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PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 25, No. 12 (December), 2024: 104660
Available online at www.jpain.org and www.sciencedirect.com

The Effect of Experimentally Induced Pain in the Cervical, Shoulder, or Orofacial Regions on Cervical Neuromuscular and Kinematic Features: A Systematic Review and Meta-analysis

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Abstract: **In this systematic review, we synthesize the literature investigating the effect of experimentally induced pain in the cervical, shoulder, or orofacial regions on cervical neuromuscular and kinematic features. Databases were searched up to November 1, 2023. A total of 29 studies using hypertonic saline injection (n = 27) or glutamate injection (n = 2) as experimental pain models were included. Meta-analyses revealed reduced upper trapezius activation during shoulder flexion/abduction when pain was induced in the upper trapezius (standardized mean difference: –.90, 95% confidence interval: [–1.29; –.51]), splenius capitis (–1.03 [–1.44; –.63]), and supraspinatus (–.63 [–1.25; –.01]), but not in the subacromial space (.22 [–.16; .60]). Furthermore, experimentally induced pain caused a caudal redistribution of activation within the upper trapezius (.96 [.58; 1.34]) but did not change the mediolateral distribution (.11 [–.22; .42]). None of these adaptations persisted after pain resolution. Low-quality evidence supported the absence of an effect of experimental pain on upper trapezius muscle activation during manual dexterity and cervical flexion/extension tasks, as well as on cervical flexor and extensor muscle activation during cervical and jaw tasks. Inconsistent and limited evidence, attributed to the large heterogeneity of task and outcomes, precluded drawing meaningful conclusions about the effects of experimentally induced pain in the cervical region on cervical kinematics. Overall, cervical muscle activation tended to decrease in response to experimentally induced pain, and the decrease of muscle activation depended on the location of the painful stimulus. These adaptations are only partially representative of muscle activation patterns observed in clinical populations.**

Perspective: ***This systematic review and meta-analysis revealed a reduced or unchanged muscle activation during experimental pain in the cervical, shoulder, or orofacial regions, depending on the task and location of nociceptive stimulation. There was inconsistent evidence on cervical kinematics. These findings enhance our understanding of neuromuscular adaptations to acute experimental pain.***

Key Words: *Experimental pain, neck pain, electromyography, kinematics, motor adaptation*

Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

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1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2024.104660

Pain is a common condition worldwide, with an estimated prevalence of 30% across countries.[1] The neck and shoulder regions have been reported as the most common sites of pain after lower back pain,[2] with estimated prevalences of 3,551 per 100,000[3] (neck pain point prevalence), 16%[4] (shoulder pain 1-year median prevalence), and 3.8 to 9.2%[5] (orofacial pain 1-year point prevalence). In 2019, neck pain ranked in the top 25 leading causes for disability in people 25 to 75 years old,[6] and is a main contributor to healthcare spending.[7,8] This major economic burden is projected to increase even further with the increasing population age.[9]

Alterations in cervical neuromuscular function and cervical spine kinematics are commonly present in individuals with pain in the neck, shoulder, and orofacial regions, and may include changes in neck muscle coordination, delayed neck muscle activity in response to perturbations and reduced range, and speed and variability of neck movements.[10–15] Although these motor adaptations to pain may provide short-term benefit to protect a painful neck region, persistent or maladaptive motor control changes are thought to be potential contributors to the development of chronic pain.[16] A comprehensive understanding of how acute pain alters neuromuscular responses in the cervical region is therefore important to improve our understanding of motor adaptations to pain, which may ultimately inform the assessment, treatment, and prevention of neck, shoulder, and/or orofacial pain.

High interindividual variability in pain severity and motor adaptations to pain exists in clinical populations.[17] Several factors, including psychosocial features such as pain catastrophizing,[18] genetics,[19] and demographic factors such as sex and age,[17] are known to contribute to individual variation in pain perception, which makes it challenging to isolate the effect of nociception on neuromuscular and kinematics features. Some of these challenges can be overcome by using experimental pain models, which allow to investigate motor strategies of the same individual with and without pain, while reducing the variability in intensity, location, and duration of pain across individuals.[10]

Experimental pain models have been used to study motor adaptations to pain in a variety of body regions and tasks. Previous systematic reviews have demonstrated that experimentally induced pain results in a generalized decrease of muscle activation during experimentally induced limb pain,[20] consistent decrease of motor unit firing rate of the painful muscle,[21] and reduced corticospinal excitability.[22] In contrast, lumbar muscle activation increases or decreases in a task-dependent manner when pain is induced in the lumbar region.[23] These findings, which show that pain induced in different body regions may induce different motor adaptations, highlight the need for further synthesis of evidence on the motor adaptations induced by experimental pain. This is especially important for the cervical region, where motor adaptations may occur due to pain in the cervical, shoulder, or orofacial regions. To date, no systematic review has explored cervical adaptations to pain, and broad conclusions based on individual studies are difficult due to methodological differences such as different locations of nociceptive stimulation and experimental tasks. Therefore, in this systematic review, we aimed to synthesize the available evidence on how pain experimentally induced in the cervical, shoulder, or orofacial regions affects cervical neuromuscular and kinematic features. We included different regions (cervical, shoulder, and orofacial) to specifically investigate whether cervical neuromuscular and kinematic adaptations depend on the location of nociceptive stimulation. Since a previous systematic review revealed that motor adaptations outlasted lumbar pain duration in a few studies,[23] we also systematically reviewed whether neuromuscular strategies' return to baseline after experimental pain in the cervical, shoulder, and orofacial region is resolved.

Review Questions

Primary Review Question

1. Is cervical neuromuscular control and/or cervical spine kinematics of healthy adults altered by experimentally induced pain in the cervical, shoulder, or orofacial regions?

Secondary Review Questions

2a. Do cervical neuromuscular and/or cervical spine kinematic adaptations depend on the region of nociceptive stimulation?

2b. Do cervical neuromuscular and/or kinematic adaptations outlast the duration of perceived pain?

Methods

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions,[24,25] reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA statement 2020[26]), and was registered on the International Prospective Register of Systematic Reviews (register CRD42021237019) on February 16, 2021. Although a systematic review protocol was not published, this systematic review followed the methods of a recent systematic review conducted by our team on the effect of experimentally induced pain on lumbar neuromuscular and kinematic features.[23]

Eligibility Criteria

The eligibility criteria for study inclusion were delineated using the PICOS framework (P: Population, I: Intervention, C: Comparator, O: Outcomes, and S: Study design).[27]

Population (P)

Healthy adults (age ≥18 years) without current or a history of musculoskeletal disorders in the neck-shoulder or orofacial region.

Intervention (I)

We included studies that evaluated the effect of pain experimentally induced in the cervical, shoulder, or orofacial regions on neuromuscular and/or kinematic adaptations in the cervical region. As in our previous systematic review,[23] only exogenous pain models, where the pain was induced by an external, controlled stimulus, chemical (eg, hypertonic saline and glutamate), thermal (eg, cold and contact heat), or electrical, were considered in this review. Conversely, studies in which pain was evoked by endogenous models (eg, delayed-onset muscle soreness, muscle fatigue, or prolonged standing protocols) were excluded because the effect of pain on the neuromuscular system risks being biased by potential confounders, such as fatigue and muscle damage. When more than 1 experimental pain model was delivered to participants at the same time, the study was included only if the effects of the intervention of interest were also assessed when delivered individually.

Comparator (C)

Only studies using a within-subject design were included in this systematic review. Four conditions were considered: experimentally induced pain (PAIN), baseline (BASE), control (CTR), and post pain (POST). PAIN refers to data collected during experimental pain, BASE refers to data collected before inducing experimental pain, CTR refers to data collected during a control, nonpainful stimulation (eg, isotonic saline injection), and POST refers to data collected after the painful stimulation. We compared PAIN to BASE, PAIN to CTR, and POST to BASE. If a study did not test all 4 conditions, only the tested conditions were considered.

Outcomes (O)

The outcomes of interest were cervical muscle activity and kinematics. Only studies assessing voluntary or automatic (eg, postural) tasks were included; studies focusing on other outcomes, for example, effect of experimental pain on the H-reflex, were excluded. The body region investigated was limited to the cervical region, implying that the outcomes of interest should be investigated in this region, and studies assessing the outcomes exclusively at remote sites were excluded.

