-Alarie et al., 2017, Massé-Alarie et al., 2012, Mhalla et al., 2010, Ngomo et al., 2015, Rio et al., 2016, Salerno et al., 2000, Schabrun et al., 2017, Schabrun et al., 2015, Strutton et al., 2005, Te et al., 2017, Tsao et al., 2011a, Tsao et al., 2008, Cardinal 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

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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 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

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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 MEP-amplitude 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).

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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

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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-

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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., 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

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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).

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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.,

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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

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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

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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

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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

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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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References

ALHASSANI, G., LISTON, M. B. & SCHABRUN, S. M. 2019. Interhemispheric Inhibition Is Reduced in Response to Acute Muscle Pain: A Cross-Sectional Study Using Transcranial Magnetic Stimulation. *Journal of Pain,* 20**,** 1091-1099.

BURNS, E., CHIPCHASE, L. S. & SCHABRUN, S. M. 2016a. Altered function of intracortical networks in chronic lateral epicondylalgia. *European Journal of Pain,* 20**,** 1166-75.

BURNS, E., CHIPCHASE, L. S. & SCHABRUN, S. M. 2016b. Primary sensory and motor cortex function in response to acute muscle pain: A systematic review and meta-analysis. *Eur J Pain,* 20**,** 1203-13.

BURNS, E., CHIPCHASE, L. S. & SCHABRUN, S. M. 2016c. Reduced short- and long-latency afferent inhibition following acute muscle pain: A potential role in the recovery of motor output. *Pain Medicine (United States),* 17**,** 1343-1352.

BURNS, E., CHIPCHASE, L. S. & SCHABRUN, S. M. 2017. Temporal and spatial characteristics of post-silent period electromyographic bursting in low back muscles: comparison between persons with and without low back pain. *International Journal of Neuroscience,* 127**,** 1074-1081.

CALDER, K. M., STASHUK, D. W. & MCLEAN, L. 2008. Motor unit potential morphology differences in individuals with non-specific arm pain and lateral epicondylitis. *Journal of NeuroEngineering and Rehabilitation,* 5.

CARDINAL, T. M., ANTUNES, L. C., BRIETZKE, A. P., PARIZOTTI, C. S., CARVALHO, F., DE SOUZA, A., DA SILVA TORRES, I. L., FREGNI, F. & CAUMO, W. 2019. Differential neuroplastic changes in fibromyalgia and depression indexed by up-regulation of motor cortex inhibition and disinhibition of the descending pain system: An exploratory study. *Frontiers in Human Neuroscience,* 13.

CHANG, W.-J., O'CONNELL, N. E., BECKENKAMP, P. R., ALHASSANI, G., LISTON, M. B. & SCHABRUN, S. M. 2018. Altered Primary Motor Cortex Structure, Organization, and Function in Chronic Pain: A Systematic Review and Meta-Analysis. *The Journal of Pain,* 19**,** 341-359.

This article is protected by copyright. All rights reserved

Accepted Article

CHEN, R. 2000. Studies of human motor physiology with transcranial magnetic stimulation. *Muscle & Nerve,* 23**,** S26-S32.

CHEN, Y. S., ZHOU, S., CARTWRIGHT, C., CROWLEY, Z., BAGLIN, R. & WANG, F. 2010. Test-retest reliability of the soleus H-reflex is affected by joint positions and muscle force levels. *J Electromyogr Kinesiol,* 20**,** 980-7.

DE OLIVEIRA SILVA, D., MAGALHÃES, F. H., FARIA, N. C., PAZZINATTO, M. F., FERRARI, D., PAPPAS, E. & DE AZEVEDO, F. M. 2016. Lower Amplitude of the Hoffmann Reflex in Women with Patellofemoral Pain: Thinking beyond Proximal, Local, and Distal Factors. *Archives of Physical Medicine and Rehabilitation,* 97**,** 1115-1120.

DEL SANTO, F., GELLI, F., SPIDALIERI, R. & ROSSI, A. 2007. Corticospinal drive during painful voluntary contractions at constant force output. *Brain Research,* 1128**,** 91-98.

DHAND, U., DAS, S. & CHOPRA, J. 1991. Patterns of H-reflex abnormality in patients with low back pain. *Electromyography and clinical neurophysiology,* 31**,** 209-213.

DIDERIKSEN, J. L., HOLOBAR, A. & FALLA, D. 2016. Preferential distribution of nociceptive input to motoneurons with muscle units in the cranial portion of the upper trapezius muscle. *Journal of Neurophysiology,* 116**,** 611-618.

DOWNS, S. H. & BLACK, N. 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health,* 52**,** 377-84.

EGGER, M., SMITH, G. D. & PHILLIPS, A. N. 1997. Meta-analysis: principles and procedures. *Bmj,* 315**,** 1533-7.

ELGUETA-CANCINO, E., MARINOVIC, W., JULL, G. & HODGES, P. W. 2019. Motor cortex representation of deep and superficial neck flexor muscles in individuals with and without neck pain. *Human Brain Mapping,* 40**,** 2759-2770.

FALLA, D., LINDSTRØM, R., RECHTER, L. & FARINA, D. 2010. Effect of pain on the modulation in discharge rate of sternocleidomastoid motor units with force direction. *Clinical Neurophysiology,* 121**,** 744-753.

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Accepted Article

FARINA, D., ARENDT-NIELSEN, L. & GRAVEN-NIELSEN, T. 2005. Experimental muscle pain reduces initial motor unit discharge rates during sustained submaximal contractions. *J Appl Physiol (1985),* 98**,** 999-1005.

FARINA, D., ARENDT-NIELSEN, L., MERLETTI, R. & GRAVEN-NIELSEN, T. 2004. Effect of experimental muscle pain on motor unit firing rate and conduction velocity. *Journal of Neurophysiology,* 91**,** 1250-9.

FARINA, D., ARENDT-NIELSEN, L., ROATTA, S. & GRAVEN-NIELSEN, T. 2008. The pain-induced decrease in low-threshold motor unit discharge rate is not associated with the amount of increase in spike-triggered average torque. *Clinical Neurophysiology,* 119**,** 43-51.

GALLINA, A., HUNT, M. A., HODGES, P. & GARLAND, S. J. 2018. Vastus lateralis motor unit firing rate is higher in females with patellofemoral pain. *Archives of physical medicine and rehabilitation*.

GINANNESCHI, F., DOMINICI, F., MILANI, P., BIASELLA, A., ROSSI, A. & MAZZOCCHIO, R. 2007. Changes in the recruitment curve of the soleus H-reflex associated with chronic low back pain. *Clinical neurophysiology,* 118**,** 111-118.

HECKMAN, C. J. & ENOKA, R. M. 2012. Motor unit. *Compr Physiol,* 2**,** 2629-82.

HIGGINS, J. P. T., THOMPSON, S. G., DEEKS, J. J. & ALTMAN, D. G. 2003. Measuring inconsistency in meta-analyses. *BMJ,* 327**,** 557-560.

HODGES, P. W. 2014. To redistribute muscle activity in pain, or not: that is the question. *Pain,* 155**,** 849-50.

HODGES, P. W., ERVILHA, U. F. & GRAVEN-NIELSEN, T. 2008. Changes in motor unit firing rate in synergist muscles cannot explain the maintenance of force during constant force painful contractions. *J Pain,* 9**,** 1169-74.

HODGES, P. W. & TUCKER, K. 2011. Moving differently in pain: a new theory to explain the adaptation to pain. *Pain,* 152**,** S90-8.

HOEHLER, F. & BUERGER, A. 1981. Facilitation of the H-reflex in low back pain. *Electromyography and clinical neurophysiology,* 21**,** 207.

This article is protected by copyright. All rights reserved

Accepted Article

HUMPHREYS, C., TRIANO, J. & BRANDL, M. 1989. Sensitivity study of H-reflex alterations in idiopathic low back pain patients vs. a healthy population. *Journal of manipulative and physiological therapeutics,* 12**,** 71-78.

KALLENBERG, L. A. & HERMENS, H. J. 2006. Motor unit action potential rate and motor unit action potential shape properties in subjects with work-related chronic pain. *European journal of applied physiology,* 96**,** 203-208.

KANDEL, E. R., SCHWARTZ, J. H., JESSELL, T. M., BIOCHEMISTRY, D. O., JESSELL, M. B. T., SIEGELBAUM, S. & HUDSPETH, A. 2000. *Principles of neural science*, McGraw-hill New York.

KNIKOU, M. 2008. The H-reflex as a probe: Pathways and pitfalls. *Journal of Neuroscience Methods,* 171**,** 1-12.

KOSIK, K. B., TERADA, M., DRINKARD, C. P., MCCANN, R. S. & GRIBBLE, P. A. 2017. Potential Corticomotor Plasticity in Those with and without Chronic Ankle Instability. *Med Sci Sports Exerc,* 49**,** 141-149.

LANDIS, J. R. & KOCH, G. G. 1977. The measurement of observer agreement for categorical data. *Biometrics,* 33**,** 159-74.

LARSEN, D. B., GRAVEN-NIELSEN, T., HIRATA, R. P. & BOUDREAU, S. A. 2018. Differential Corticomotor Excitability Responses to Hypertonic Saline-Induced Muscle Pain in Forearm and Hand Muscles. *Neural Plasticity,* 2018 (no pagination).

LE PERA, D., GRAVEN-NIELSEN, T., VALERIANI, M., OLIVIERO, A., DI LAZZARO, V., TONALI, P. A. & ARENDT-NIELSEN, L. 2001. Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clinical Neurophysiology,* 112**,** 1633-1641.

LEROUX, A., BÉLANGER, M. & BOUCHER, J. P. 1995. Pain effect on monosynaptic and polysynaptic reflex inhibition. *Archives of Physical Medicine and Rehabilitation,* 76**,** 576-582.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GØTZSCHE, P. C., IOANNIDIS, J. P. A., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLOS Medicine,* 6**,** e1000100.

This article is protected by copyright. All rights reserved

Accepted Article

LUND, J. P., DONGA, R., WIDMER, C. G. & STOHLER, C. S. 1991. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol,* 69**,** 683-94.

MARTIN, P. G., WEERAKKODY, N., GANDEVIA, S. C. & TAYLOR, J. L. 2008. Group III and IV muscle afferents differentially affect the motor cortex and motoneurones in humans. *J Physiol,* 586**,** 1277-89.

MARTINEZ-VALDES, E., LAINE, C. M., FALLA, D., MAYER, F. & FARINA, D. 2016. High-density surface electromyography provides reliable estimates of motor unit behavior. *Clin Neurophysiol,* 127**,** 2534-41.