The evaluation of muscle activity included the use of electromyography (intramuscular and surface), ultrasound, and functional magnetic resonance imaging to measure the recruitment, intensity, and onset of muscle activation. The measurement tools considered for the evaluation of cervical spine kinematics were motion analysis systems (eg, optoelectronic systems and inertial measurement units) and the outcome domains of interest were range of motion, movement speed, movement quality, and variability.

Study Design (S)

The eligible study designs were randomized trials (crossover randomized controlled trials only) and nonrandomized studies of interventions (repeated measures design).

Information Sources and Search Strategy

Studies published up to January 30, 2021 were initially searched by 1 reviewer (H.V.C.), and the search was updated up to November 1, 2023 by the same reviewer. Similar to our previous systematic review,[23] the following electronic databases were used: MEDLINE (Ovid interface), Excerpta Medica Database (Ovid interface), CINAHL Plus (EBSCO interface), Pubmed, and Web of Science (Clarivate Analytics), ZETOC. Hand-searching was conducted for key journals (*PAIN*, *European Journal of Pain*, *Journal of Pain*, *Journal of Electromyography and Kinesiology*, *Journal of Neurophysiology, and Musculoskeletal Science and Practice*). The reference lists of included studies and relevant reviews were checked. To minimize the risk of publication bias, OpenGrey, Ethos database, and conference proceedings were searched to screen gray literature.

The search strategy comprised a combination of medical subject headings with free-text terms. The main concepts of the search strategy were the intervention and the body regions stimulated as follows:

("experimental pain" OR "pain model") AND ("region/body structure").

Where "*experimental pain*" identified the free-text words usually adopted to report the use of experimental pain in a study (eg, experimentally induced pain), "*pain model*" included the interventions (eg, hypertonic saline) and "*region/body structure*" included the region/body structure where the pain was induced (eg, "neck pain"). The search strategy used for the MEDLINE (Ovid Interface) database is reported in Supplementary File 1.

Study Selection

All potentially eligible records were retrieved from databases and duplicates were removed by 1 reviewer (H.V.C.). Based on the eligibility criteria, 2 independent reviewers (H.V.C. and C.O.) screened the title and abstract of all studies. Subsequently, full texts of the remaining studies were independently screened by the same 2 reviewers. Any disagreements were discussed and, when necessary, a third reviewer (A.G.) was consulted for arbitration. The agreement between the 2 reviewers was assessed using Cohen's kappa statistic.

Data Extraction Process and Data Items

Data extraction was conducted by 1 reviewer (H.V.C.) using a custom form (adapted from Devecchi et al[28]) and checked for accuracy by a second reviewer (C.O.). Multiple reports of the same study were collated.[26] The data extracted included the characteristics of participants (eg, sample size, age, and gender), the intervention characteristics (eg, experimental pain model, specific region stimulated, and average pain induced), the comparator condition specifications (BASE, CTR,

and/or POST), and the main results. When the study results were reported only in graphs, WebPlotDigitizer software (version 4.4; Pacifica, California) was used to extract the data from figures.[25]

Quality Assessment

Two independent reviewers (H.V.C. and C.O.) assessed the risk of bias of the included studies. Specifically, we used the risk-of-bias tool (RoB2)[29] to evaluate crossover randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions tool[30] to evaluate the repeated measures studies. Any disagreement was resolved through discussion and, when necessary, a third reviewer (A.G.) was consulted for arbitration. The risk-of-bias assessment was used to summarize the quality of evidence for each outcome domain.[31]

Data Synthesis and Meta-analysis

The summary data (means and standard deviation) were extracted for each condition investigated (BASE, CTR, PAIN, and POST). To answer the primary review question, cervical spine neuromuscular control and cervical kinematics evaluated at BASE and CTR were separately compared with PAIN (ie, BASE vs PAIN and CTR vs PAIN). Data from BASE and CTR intervention were not pooled for quantitative synthesis because the latter provides a higher quality of evidence controlling for potential confounders. Specifically, for each key outcome measure, PAIN was compared with either BASE or CTR, whichever comparator was most common across the studies reviewed. To address the secondary review question 2b, the POST condition was compared with BASE condition, if the POST condition was assessed during the same experimental session.

As in our previous systematic review,[23] findings from studies were summarized based on the outcome domain investigated, the pain location, the tissue target by the pain model, and the comparison conducted, using the standardized mean difference (SMD, Cohen's d) and 95% confidence intervals. The following equations were used for SMD calculation (d) and variance ($v(d)$):

$$d = \frac{\bar{X}_{\text{condition}} - \bar{X}_{\text{comparator}}}{\text{SD}_{\text{diff}}}$$

$$v(d) = \frac{1}{\text{n}} + \frac{d^2}{2\text{n}}$$

where n is the sample size, $\bar{X}_{\text{condition}}$ is the group mean for PAIN or POST conditions, $\bar{X}_{\text{comparator}}$ is the group mean for BASE or CTR conditions, and SD_{diff} is the standard deviation of the difference. For studies that expressed $\bar{X}_{\text{condition}}$ as a proportion of $\bar{X}_{\text{comparator}}$ (eg, % change from BASE), $\text{SD}_{\text{condition}}$ was defined as SD_{diff}. When the was not available, its value was estimated from $\text{SD}_{\text{condition}}$ and $\text{SD}_{\text{comparator}}$ according to the formula

$$\text{SD}_{\text{diff}} = \sqrt{\text{SD}^2_{\text{condition}} + \text{SD}^2_{\text{comparator}} - (2 \times r \times \text{SD}_{\text{condition}} \times \text{SD}_{\text{comparator}})}$$

where r is the correlation coefficient between $\bar{X}_{\text{condition}}$ and $\bar{X}_{\text{comparator}}$. Considering no studies provided the r value, we adopted a conservative approach ($r = .5$) to estimate the SD_{diff}. Finally, when the P value of the comparison between conditions was reported in the study, its value was used to obtain the t value and directly calculate the SMD as follows[32]:

$$d = \frac{t}{\sqrt{\text{n}}}$$

Quantitative synthesis using a random-effect meta-analysis with an inverse-variance method was conducted when consistency across at least 2 studies was met. Random-effect meta-analysis was used because not all studies estimated the same intervention effect (ie, pain characteristics and tasks varied across studies). The between-study heterogeneity was analyzed using the I^2 statistic.[24] Specifically, heterogeneity was assessed in subgroups, based on the different regions pain was experimentally induced, to explore the secondary review question 2a. Considering the difficulty to obtain studies with a homogeneous methodology in each subgroup, results from subgroup analysis were described narratively. When only 1 study was available or it was not possible to perform meta-analyses due to the lack of methodological homogeneity, results were reported narratively and, when possible, graphically with a forest plot. All analyses were conducted in R using the package "*meta*" (RStudio environment version 1.4.1103; R Foundation for Statistical Computing, Vienna, Austria). The α threshold for all tests was set at .05.

Quality of Evidence

When possible, the main findings were synthesized in a summary of findings table where the certainty of evidence was rated as "very low," "low," "moderate," and "high" using the Grading of Recommendations Assessment, Development, and Evaluation approach.[31] When a large effect estimate or dose response gradient was present, the certainty of evidence was upgraded.[33] The domains that downgraded the quality of evidence were study limitations, publication bias, imprecision, inconsistency, and indirectness.[33] The study limitations were rated with the risk-of-bias tools previously described. Moreover, the reasons for downgrading or upgrading the quality of evidence were provided.