MARTINEZ-VALDES, E., NEGRO, F., FARINA, D. & FALLA, D. 2020. Divergent response of low- versus high-threshold motor units to experimental muscle pain. *Journal of Physiology,* 598**,** 2093-2108.

MASSÉ-ALARIE, H., BEAULIEU, L.-D., PREUSS, R. & SCHNEIDER, C. 2017. The side of chronic low back pain matters: evidence from the primary motor cortex excitability and the postural adjustments of multifidi muscles. *Experimental brain research,* 235**,** 647-659.

MASSÉ-ALARIE, H., BEAULIEU, L. D., PREUSS, R. & SCHNEIDER, C. 2016. Corticomotor control of lumbar multifidus muscles is impaired in chronic low back pain: concurrent evidence from ultrasound imaging and double-pulse transcranial magnetic stimulation. *Experimental Brain Research,* 234**,** 1033-1045.

MASSÉ-ALARIE, H., FLAMAND, V. H., MOFFET, H. & SCHNEIDER, C. 2012. Corticomotor control of deep abdominal muscles in chronic low back pain and anticipatory postural adjustments. *Experimental Brain Research,* 218**,** 99-109.

MATRE, D. A., SINKJAER, T., SVENSSON, P. & ARENDT-NIELSEN, L. 1998. Experimental muscle pain increases the human stretch reflex. *Pain,* 75**,** 331-9.

MAZZOCCHIO, R., SCARFÒ, G. B., MARIOTTINI, A., MUZII, V. F. & PALMA, L. 2001. Recruitment curve of the soleus H-reflex in chronic back pain and lumbosacral radiculopathy. *BMC Musculoskeletal Disorders,* 2**,** 1-8.

MCHUGH, M. L. 2012. Interrater reliability: the kappa statistic. *Biochemia medica,* 22**,** 276-282.

This article is protected by copyright. All rights reserved

Accepted Article

MCKENZIE, J. E. & BRENNAN, S. E. 2019. Synthesizing and presenting findings using other methods. *Cochrane Handbook for Systematic Reviews of Interventions*, 321-347.

MCNEIL, C., BUTLER, J., TAYLOR, J. & GANDEVIA, S. 2013. Testing the excitability of human motoneurons. *Frontiers in Human Neuroscience,* 7.

MHALLA, A., DE ANDRADE, D. C., BAUDIC, S., PERROT, S. & BOUHASSIRA, D. 2010. Alteration of cortical excitability in patients with fibromyalgia. *Pain,* 149**,** 495-500.

MINAMI, I., AKHTER, R., ALBERSEN, I., BURGER, C., WHITTLE, T., LOBBEZOO, F., PECK, C. & MURRAY, G. 2013. Masseter motor unit recruitment is altered in experimental jaw muscle pain. *Journal of dental research,* 92**,** 143-148.

MISIASZEK, J. E. 2003. The H-reflex as a tool in neurophysiology: its limitations and uses in understanding nervous system function. *Muscle Nerve,* 28**,** 144-60.

MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. & THE, P. G. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine,* 6**,** e1000097.

NATHAN, P. W., IGGO, A., IVERSEN, L. L. & CERVERO, F. 1985. Pain and nociception in the clinical context. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences,* 308**,** 219-226.

NGOMO, S., MERCIER, C., BOUYER, L. J., SAVOIE, A. & ROY, J. S. 2015. Alterations in central motor representation increase over time in individuals with rotator cuff tendinopathy. *Clinical Neurophysiology,* 126**,** 365-371.

PARK, J. & HOPKINS, J. T. 2013. Induced anterior knee pain immediately reduces involuntary and voluntary quadriceps activation. *Clinical Journal of Sport Medicine,* 23**,** 19-24.

PARKER, R. S., LEWIS, G. N., RICE, D. A. & MCNAIR, P. J. 2016. Is Motor Cortical Excitability Altered in People with Chronic Pain? A Systematic Review and Meta-Analysis. *Brain Stimulation,* 9**,** 488-500.

PAZZINATTO, M. F., DE OLIVEIRA SILVA, D., FERREIRA, A. S., WAITEMAN, M. C., PAPPAS, E., MAGALHÃES, F. H. & AZEVEDO, F. M. D. 2019. Patellar Tendon Reflex and Vastus Medialis Hoffmann Reflex Are Down Regulated and Correlated in Women With Patellofemoral Pain. *Archives of Physical Medicine and Rehabilitation,* 100**,** 514-519.

This article is protected by copyright. All rights reserved

Accepted Article

POORTVLIET, P. C., TUCKER, K. J. & HODGES, P. W. 2015. Experimental pain has a greater effect on single motor unit discharge during force-control than position-control tasks. *Clinical Neurophysiology,* 126**,** 1378-1386.

RICE, D. A., GRAVEN-NIELSEN, T., LEWIS, G. N., MCNAIR, P. J. & DALBETH, N. 2015. The effects of experimental knee pain on lower limb corticospinal and motor cortex excitability. *Arthritis Research and Therapy,* 17.

RIO, E., KIDGELL, D., MOSELEY, G. L. & COOK, J. 2016. Elevated corticospinal excitability in patellar tendinopathy compared with other anterior knee pain or no pain. *Scandinavian journal of medicine & science in sports,* 26**,** 1072-1079.

ROHEL, A., BOUFFARD, J., PATRICIO, P., MAVROMATIS, N., BILLOT, M., ROY, J.-S., BOUYER, L., MERCIER, C. & MASSE-ALARIE, H. 2021. The effect of experimental pain on the excitability of the corticospinal tract in humans: A systematic review and meta-analysis. *European Journal of Pain,* n/a.

SALERNO, A., THOMAS, E., OLIVE, P., BLOTMAN, F., PICOT, M. C. & GEORGESCO, M. 2000. Motor cortical dysfunction disclosed by single and double magnetic stimulation in patients with fibromyalgia. *Clinical Neurophysiology,* 111**,** 994-1001.

SCHABRUN, S. M., CHRISTENSEN, S. W., MRACHACZ-KERSTING, N. & GRAVEN-NIELSEN, T. 2016. Motor Cortex Reorganization and Impaired Function in the Transition to Sustained Muscle Pain. *Cerebral Cortex,* 26**,** 1878-90.

SCHABRUN, S. M., ELGUETA-CANCINO, E. L. & HODGES, P. W. 2017. Smudging of the Motor Cortex Is Related to the Severity of Low Back Pain. *Spine (Phila Pa 1976),* 42**,** 1172-1178.

SCHABRUN, S. M. & HODGES, P. W. 2012. Muscle pain differentially modulates short interval intracortical inhibition and intracortical facilitation in primary motor cortex. *Journal of Pain,* 13**,** 187-194.

SCHABRUN, S. M., HODGES, P. W., VICENZINO, B., JONES, E. & CHIPCHASE, L. S. 2015. Novel adaptations in motor cortical maps: the relation to persistent elbow pain. *Medicine & Science in Sports & Exercise,* 47**,** 681-90.

This article is protected by copyright. All rights reserved

Accepted Article

SCHABRUN, S. M., JONES, E., KLOSTER, J. & HODGES, P. W. 2013. Temporal association between changes in primary sensory cortex and corticomotor output during muscle pain. *Neuroscience,* 235**,** 159-164.

SEMINOWICZ, D. A., THAPA, T. & SCHABRUN, S. M. 2019. Corticomotor Depression is Associated With Higher Pain Severity in the Transition to Sustained Pain: A Longitudinal Exploratory Study of Individual Differences. *Journal of Pain,* 20**,** 1498-1506.

SHAMSEER, L., MOHER, D., CLARKE, M., GHERSI, D., LIBERATI, A., PETTICREW, M., SHEKELLE, P., STEWART, L. A. & GROUP, P.-P. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ,* 350**,** g7647.

SMITH, V., DEVANE, D., BEGLEY, C. M. & CLARKE, M. 2011. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Med Res Methodol,* 11**,** 15.

SOHN, M. K., GRAVEN-NIELSEN, T., ARENDT-NIELSEN, L. & SVENSSON, P. 2004. Effects of experimental muscle pain on mechanical properties of single motor units in human masseter. *Clinical Neurophysiology,* 115**,** 76-84.

SOHN, M. K., GRAVEN-NIELSEN, T., ARENDT-NIELSEN, L. & SVENSSON, P. 2000. Inhibition of motor unit firing during experimental muscle pain in humans. *Muscle & nerve,* 23**,** 1219-1226.

STECCO, C. 2014. *Functional atlas of the human fascial system*, Elsevier Health Sciences.

STERLING, M., JULL, G. & WRIGHT, A. 2001. The effect of musculoskeletal pain on motor activity and control. *The Journal of Pain,* 2**,** 135-145.

STRUTTON, P. H., THEODOROU, S., CATLEY, M., MCGREGOR, A. H. & DAVEY, N. J. 2005. Corticospinal excitability in patients with chronic low back pain. *Journal of Spinal Disorders & Techniques,* 18**,** 420-4.

SUMMERS, S. J., CHALMERS, K. J., CAVALERI, R. & CHIPCHASE, L. S. 2020. Fear of movement is associated with corticomotor depression in response to acute experimental muscle pain. *Experimental Brain Research,* 238**,** 1945-1955.

This article is protected by copyright. All rights reserved

Accepted Article

SUMMERS, S. J., CHIPCHASE, L. S., HIRATA, R., GRAVEN-NIELSEN, T., CAVALERI, R. & SCHABRUN, S. M. 2019. Motor adaptation varies between individuals in the transition to sustained pain. *Pain,* 160**,** 2115-2125.

SVENSSON, P., DE LAAT, A., GRAVEN-NIELSEN, T. & ARENDT-NIELSEN, L. 1998. Experimental jaw-muscle pain does not change heteronymous H-reflexes in the human temporalis muscle. *Experimental Brain Research,* 121**,** 311-318.

SVENSSON, P., MILES, T. S., MCKAY, D. & RIDDING, M. C. 2003. Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. *European Journal of Pain,* 7**,** 55-62.

TE, M., BAPTISTA, A. F., CHIPCHASE, L. S. & SCHABRUN, S. M. 2017. Primary motor cortex organization is altered in persistent patellofemoral pain. *Pain Medicine (United States),* 18**,** 2224-2234.

THOMPSON, C. S., HILLER, C. E. & SCHABRUN, S. M. 2019. Altered spinal-level sensorimotor control related to pain and perceived instability in people with chronic ankle instability. *Journal of Science and Medicine in Sport,* 22**,** 425-429.