Results

Search and Selection of Studies

A flowchart for the selection of studies is presented in Fig 1. After screening the title and abstract of 9,366 records (Cohen's Kappa = .94, almost perfect agreement between reviewers[34]), the full text of 91 reports (67 from databases and 24 from hand-searching) was assessed and, ultimately, 44 reports were included in the review (Cohen's Kappa = .92, almost perfect agreement between reviewers[34]). Of these included reports, 9 were abstracts of an included study and 6 were studies that used the same participants as another included study. After collating these 15 reports with their

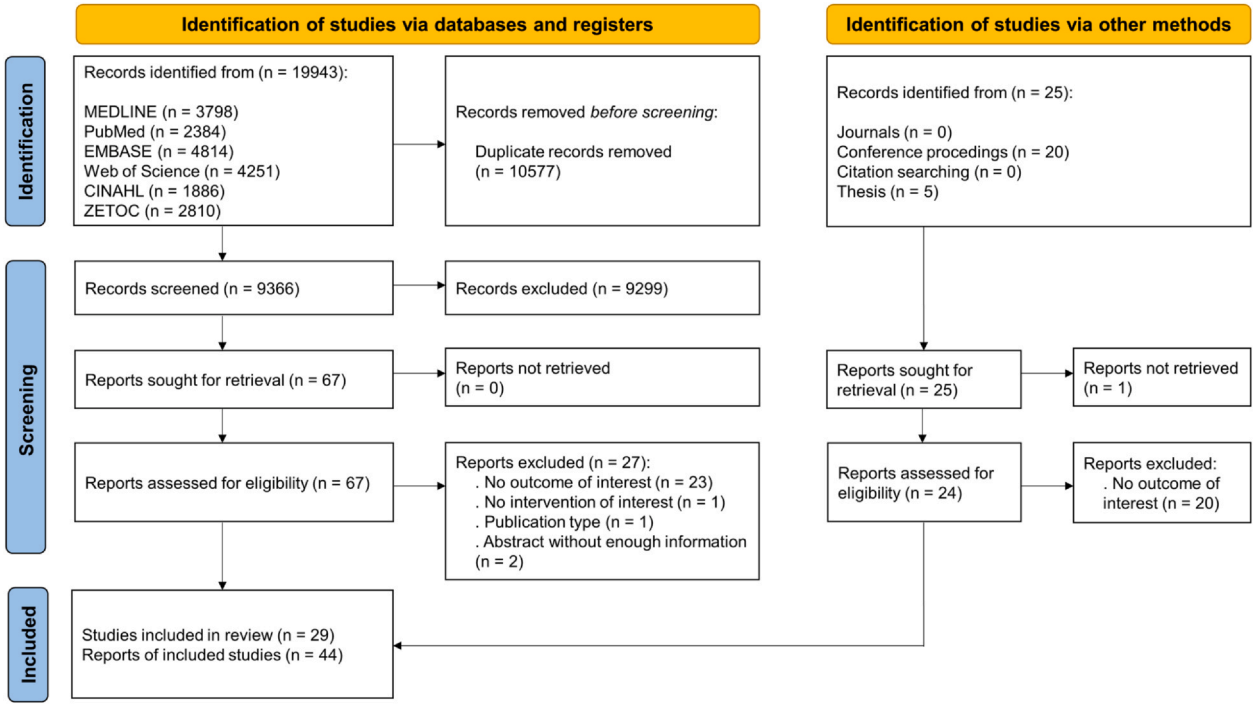

Figure 1. PRISMA flow diagram.

corresponding paper (for details see Supplementary File 1), a total of 29 studies were included in the review.

Characteristics of the Included Studies

The 29 studies included a total of 483 healthy participants (170 females, ~35%). Pain was induced in the cervical (N = 20 studies), shoulder (N = 5 studies), and orofacial (N = 3 studies) regions. In 1 study, pain was induced in both the cervical and orofacial regions. Most of the studies (n = 27) used hypertonic saline injection as an experimental model and another 2 studies used glutamate injection.[35,36] The average pain intensity level reported by participants ranged from 22 to 56 out of 100 using a visual analogue scale, and 21 to 48 out of 100 using a numerical rating scale. PAIN was compared with BASE in 14 studies, CTR only (isotonic saline solution injection) in 1 study, and with both conditions in 14 studies. POST was assessed in 9 studies, with 5 studies assessing post pain soon after the painful sensation had ceased[35,37–40] and 4 studies assessing pain 10 to 30 minutes after the painful injection.[41–44] The average pain intensity level reported by participants for POST in 2 studies ranged from 5 to 8 out of 100 using the visual analogue scale.[41,44] Key outcome measures assessed were muscle activation (eletromyography (EMG) amplitude N = 21, T2 shifts N = 3), changes in regional activation (N = 5), motor unit discharge rate (N = 1), cervical spine kinematics (N = 6), and muscle timing of activation (N = 2). Further information on the characteristics of the included studies is provided in Table 1.

Risk of Bias

A summary of the risk-of-bias assessment for repeated measures design studies is presented in Fig 2A (individual studies) and Fig 2B (overall). Several studies were rated as moderate in domain 1 due to potential confounding factors and carry-over effects between conditions (eg, repeated measures with a short washout period). One study was rated as serious due to fear of injection reported by participants and the potential effect of fatigue during the task.[48] In domain 4, the method to induce pain (injection) when compared with BASE only, was considered a co-intervention in several studies and was rated as moderate. Three studies also used multiple painful injections to reach the target level of pain[46-48] and 1 study reported/analyzed perceived pain for only half the sample of participants recruited, who did not take part in the assessment of muscle activity[55] and were therefore rated as serious. In domain 5, 2 studies had some missing data[62,63] and in domain 6, several studies did not blind participants to the intervention or had systematic errors in the outcome measure[45] and were rated as moderate. Three studies displayed some selection in the results reported[41,49] and were rated moderate, while 1 study did not report the results of several muscles assessed[45] and was therefore rated as serious in domain 7.

A summary of the risk-of-bias assessment for the crossover randomized controlled trials is presented in Fig 3A (individual studies) and Fig 3B (overall). Specific details of how conditions were randomized were not provided, so all studies were rated as moderate in domain 1. Studies that assessed multiple conditions on the same day (eg, PAIN vs CTR) were considered to have potential carry-over effects and were rated as moderate in domain S (bias arising from period and carry-over effects). For domain 2, 2 studies were rated as moderate as it was not clear if participants were blinded to the conditions or not. In the final domain, 1 study provided muscle-onset timing data for BASE only[37] and 1 study

Table 1. Methodological Characteristics of Included Studies

STUDY	DESIGN AND CONDITIONS	N (F/M)	AGE (YEARS) MEAN ± SD	EXPERIMENTAL PAIN MODEL (COMPARISON)	BODY REGION STIMULATED (SIDE) SPECIFIC TISSUE	AVERAGE PAIN LEVEL (OUT OF 100) MEAN ± SD	TASK INVESTIGATED	OUTCOME DOMAIN	OUTCOME MEASUREMENT TOOL	BODY REGION/ MUSCLES ASSESSED
Ashton-Miller et al[45]	*RM* 1. CTR 2. PAIN	10 (0/10)	26.7 ± 7.5	PAIN: HSI CTR: ISO (HSI × ISO)	Cervical (left) SCM	VAS 25 ± 19*	Isometric cervical flexion	Muscle activity	Bipolar sEMG	Bilateral (C4): IHY SCM SPC ES
Bandholm et al[41]	*RM* 1. BASE 2. PAIN 3. POST	9 (NR)	27.7 range: 22 to 37	PAIN: HSI (BASE × HSI × POST)	Shoulder (right) SUP	VAS Isometric task: 32 ± 15 Dynamic task: 33 ± 18	Isometric shoulder abduction Dynamic shoulder abduction	Muscle activity	iEMG and bipolar sEMG	Right side: UTR LTR SA
Cagnie et al[46]	*RM* 1. BASE 2. PAIN	15 (8/7)	24.0 ± 3.2	PAIN: HSI (BASE × HSI)	Cervical (right) UTR	NRS 48 ± 11 (after rep 1 of 3)	Isometric cervical extension	Muscle activity	mfMRI	Bilateral (C2–C3 and C7–T1): MUL/SCE SSC (C2–C3) SPC
Cagnie et al[47]	*RM* 1. BASE 2. PAIN	14 (7/7)	23.3 ± 2.0	PAIN: HSI (BASE × HSI)	Cervical (right) UTR	VAS 56 ± 19 (after rep 1 of 3)	Cranio-cervical flexion	Muscle activity	mfMRI	Bilateral: LCA (C0–C1, C2–C3) LCO (C2–C3, C6–C7) SCM (C2–C3, C6–C7)
Castelein et al[48]	*RM* 1. BASE 2. PAIN	25 (16/9)	30.5 ± 12.5	PAIN: HSI (HSI × BASE)	Shoulder (dominant side) SUP	NRS 48 ± 19 (after set 1 of 3)	Dynamic shoulder abduction	Muscle activity	mfMRI	Dominant side: UTR MTR LTR SA
Christensen et al[37]	*CO* 1. BASE 2/5. PAIN/CTR 3. POST 4. BASE 2/5. PAIN/CTR 6. POST	25 (13/12)	M: 28.0 ± 5.4 F: 25.9 ± 3.8	PAIN: HSI (HSI × ISO, BASE × HSI × POST)	Cervical (side randomized) SPC	NR	Dynamic shoulder abduction	Muscle activity Muscle timing	Bipolar sEMG	Bilateral: UTR MTR LTR SA

Table 1 (*Continued*)