TSAO, H., DANNEELS, L. A. & HODGES, P. W. 2011a. ISSLS prize winner: Smudging the motor brain in young adults with recurrent low back pain. *Spine,* 36**,** 1721-7.

TSAO, H., GALEA, M. P. & HODGES, P. W. 2008. Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. *Brain,* 131**,** 2161-71.

TSAO, H., TUCKER, K. J. & HODGES, P. W. 2011b. Changes in excitability of corticomotor inputs to the trunk muscles during experimentally-induced acute low back pain. *Neuroscience,* 181**,** 127-133.

TUCKER, K., BUTLER, J., GRAVEN-NIELSEN, T., RIEK, S. & HODGES, P. 2009a. Motor unit recruitment strategies are altered during deep-tissue pain. *Journal of Neuroscience,* 29**,** 10820-10826.

TUCKER, K., BUTLER, J., GRAVEN-NIELSEN, T., RIEK, S. & HODGES, P. 2009b. Motor Unit Recruitment Strategies Are Altered during Deep-Tissue Pain. *The Journal of Neuroscience,* 29**,** 10820.

This article is protected by copyright. All rights reserved

Accepted Article

TUCKER, K., LARSSON, A. K., OKNELID, S. & HODGES, P. 2012. Similar alteration of motor unit recruitment strategies during the anticipation and experience of pain. *Pain,* 153**,** 636-43.

TUCKER, K. J. & HODGES, P. W. 2010. Changes in motor unit recruitment strategy during pain alters force direction. *European Journal of Pain,* 14**,** 932-938.

VOS, T., ABAJOBIR, A. A., ABATE, K. H., ABBAFATI, C., ABBAS, K. M., ABD-ALLAH, F., ABDULKADER, R. S., ABDULLE, A. M., ABEBO, T. A., ABERA, S. F., ABOYANS, V., ABU-RADDAD, L. J., ACKERMAN, I. N., ADAMU, A. A., ADETOKUNBOH, O., AFARIDEH, M., AFSHIN, A., AGARWAL, S. K., AGGARWAL, R., AGRAWAL, A., AGRAWAL, S., AHMADIEH, H., AHMED, M. B., AICHOUR, M. T. E., AICHOUR, A. N., AICHOUR, I., AIYAR, S., AKINYEMI, R. O., AKSEER, N., AL LAMI, F. H., ALAHDAB, F., AL-ALY, Z., ALAM, K., ALAM, N., ALAM, T., ALASFOOR, D., ALENE, K. A., ALI, R., ALIZADEH-NAVAEI, R., ALKERWI, A. A., ALLA, F., ALLEBECK, P., ALLEN, C., AL-MASKARI, F., AL-RADDADI, R., ALSHARIF, U., ALSOWAIDI, S., ALTIRKAWI, K. A., AMARE, A. T., AMINI, E., AMMAR, W., AMOAKO, Y. A., ANDERSEN, H. H., ANTONIO, C. A. T., ANWARI, P., ÄRNLÖV, J., ARTAMAN, A., ARYAL, K. K., ASAYESH, H., ASGEDOM, S. W., ASSADI, R., ATEY, T. M., ATNAFU, N. T., ATRE, S. R., AVILA-BURGOS, L., AVOKPHAKO, E. F. G. A., AWASTHI, A., BACHA, U., BADAWI, A., BALAKRISHNAN, K., BANERJEE, A., BANNICK, M. S., BARAC, A., BARBER, R. M., BARKER-COLLO, S. L., BÄRNIGHAUSEN, T., BARQUERA, S., BARREGARD, L., BARRERO, L. H., BASU, S., BATTISTA, B., BATTLE, K. E., BAUNE, B. T., BAZARGAN-HEJAZI, S., BEARDSLEY, J., BEDI, N., BEGHI, E., BÉJOT, Y., BEKELE, B. B., BELL, M. L., BENNETT, D. A., BENSENOR, I. M., BENSON, J., BERHANE, A., BERHE, D. F., BERNABÉ, E., BETSU, B. D., BEURAN, M., BEYENE, A. S., BHALA, N., et al. 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet,* 390**,** 1211-1259.

WANG, H. K., LIN, K. H., WU, Y. K., CHI, S. C., SHIH, T. T. F. & HUANG, Y. C. 2011. Evoked spinal reflexes and force development in elite athletes with middle-portion achilles tendinopathy. *Journal of Orthopaedic and Sports Physical Therapy,* 41**,** 785-794.

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WOO, C.-W., SCHMIDT, L., KRISHNAN, A., JEPMA, M., ROY, M., LINDQUIST, M. A., ATLAS, L. Y. & WAGER, T. D. 2017. Quantifying cerebral contributions to pain beyond nociception. *Nature Communications,* 8**,** 14211.

YANG, C. C., SU, F. C., YANG, P. C., LIN, H. T. & GUO, L. Y. 2016. Characteristics of the motor units during sternocleidomastoid isometric flexion among patients with mechanical neck disorder and asymptomatic individuals. *PLoS ONE,* 11.

YAVUZ, U. Ş., NEGRO, F., FALLA, D. & FARINA, D. 2015. Experimental muscle pain increases variability of neural drive to muscle and decreases motor unit coherence in tremor frequency band. *Journal of Neurophysiology,* 114**,** 1041-1047.

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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.

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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 study
Reviewer 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.

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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 both experimental and clinical pain conditions. Grey shading indicates that the variable was not measured 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)

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SF. 1– Prisma Checklist

SF. 2 – Search String

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

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

Population	Intervention	Outcome	
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	Motor activity	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

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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	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 / Motor Evoked Potentials (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

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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	Outcome	Score R1|R2	Author and Year	Outcome	Score 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 et al., 2011	MEP	11|10	Massé-Alarie et al., 2017	MEP	13|10

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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|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 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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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), NGF (Nerve Growth Factor)

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
					Tibialis Anterior	Tibialis Anterior	No Change
	H-Reflex Amplitude	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Change
	H-Reflex Latency	Le Pera et al., 2001	11	HyperS 5%	R-Flexor Carpi Radialis	R-Flexor Carpi Radialis	No Change
Post Pain	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

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
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)
							Increased	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	Sustained Pain (Day 1, 2)
							Increased	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)
		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)
		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)
							Increased	Sustained Pain (Day 4)
	MEP area (mV2)	Del Santo et al., 2007	8	Ascorbic Acid 40mg/0.2 ml	Abductor Digiti Minimi	Abductor Digiti Minimi	Increased	Abductor Digiti Minimi Contraction
				Ascorbic Acid	Biceps Brachii	Biceps Brachii	Increased	Biceps Brachii Contraction

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			90mg/0.5 ml				
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	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)
	Summers et al., 2019	28	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	Decreased	Sustained Pain (Day 2, 4)
	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	Decreased	
					Extensor Carpi Radialis	No Change	
	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)

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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	Increased	
				R-Vastus Medialis		
				R-Biceps Femoris	No Change	
				R-Tibialis Anterior		
Schabrun et al., 2013	12	HyperS 5%	R-First Dorsal Interosseus	R-First Dorsal Interosseus	No Change	
Martin et al., 2007	6	HyperS 5%	Biceps Brachii	Biceps Brachii	No Change	
				Trapezius		
	7			Biceps Brachii	Decreased	Biceps Brachii contraction
				Trapezius		
	6			Biceps Brachii	No Change	Biceps Brachii constant contraction
				Trapezius		
				Biceps Brachii		Trapezius constant contraction
				Trapezius	Decreased	
Le Pera et al., 2001	10	HyperS 5%	R-Abductor Digiti Minimi	R-Abductor Digiti Minimi	Decreased	
			R-First Dorsal Interosseus	R-Abductor Digiti Minimi (NP)	Decreased	

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			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	
	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		
	Resting Motor Threshold	Seminowicz et al., 2019	20	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	
		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	Schabrun et	12	NGF 5 µg	R-Extensor Carpi	R-Extensor Carpi	No Change	Sustained Pain (Day 14)

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	Peaks	al., 2016		(0.2 mL)	Radialis Brevis	Radialis Brevis		
	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 (mV2)	Del Santo et al., 2007	8	Ascorbic Acid 40mg/0.2 ml	Abductor Digiti Minimi	Abductor Digiti Minimi	No Change	Abductor Digiti Minimi Contraction
				Ascorbic Acid 90mg/0.5 ml	Biceps Brachii	Biceps Brachii		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	No Change	
		Seminowicz et al., 2019	20	NGF	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	Sustained Pain (Day 14)

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		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)	R-Extensor Carpi Radialis Brevis	R-Extensor Carpi Radialis Brevis	No Change	Sustained Pain (Day 14)
				HyperS 5%			Increased	Following sustained pain from NGF
		Rice et al., 2015	18	HyperS 5.8%	R-Infrapatellar Fat Pad	R-Vastus Lateralis	No Change	
						R-Vastus Medialis		
						R-Biceps Femoris		
						R-Tibialis Anterior		
		Schabrun et al., 2013	12	HyperS 5%	R-First Dorsal Interosseus	First Dorsal Interosseus	Decreased	
		Schabrun and	11	HyperS 5%	R-First Dorsal	R-First Dorsal	Decreased	

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		Hodges, 2012			Interosseus	Interosseus		
						R-Abductor Digiti Minimi (NP)		
		Tsao et al., 2011	9	HyperS 5%	ISL	Transversus Abdominus -C	Decreased	Transversus Abdominus rest
						Transversus Abdominus-I	No Change	
						External Oblique-C	Increased	
						External Oblique-I		
						Internal Oblique-C	No Change	
						Internal Oblique-I		
						Rectus Abdominus-C	Decreased	
						Rectus Abdominus-I	No Change	
						Lumbar Erector Spinae-C	Increased	
						Lumbar Erector Spinae-I		
						Transversus Abdominus -C	No Change	Transversus Abdominus contraction

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						Transversus Abdominus-I		
						External Oblique-C	Increased	
						External Oblique-I	No Change	
						Internal Oblique-C		
						Internal Oblique-I		
						Rectus Abdominus-C		
						Rectus Abdominus-I		
						Lumbar Erector Spinae-C		
						Lumbar Erector Spinae-I		
		Martin et al., 2007	6	HyperS 5%	Biceps Brachii	Biceps Brachii	No Change	
						Trapezius		
			7			Biceps Brachii	Decreased	Biceps Brachii contraction
						Trapezius		
			6			Biceps Brachii	No Change	Biceps Brachii constant contraction
						Trapezius		