STUDY	DESIGN AND CONDITIONS	N (F/M)	AGE (YEARS) MEAN ± SD	EXPERIMENTAL PAIN MODEL (COMPARISON)	BODY REGION STIMULATED (SIDE) SPECIFIC TISSUE	AVERAGE PAIN LEVEL (OUT OF 100) MEAN ± SD	TASK INVESTIGATED	OUTCOME DOMAIN	OUTCOME MEASUREMENT TOOL	BODY REGION/ MUSCLES ASSESSED
Christensen et al[39]	*CO* 1. BASE 2/5. PAIN/CTR 3. POST 4. BASE 2/5. PAIN/CTR 6. POST	25 (13/12)	M: 24.3 ± 3.0 F: 24.4 ± 3.4	PAIN: HSI (HSI × ISO, BASE × HSI × POST)	Cervical (bilateral) SPC	NR	Dynamic shoulder abduction	Muscle activity	Bipolar sEMG	Bilateral: UTR MTR LTR SA
Dideriksen et al[49]	*RM* 1. BASE 2. CTR (cranial or caudal) 3. PAIN (cranial or caudal)	12 (6/6)	26.5 ± 5.1	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical (right) UTR (cranial or caudal)	NRS Cranial: 23 ± 22 Caudal: 25 ± 24*	Isometric shoulder abduction	Muscle activity EMG centroid coordinates Motor unit discharge rate	High-density sEMG	Right: UTR
Diederichsen et al[50]	*RM* 1. BASE 2. PAIN (SUP) 3. PAIN (subacromial)	11 (0/11)	24.9 ± 2.1	PAIN: HSI (BASE × HSI)	Shoulder (right) SUP Subacromial	VAS SUP: 29 ± 37 Subacromial: 22 ± 27*	Dynamic shoulder abduction	Muscle activity	iEMG and bipolar sEMG	Unilateral: UTR LTR SA
Dupuis et al[40]	*RM* 1. BASE 2. PAIN 3. POST	20 (10/10)	26.6 ± 3.8	PAIN: HSI (BASE × HSI, BASE × POST)	Shoulder (dominant side) Subacromial	NRS 46 ± 24	Multidirectional reaching task	Muscle activity Muscle timing	Bipolar sEMG	Right: UTR AD MD
Falla et al[51]	*CO* 1. BASE 2/3. CTR 2/3. PAIN	9 (4/5)	27.2 ± 4.4	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical (right) UTR	NRS 20 ± 15*	Dynamic shoulder flexion	Muscle activity	High-density sEMG and bipolar sEMG	Bilateral: SCM SPC UTR
Falla et al[52]	*RM* 1. BASE 2. CTR (SCM or SPC) 3. PAIN (SCM or SPC)†	14 (6/8)	26.3 ± 3.6	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical (side randomized) SCM or SPC	NRS SCM: 26 ± 14 SPC: 26 ± 14*	Isometric cervical flexion and extension	Muscle activity	High-density sEMG and bipolar sEMG	Bilateral: SCM SPC UTR
Falla et al[53]	*RM* 1. BASE 2. CTR 3. PAIN	18 (9/9)	M: 26.0 ± 4.3 F: 28.2 ± 10.0	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical (right) UTR	NRS M: 21 ± 10 F: 29 ± 20*	Isometric shoulder abduction	Muscle activity EMG centroid coordinates	High-density sEMG	Right: UTR

Table 1 (*Continued*)

STUDY	DESIGN AND CONDITIONS	N (F/M)	AGE (YEARS) MEAN ± SD	EXPERIMENTAL PAIN MODEL (COMPARISON)	BODY REGION STIMULATED (SIDE) SPECIFIC TISSUE	AVERAGE PAIN LEVEL (OUT OF 100) MEAN ± SD	TASK INVESTIGATED	OUTCOME DOMAIN	OUTCOME MEASUREMENT TOOL	BODY REGION/ MUSCLES ASSESSED
Falla et al[54]	*RM* 1. BASE 2. CTR 3. PAIN	10 (10/0)	40.9 ± 10.2	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical (right) UTR	NRS 29 ± 19*	Isometric shoulder abduction	Muscle activity EMG centroid coordinate	High-density sEMG	Right: UTR
Falla et al[42]	*RM* 1. BASE 2. CTR 3. PAIN 4. POST	10 (0/10)	26.2 ± 3.1	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI × POST)	Cervical (right) UTR	NRS 19 ± 19*	Box lifting task	Muscle activity EMG centroid coordinates	High-density sEMG	Right: UTR
Ge et al[43]	*CO* 1. BASE 2/3. CTR 2/3. PAIN 4. POST	19 (9/10)	M: 24 ± 3 F: 25 ± 1	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI × POST)	Cervical (bilateral) UTR	NR	Isometric shoulder abduction (short and sustained)	Muscle activity	Bipolar sEMG	Bilateral: UTR
Gizzi et al[38]	*CO* 1. BASE 2/3. CTR 2/3. PAIN 4. POST	8 (NR)	24.1 ± 1.9	PAIN: HSI CTR: ISO (BASE × HSI × POST)	Cervical (right) SPC	NRS 36 ± 7	Multiplanar head movements	Muscle activity Kinematics	Bipolar sEMG 3D motion capture system	Bilateral: SHYO SCM SCA SPC UTR LTR
Madeleine et al[55]	*RM* 1. BASE 2. PAIN	10 (0/20)	26.1 ± 2.6	PAIN: HSI (BASE × HSI)	Cervical (right) UTR	VAS 49 ± 20	Knife cutting task	Muscle activity Kinematics	Bipolar sEMG 3D motion capture system	Right: UTR
Madeleine et al[44]	*CO* 1. BASE 2/4. CTR 3. POST 1 2/4. PAIN 5. POST 2	10 (0/10)	23.9 ± 1.9	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI × POST)	Cervical (side randomized) UTR	VAS NR	Isometric shoulder abduction	Muscle activity EMG centroid coordinates	High-density sEMG	Right or left: UTR
Pasinato et al[36]	*CO* 1. BASE 2/3. CTR 2/3. PAIN	28 (0/28)	20.6 ± 2.0	PAIN: GI (GI × ISO, BASE × GI)	Orofacial (side randomized) MA	VAS 34 ± 20*	Chewing task	Muscle activity	Bipolar sEMG	Bilateral: MA SCM

Table 1 (*Continued*)

STUDY	*DESIGN AND CONDITIONS*	*N (F/M)*	*AGE (YEARS) MEAN ± SD*	*EXPERIMENTAL PAIN MODEL (COMPARISON)*	*BODY REGION STIMULATED (SIDE) SPECIFIC TISSUE*	*AVERAGE PAIN LEVEL (OUT OF 100) MEAN ± SD*	*TASK INVESTIGATED*	*OUTCOME DOMAIN*	*OUTCOME MEASUREMENT TOOL*	*BODY REGION/ MUSCLES ASSESSED*
Qu et al[56]	*CO* 1. BASE 2/4. CTR 3. BASE 2/4. PAIN†	15 (4/11)	27.4 ± 6.5	PAIN: HSI CTR: ISO (HSI × ISO, BASE × HSI)	Cervical C4/C5 interspinous ligament	VAS 22 ± 15*	Cervical flexion and extension	Kinematics	Videofluoroscope system	C0 to C7
Qu et al[57]	*RM* 1. BASE 2. PAIN (MUL or UTR) 3. BASE 4. PAIN (MUL or UTR)†	15 (6/9)	25.1 ± 4.7	PAIN: HSI (BASE × HSI)	Cervical (right) MUL or UTR	VAS MUL: 34 ± 19 UTR: 28 ± 18	Cervical flexion and extension	Kinematics	Videofluoroscope system	C0 to C7
Samani et al[58]	*RM* 1. BASE 2. PAIN	12 (0/12)	22 ± 3	PAIN: HSI (BASE × HSI)	Cervical (right) UTR	VAS 49 ± 15	Computer mouse task	Muscle activity	Bipolar sEMG	Right: TR (4 regions)
Samani et al[59]	*RM* 1. BASE 2. PAIN	12 (0/12)	24.3 ± 3.2	PAIN: HSI (BASE × HSI)	Cervical (right) UTR	VAS 55 ± 5	Computer mouse task	Muscle activity	Bipolar sEMG	Bilateral: UTR
Sole et al[60]	*RM* 1/2. BASE 1/2. PAIN	20 (10/10)	22.3 (SD NR)	PAIN: HSI (BASE × HSI)	Shoulder (right) Subacromial space	VAS 50 ± 27	Dynamic shoulder abduction	Muscle activity	iEMG and bipolar sEMG	Right: UTR LTR SA
Svensson et al[35]	*CO* 1. BASE 2/4. PAIN SP/MA 3. POST 2/4. CTR MA/SP 5. BASE 6/8. PAIN MA/SP 7. POST 6/8. CTR SP/MA†	19 (0/19)	26.4 (SD NR)	PAIN: GI CTR: ISO (HSI × ISO, BASE × HSI × POST)	Orofacial/ cervical (right) MA SP	VAS MA: 45 ± 1 SP: 32 ± 1	Head movement and jaw clench	Muscle activity	iEMG and bipolar sEMG	Bilateral: MA Right: SCM SP