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						Biceps Brachii	No Change	Trapezius constant contraction
						Trapezius	Decreased	
		Svensson et al., 2003	10	HyperS 5.8%	R-First Dorsal Interosseus	R-First Dorsal Interosseus	Decreased	
						R-Flexor Carpi Ulnaris (NP)	No Change	
			2		R-First Dorsal Interosseus	R-First Dorsal Interosseus	Decreased	Descending tract stimulation
		Le Pera et al., 2001	10	HyperS 5%	R-Abductor Digiti Minimi	R-Abductor Digiti Minimi	Decreased	
					R-First Dorsal Interosseus	R-Abductor Digiti Minimi (NP)	No Change	
			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	
	MEP Latency	Tsao et al., 2011	9	HyperS 5%	ISL	Transversus Abdominus -C	No Change	Transversus Abdominus rest

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						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	No Change	Transversus Abdominus contraction
						Transversus Abdominus-I		
						External Oblique-C		
						External Oblique-I		
						Internal Oblique-C		

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						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-First Dorsal Interosseus	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		

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	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)		

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

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Table 4-3 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	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
						Abductor Digiti Minimi		alpha band
	Conduction Velocity	Farina et al., 2008	16	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	No Change	
		Farina et al., 2005	11	HyperS 5.8%	Tibialis Anterior Right	Tibialis Anterior Right	No Change	
						Tibialis Anterior Left (NP)		
		Farina et al., 2004	12	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior right	No Change	

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	Discharge rate (Hz)	Martinez-Valdes et al., 2020	15	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	Decreased	20% MVC
							Increased	70% MVC
		Dideriksen et al., 2016	12	HyperS 5.8%	Trapezius	Trapezius	Decreased	Cranial region
						Trapezius	No Change	Caudal region
		Poortvliet et al., 2015	13	HyperS 5%	Infrapatellar Fat Pad	Vastus Medialis	Decreased	
						Vastus Lateralis		
						Biceps Femoris		
						Semitendinosus		
						Tensor Fasciae Latae		
		Tucker et al., 2012	9	HyperS 5%	Infrapatellar Fat Pad	Vastus Medialis	Decreased	
						Vastus Lateralis		
		Tucker and Hodges, 2010	9	HyperS 5%	Infrapatellar Fat Pad	Vastus Medialis	Decreased	
						Vastus Lateralis		
		Tucker et al., 2009	8	HyperS 5%	Infrapatellar Fat Pad	Vastus Medialis	Decreased	
						Vastus Lateralis		
			7		Flexor Pollicus Longus	Flexor Pollicus Longus	Decreased	
		Hodges et al., 2008	10	HyperS 5%	Gastrocnemius lateral	Gastrocnemius	Decreased	
						Soleus		
		Farina et al.,	16	HyperS 5.8%	Tibialis Anterior	Tibialis Anterior	Decreased	

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		2008						
		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	

hyperS (Hypertonic saline)

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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 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

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		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

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

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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 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
	Strutton et al., 2005	24	11	cLBP	Erector Spinae	Increased

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Cortical peaks (n)	Elgueta-Cancino et al., 2019	10	10	cNP	Superficial Neck Flexors	Decreased
					Deep Neck Flexors	
	Te et al., 2017	11	11	PFP	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	

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	Schabrun et al., 2015	11	11	LE	Extensor Digitorum Extensor Carpi Radialis Brevis	Increased
	Tsao et al., 2011	9	11	LBP	Multifidus Lumbar Erector Spinae	Decreased
	Tsao et al., 2008	11	11	LBP	Transversus Abdominus	Increased
Map Area	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

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	Ngomo et al., 2015	39	39	RCT	Infraspinatus	No Change
	Mhalla et al., 2010	46	21	Fibromyalgia	First Dorsal Interosseus	Decreased
	Salerno et al., 2000	13	13	Fibromyalgia	First Dorsal Interosseus	No Change
					Tibialis Anterior	
MEP Area	Strutton et al., 2005	24	11	cLBP	Erector Spinae	No Change
MEP Latency (ms)	Tsao et al., 2011	9	11	LBP	Multifidus	No Change
					Lumbar Erector Spinae	
	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	No Change
					Tibialis Anterior	
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

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					Tibialis Anterior	
SP Duration (ms)	Cardinal et al., 2019	17	41	Fibromyalgia	First Dorsal Interosseus	Decreased
	Massé-Alarie et al., 2017	19	13	cLBP (Right)	Multifidus	No Change
		16	13	cLBP (Left)	Multifidus	No Change
	Burns et al., 2017	11	11	LBP	Paraspinal Muscles	No 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	Fibromyalgia	First Dorsal Interosseus Tibialis Anterior	Decreased

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)

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Table 4-6 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 (n)		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)
						No Change	30N(circular contractions)
						No Change	constant force directions
Discharge rate	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

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

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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 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		2 (2)	-	2	-	MA	-	-	-	-	-

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(Post Pain)					

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

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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.