Table 1 (*Continued*)

STUDY	DESIGN AND CONDITIONS	N (F/M)	AGE (YEARS) MEAN ± SD	EXPERIMENTAL PAIN MODEL (COMPARISON)	BODY REGION STIMULATED (SIDE) SPECIFIC TISSUE	AVERAGE PAIN LEVEL (OUT OF 100) MEAN ± SD	TASK INVESTIGATED	OUTCOME DOMAIN	OUTCOME MEASUREMENT TOOL	BODY REGION/ MUSCLES ASSESSED
Wang et al[61]	*RM* 1. BASE 2. PAIN	30 (18/12)	M: 37.8 ± 2.1 F: 35.8 ± 4.1	PAIN: HSI (BASE × HSI)	Cervical (right) MUL	VAS NR	Repositioning after cervical flexion	Kinematics	Videofluoroscope system	C0 to C7
Wiesinger et al[62]	*RM* 1. BASE 2. PAIN	38 (22/16)	Range: M: 20 to 29 F: 19 to 33	PAIN: HSI (BASE × HSI)	Orofacial (side randomized) MA	VAS: M: 37 ± 20 F: 44 ± 17*	Jaw opening-closing movement	Kinematics	3D motion capture system	Head and jaw
Wiesinger et al[63]	*RM* 1. BASE 2. PAIN	21 (0/21)	Range: 20 to 34	PAIN: HSI (BASE × HSI)	Orofacial (side randomized) MA	VAS: 36 ± 19*	Jaw opening-closing movement	Kinematics	3D motion capture system	Head and jaw

Abbreviation: 3D, three dimensional; NR, not reported; F/M, Female/Male; SD, standard deviation; SUP, supraspinatus.
NOTE. *Design*: RM, repeated measures study; CO, crossover randomized controlled trial. *Conditions*: CTR, control; BASE, baseline. *Pain models and control*: HSI, hypertonic saline injection; ISO, isotonic saline injection; CAP, capsaicin; GI, glutamate injection. *Muscles*: AD, anterior deltoid; MD, middle deltoid; INFRA, infraspinatus; ES, erector spinae; IHY, infrahyoid; LCA, longus capitis; LCO, longus colli; LTR, lower trapezius; MA, Masseter; MTR, medial trapezius; MUL, multifidus; SA, serratus anterior; SCA, anterior scalenus; SCE, semispinalis cervicis; SCM, sternocleidomastoid; SHYO, sternohyoideus; SP, splenius; SPC, splenius capitis; SSC, semispinalis capitis; TR, trapezius; UTR, upper trapezius. *Pain rating scale*: VAS, visual analogue scale; NRS, numerical rating scale. *Outcome tool*: sEMG, surface EMG; iEMG, intramuscular EMG; mfMRI, muscle functional MRI.
*Values estimated from figures using WebPlotDigitizer.
†Conditions repeated on separate days and randomized.

compared PAIN with BASE only, although presented data for BASE, CTR, and PAIN,[51] and was therefore rated as moderate.

Results of Syntheses

Supplementary File 2 contains a table that provides all the effect sizes extracted from each study.

Muscle Activation

Upper trapezius. In the 14 studies that assessed EMG amplitude of the upper trapezius, pain was induced in 15 regions, with 1 study assessing pain both in the supraspinatus and subacromial space.[50] Pain was induced in the upper trapezius (N = 7), splenius capitis (N = 2), subacromial space (N = 3), and supraspinatus (N = 3) compared with BASE, during shoulder flexion and abduction tasks (Fig 4). Meta-analyses were performed using all 14 studies and grouped based on the location of nociceptive stimulus. Random effects models revealed a significant reduction of upper trapezius EMG amplitude during PAIN induced in the upper trapezius (SMD: −.90, 95% confidence interval: [−1.29; −.51], $P < .001$, $I^2 = 11\%$; Fig 4A), splenius capitis (−1.03 [−1.44; −.63], $P < .001$, $I^2 = 0\%$; Fig 4B), and supraspinatus (−.63 [−1.25; −.01], $P = .045$, $I^2 = 49\%$; Fig 4C). Similar pooled mean effects were observed for both upper trapezius and splenius capitis locations when PAIN was compared with CTR (Supplementary Fig 1). In contrast, no overall effect on EMG amplitude was observed during pain induced in the subacromial space (.22 [−.16; .60], $P = .25$, $I^2 = 28\%$; Fig 4D). However, although the level of heterogeneity can be considered as not important ($I^2 < 40\%$[24]) in most cases, heterogeneity was larger when pain was induced in the subacromial space ($I^2 = 28\%$ [0%; 92%]) and supraspinatus ($I^2 = 49\%$ [0%; 85%]) compared with upper trapezius ($I^2 = 11\%$ [0%; 74%]) and splenius capitis ($I^2 = 0\%$).

The results comparing upper trapezius EMG amplitude during heterogeneous tasks are provided in Supplementary Fig 2. Overall, no effect of PAIN on upper trapezius EMG amplitude was observed during manual dexterity tasks,[55,58,59] however, some effects were noted during cervical flexion and extension tasks. Specifically, when pain was induced in the sternocleidomastoid, 1 study[52] reported lower EMG amplitude of the upper trapezius during PAIN compared with BASE (−1.13 [−1.92; −.34]) and CTR (−1.04 [−1.79; −.28]) during a cervical flexion task performed at 55 to 60% of maximal voluntary contraction (MVC) (Supplementary Fig 2). Conversely, when pain was induced in the splenius capitis, the same study[52] reported an increase in upper trapezius EMG amplitude during a cervical extension task performed at 50 to 60% MVC during PAIN, compared with BASE (.81 [.13; 1.48]).

Five studies investigated the redistribution of activation between regions within the upper trapezius during PAIN compared with BASE. Meta-analyses of the x (mediolateral direction) and y (cranio-caudal direction) centroid coordinates of the EMG amplitude distribution recorded with high-density surface EMG demonstrated that PAIN induced

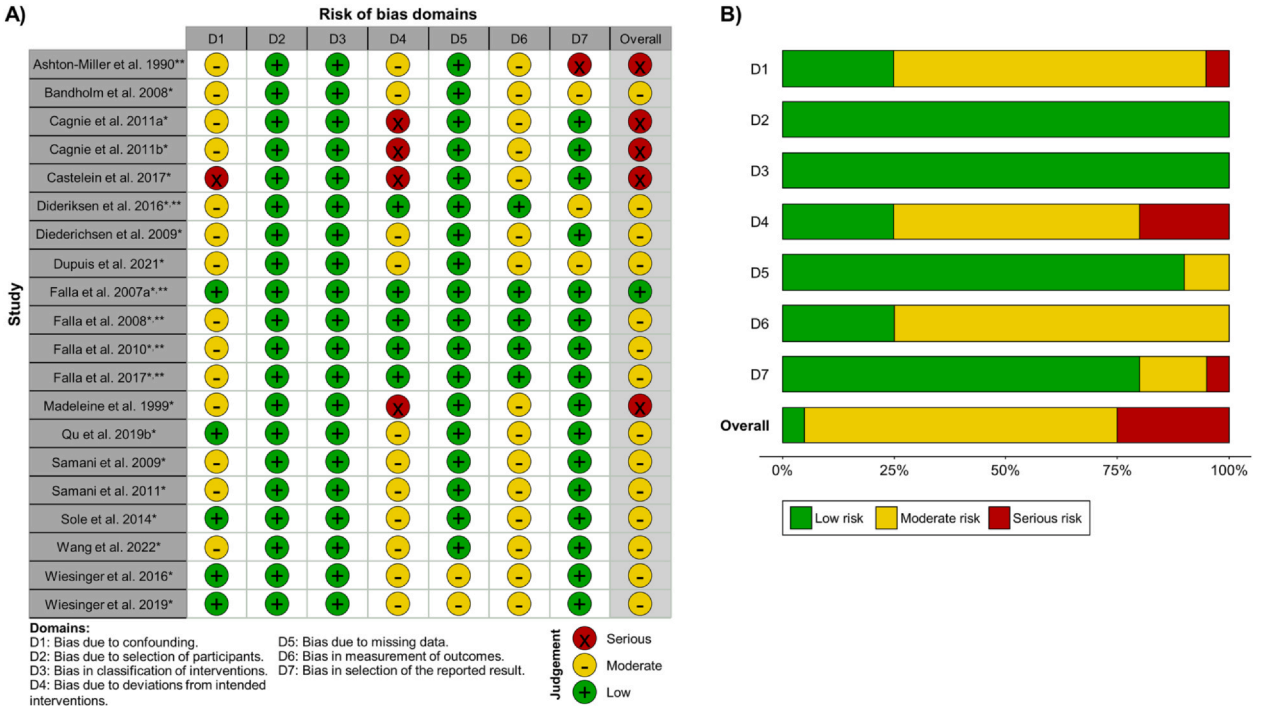

Figure 2. Risk-of-bias assessment of included studies with a repeated measures design using ROBINS-I tool. For each domain, risk of bias is presented for each study (**A**) and overall (**B**). * Indicates studies that compared pain versus baseline. ** Indicates studies that compared pain versus isotonic. Note that 5 studies included both comparisons. For all of them, the overall risk of bias was the same regardless of the comparison. ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions.

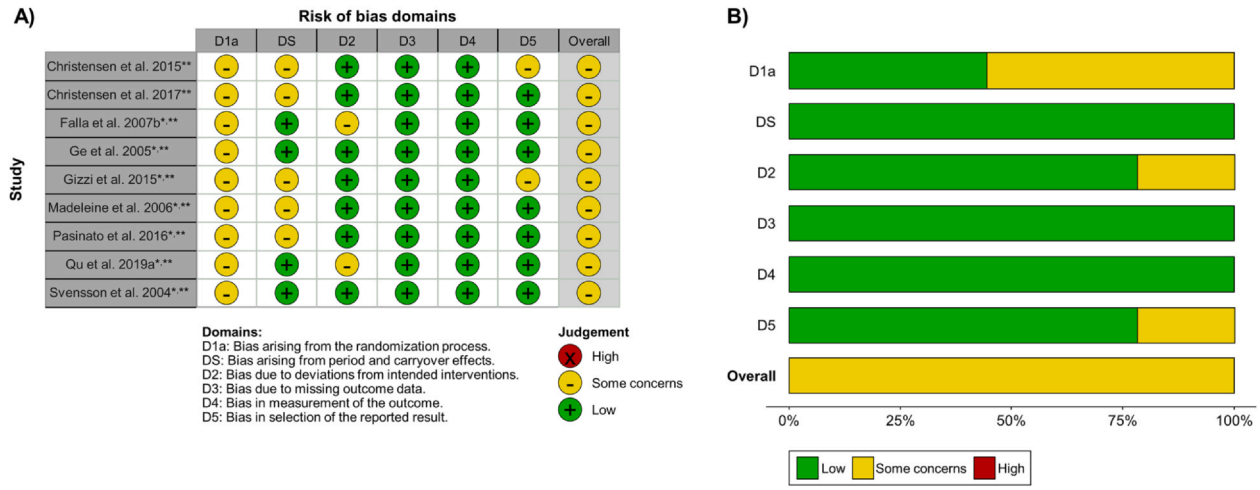

Figure 3. Risk-of-bias assessment of included studies with a crossover randomized design using RoB2 tool. For each domain, risk of bias is presented for each study (**A**) and overall (**B**). * Indicates studies that compared pain versus baseline. ** Indicates studies that compared pain versus isotonic. Note that 7 studies included both comparisons. For all of them, the overall risk of bias was the same regardless of the comparison.

a shift of the centroid toward the caudal region of the upper trapezius (.96 [.58; 1.34], $P < .001$, $I^2 = 0\%$), but no change was observed for the x-axis coordinate (.11 [–.22; .42], $P = .49$, $I^2 = 0\%$ [0%; 79%]; Fig 5A). Similar results were observed when PAIN was compared with CTR (Supplementary Fig 3).

Only 1 study assessed upper trapezius motor unit discharge rates[49] in response to pain induced in the cranial and caudal region of the muscle. In this review, only results when pain was induced in the most cranial region of the muscle were considered. Cranial motor unit (N = 14) discharge rates decreased (SMD: –1.08 to –1.54), whereas the discharge rates of caudal motor units (N = 8) remained the same (Fig 5B).

Neck flexor muscles. EMG amplitude of the sternocleidomastoid during PAIN compared with BASE was assessed in 6 studies during a variety of cervical and jaw movement tasks. Given the range of tasks assessed and the different locations of nociceptive stimulus, meta-analyses were not performed, but data from 5 studies are presented with a forest plot in Fig 6. We did

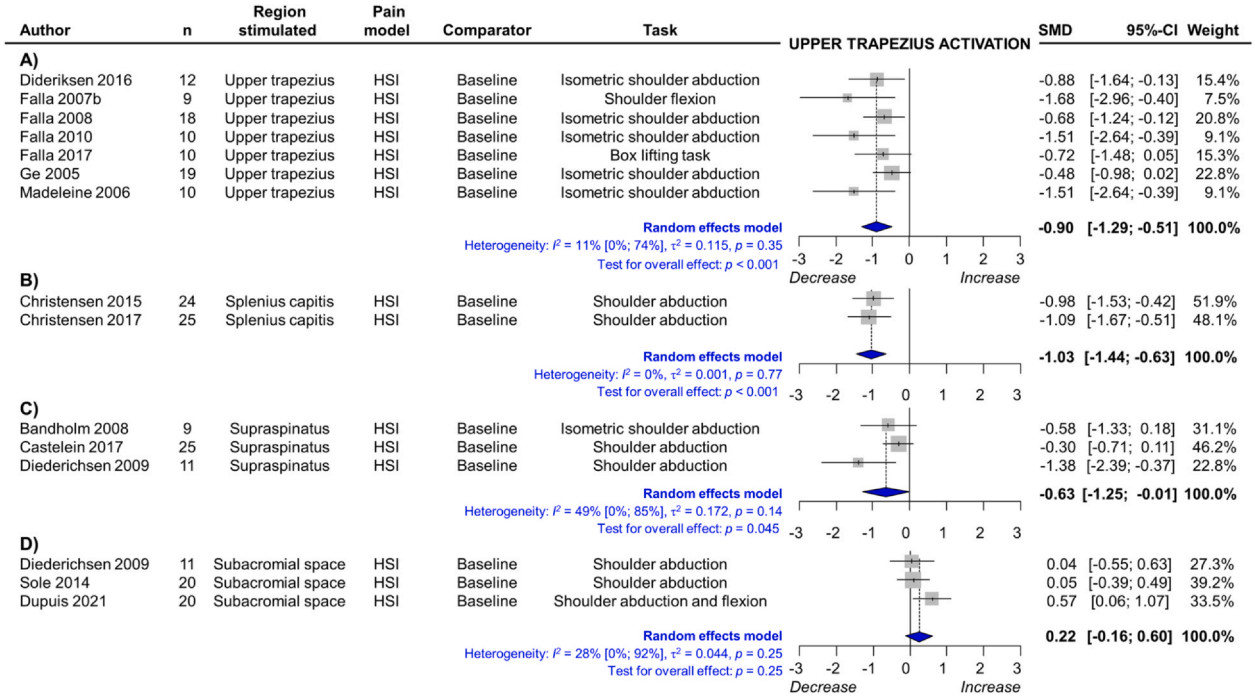

Figure 4. Forest plot with meta-analysis on upper trapezius activation during shoulder flexion and abduction tasks, after HSI in the upper trapezius (**A**), splenius capitis (**B**), supraspinatus (**C**), and subacromial space (**D**) (random-effect model). SMD and 95% confidence interval (95% CI) are reported. Muscle activation represents EMG amplitude recorded with surface EMG. Pain model: hypertonic saline injection (HSI). EMG, eletromyography.