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
MEP Amplitude	Painful Muscle	12 (18)	1	3	4	4	MEPA	9 (12)	1	6	2	-
	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)	-	4	-	-
	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)	2	2	-	-
	Painful Muscle (PP)	3 (3)	-	3	-	-						
	Control Muscle (PP)	1 (1)	-	1	-	-						
MEP Area	During Pain	1 (2)	1	-	-	-	MEP Area	1 (1)	-	1	-	-
	Post Pain	1 (2)	-	1	-	-						

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Map Volume	During Pain	3 (3)	-	1	1	1	Map Volume	8 (14)	2	3	3	-
	Post Pain	3 (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	-
Cortical Peaks		1 (1)	-	-	-	1	Cortical Peaks	4 (9)	-	-	3	1

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)

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Table 5-3 - Summary of compiled results for changes in motor unit behaviour 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**	**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

CV (Conduction Velocity)

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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	-	-

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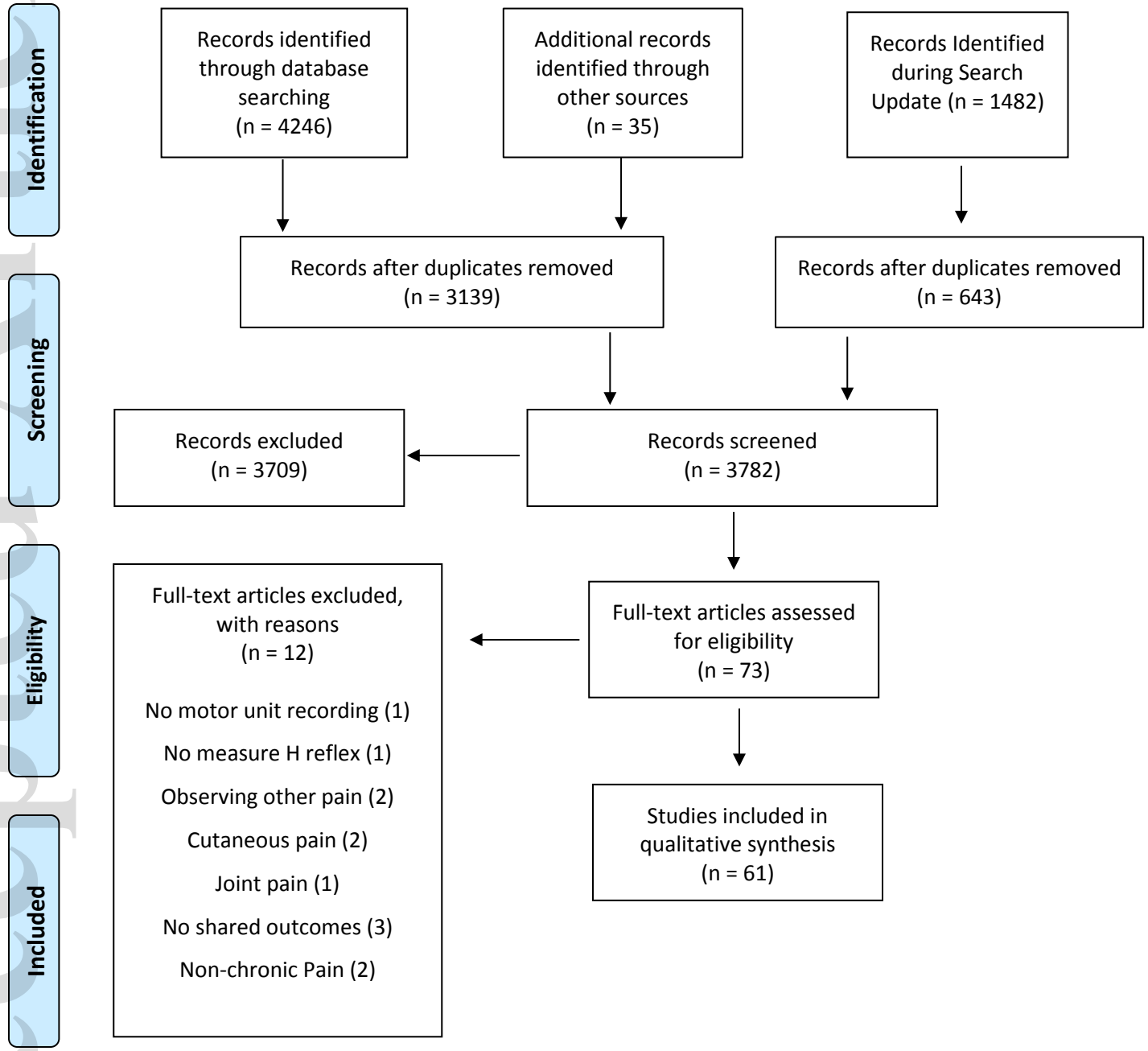
PRISMA 2009 Flow Diagram



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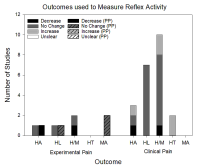

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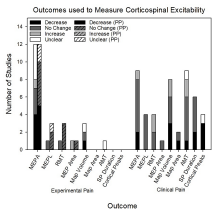

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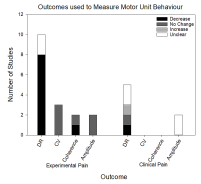

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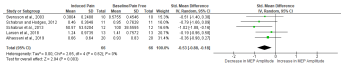

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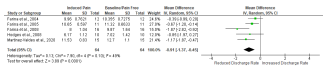

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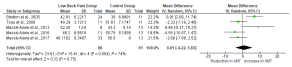

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