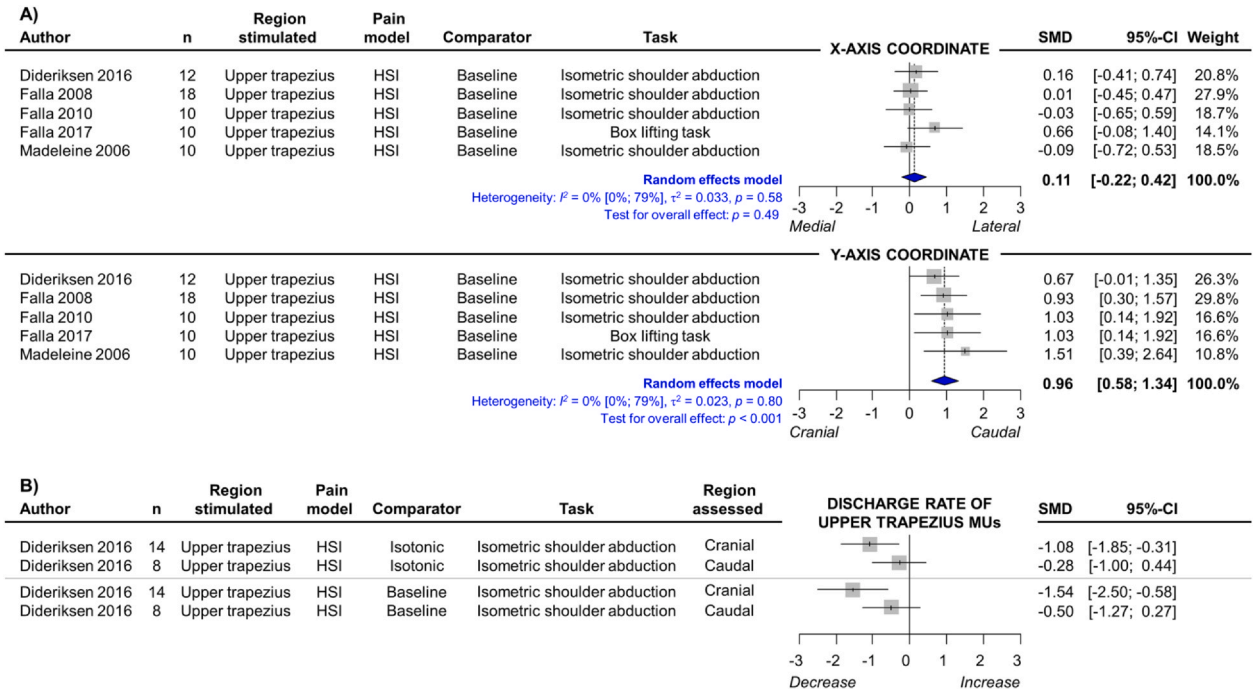

Figure 5. Forest plot with meta-analysis on EMG centroid coordinates of the upper trapezius (**A**) and forest plot without meta-analysis on discharge rate of upper trapezius motor units (**B**). SMD and 95% confidence interval (95% CI) are reported. Centroid coordinates and discharge rates recorded with high-density surface EMG. The n in (**B**) indicates the number of motor units assessed. Pain model: hypertonic saline injection (HSI). EMG, eletromyography.

not present the effect sizes of 1 study,[45] because the standard deviation of the sternocleidomastoid muscle activity and the results for PAIN compared with CTR for other muscles assessed were not reported, so it was not possible to extract its summary data. Overall, while several studies reported no effect of PAIN on sternocleidomastoid EMG amplitude, 2 studies demonstrated a decrease of sternocleidomastoid EMG amplitude during cervical flexion at 25 to 60% of MVC[52] (−1.13 [−1.92; −.34]) and cervical rotation[35] (−.61 [−1.14;

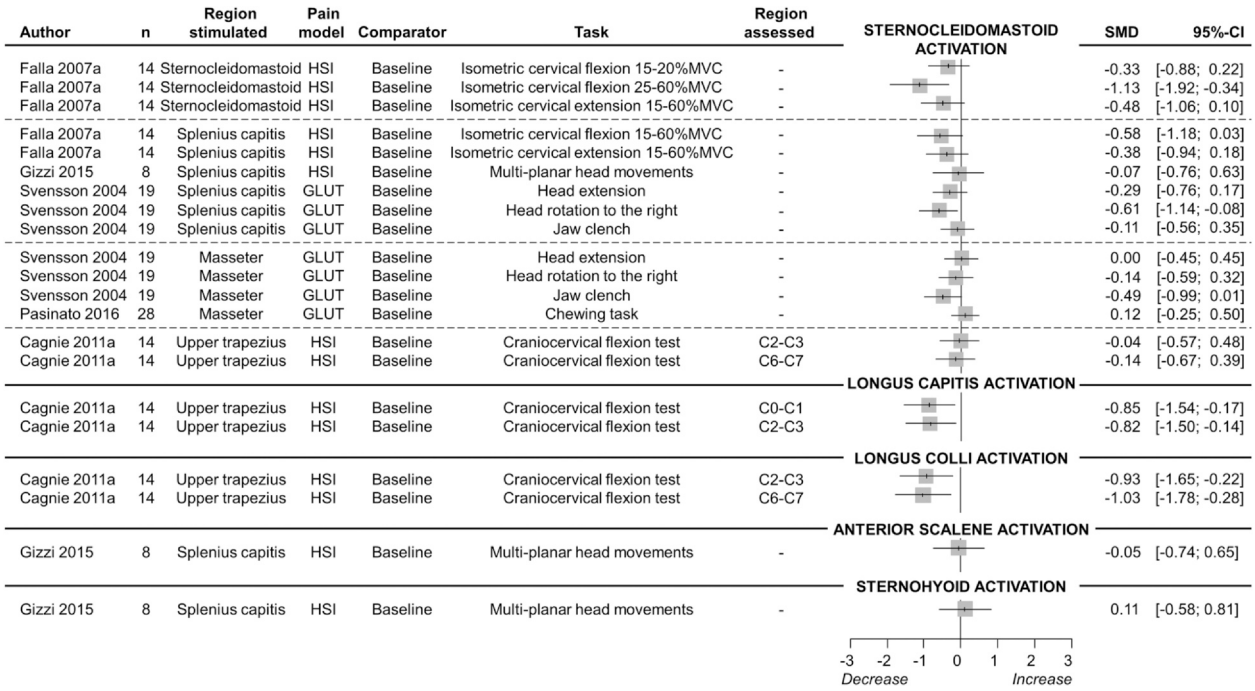

Figure 6. Forest plot without meta-analysis of cervical flexor activation during cervical and head tasks. SMD and 95% confidence interval (95% CI) are reported. Muscle activation represents EMG amplitude recorded with surface EMG. Pain model: hypertonic saline injection (HSI); glutamate (GLUT). EMG, eletromyography.

–.08]) during PAIN induced in the sternocleidomastoid or splenius capitis. In addition, 1 study[35] demonstrated a trend for a decrease in sternocleidomastoid EMG amplitude during PAIN induced in the masseter during a jaw clench task (–.49 [–.99; .01]). Conversely, Ashton-Miller et al[45] found a significant increase in sternocleidomastoid EMG amplitude at rest during PAIN induced in the sternocleidomastoid, however, no changes were observed during an isometric cervical flexion task. No other changes in sternocleidomastoid EMG amplitude during PAIN compared with BASE were found. Comparison of sternocleidomastoid EMG amplitude during CTR compared with PAIN is presented in Supplementary Fig 4A and demonstrated similar effects when compared with BASE.

A decrease in EMG amplitude of the longus capitis and longus colli during PAIN was reported, however, this was only assessed in 1 study with serious risk of bias.[47] Conversely, no changes in anterior scalene,[38,41] sternohyoid,[38] and infrahyoid[45] EMG amplitude were reported during PAIN induced to the splenius capitis and sternocleidomastoid, respectively.

Neck extensor muscles. Four studies investigated the effect of glutamate (N = 1) and hypertonic saline injection (N = 3) on splenius capitis EMG amplitude during cervical isometric and dynamic movements and jaw clenching tasks, compared with BASE. The location of the nociceptive stimulus varied between studies, thus, forest plots without meta-analyses are shown (Fig 7). Two studies demonstrated a decrease in EMG amplitude of the splenius capitis during cervical extension performed at 20 to 60% MVC during PAIN induced in the upper trapezius[46] (–.80 [–1.44; –.15]), sternocleidomastoid[52] (–.81 [–1.48; –.13]), or splenius capitis[52] (–.81 [–1.48; –.13]). When different muscle regions were considered, Cagnie et al[46] only reported a decrease in splenius capitis EMG amplitude at the C7 to T1 region and no change at C2 to C3. With respect to contraction intensity, Falla et al[52] only found changes in splenius capitis EMG amplitude at 40 to 60% MVC during PAIN and no changes were found at lower % MVC (Fig 7). No other changes in EMG amplitude were observed during the other cervical and jaw tasks (Fig 7). Comparison of splenius capitis EMG amplitude during CTR compared with PAIN is presented in Supplementary Fig 4B, and no changes in EMG amplitude were observed.[35,45,52]

A trend for a decrease in multifidus/semispinalis cervicis EMG amplitude was reported in the C7 to T1 region (–.57 [–1.15; .01]), however this was based on 1 study with a serious risk of bias.[46] One study with a serious risk of bias also reported no differences in erector spinae EMG amplitude at the C4 level during PAIN compared with CTR in the sternocleidomastoid.[45]

Summary of findings and certainty of evidence. Overall, there is moderate quality of evidence to support that experimentally induced pain results in a reduced activation of the upper trapezius muscle during shoulder flexion/abduction tasks, with the location of nociceptive stimulation explaining some inconsistency across studies (Table 2). Moreover, there is moderate quality of evidence indicating that experimentally induced pain induces a caudal redistribution of activation within the upper trapezius muscle during shoulder flexion/abduction tasks, but no change in the mediolateral distribution of activation (Table 3). Despite inconsistency potentially

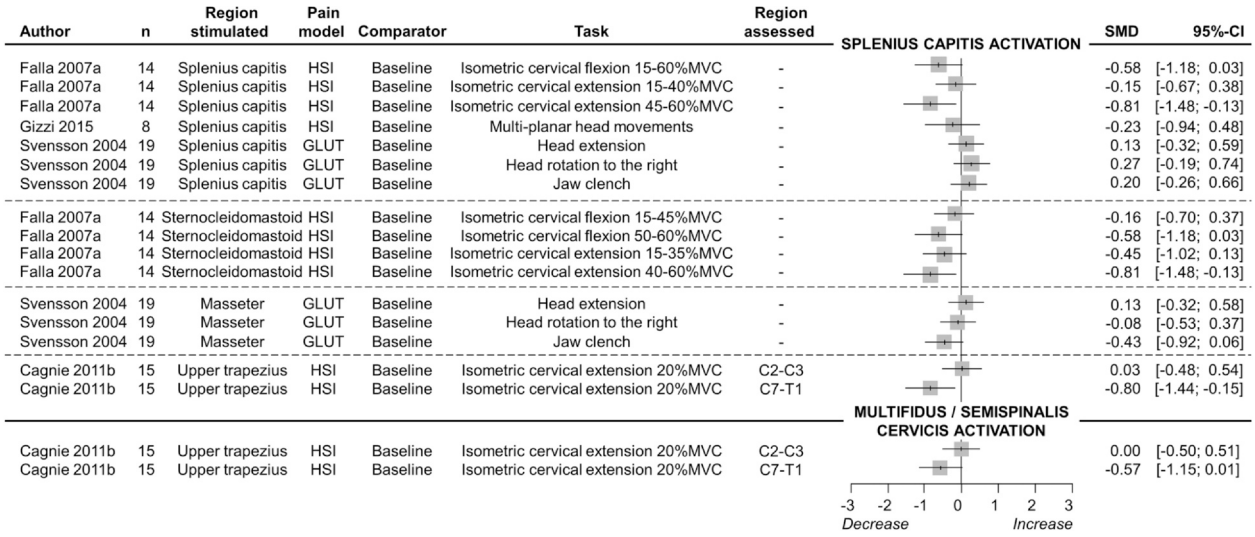

Figure 7. Forest plot without meta-analysis of cervical extensor muscle activation during cervical and head tasks. SMD and 95% confidence interval (95% CI) are reported. Muscle activation represents EMG amplitude recorded with surface EMG. Pain model: hypertonic saline injection (HSI); glutamate (GLUT). EMG, eletromyography.

introduced by the task performed and the intensity of the task, low quality of evidence supports the absence of changes of upper trapezius muscle activation during manual dexterity and isometric/dynamic tasks of cervical flexion/extension (Table 2). Only 1 study[52] showed reduced and increased activation of the upper trapezius when pain was induced in the sternocleidomastoid and splenius capitis, respectively, but the evidence is too limited to draw meaningful conclusions. Moreover, limited evidence supports a pain-induced decrease in the discharge rate of cranial, but not caudal motor units of the upper trapezius during an isometric shoulder abduction task (Table 3). Low quality of evidence supports no effect of experimental pain on neck flexor and extensor muscle activation during cervical and jaw tasks (Table 2). However, there was inconsistency across studies explained by the task performed, the intensity of the task, the experimental model, and the region stimulated.

Muscle Timing

One study investigated the effect of pain on the onset of upper trapezius activity during a dynamic shoulder abduction task.[37] Although the summary data were not reported in the study, no differences were found in the onset time of upper trapezius activation during PAIN compared with CTR and BASE. Another study[40] investigated the effect of pain induced in the upper trapezius during a multidirectional reaching task on the mean time to reach the peak EMG amplitude and did not identify significant changes during PAIN compared with BASE (.44 [–.04; .92]).

Cervical Kinematics

Cervical kinematics changes during pain induced in the cervical (N = 5) and orofacial (N = 2) regions were assessed in 7 studies during a variety of tasks.[38,55-57,62,63] Given the range of different tasks, the locations of the nociceptive stimulus, and outcomes evaluated, meta-analyses were not performed, and the results are presented narratively. Overall, pain induced in splenius capitis did not affect the kinematics of multiplanar head movements.[38] In contrast, the work cycle duration during a knife cutting task[55] and the head movement amplitude during a jaw open-close movement[62,63] increased during PAIN in the upper trapezius and masseter muscles, respectively. When the total motion of cervical joints was assessed during PAIN induced in the C4/C5 interspinous ligament[56] and upper trapezius/multifidus muscles,[57] the results varied depending on the cervical joint and movement phase evaluated. Moreover, the average absolute error of cervical joint repositioning following active cervical flexion increased during PAIN induced in the cervical multifidus muscle.[61] A summary of findings on the cervical kinematics results is provided in Table 4 and, overall, the large heterogeneity in the outcome measurements across studies does not allow to draw meaningful conclusions.

Post Pain Condition Results

Seven studies evaluated the upper trapezius EMG amplitude during POST, when participants performed shoulder flexion and abduction tasks. The pooled mean effect of 3 studies that induced pain in the upper trapezius[42–44] revealed that upper trapezius activation during POST was not different from BASE (–.35 [–.76; .06], $P = .091$, $I^2 = 4\%$ [0%: 90%]; Fig 8A). The 2 studies that induced pain in the splenius capitis[37,39] also demonstrated no differences in upper trapezius EMG amplitude compared with BASE (.22 [–.07; .51], $P = .13$, $I^2 = 0\%$; Fig 8B). When the location of the nociceptive stimulus was the supraspinatus, Bandholm et al[41] reported no differences in upper trapezius activation between POST and BASE (–.19 [–.85; .48]). One study investigated upper trapezius EMG amplitude during POST when the location of the nociceptive stimulus was

Table 2. Effects of Experimentally Induced Pain in the Cervical, Shoulder, or Orofacial Regions on Cervical Muscle Activity—Summary of Findings and Certainty of Evidence (GRADE)

Region stimulated - task - n studies (n part)	*Muscle activation changes*			*Findings and certainty of evidence*	*Comments*
	Decreased	*No change*	*Increased*		
Upper trapezius muscle					
Upper trapezius/splenius capitis/ subacromial space/supraspinatus - *Shoulder abduction and flexion* - 14 (222)	Dideriksen et al.[49] Falla et al.[51] Falla et al.[53] Falla et al.[54] Madeleine et al.[44] Christensen et al.[37] Christensen et al.[39] Diederichsen et al.[50]	Diederichsen et al.[50] Sole et al.[60] Bandholm et al.[41] Castelein et al.[48] Falla et al.[42] Ge et al.[43]	Dupuis et al.[40]	Reduced activation of the upper trapezius during shoulder flexion/abduction tasks. MODERATE quality of evidence.[c]	Heterogeneity explained by the location of nociceptive stimuli. Consistent findings when the cervical region is stimulated and heterogeneity when the shoulder region is stimulated.
Upper trapezius/splenius capitis/ sternocleidomastoid - *Manual dexterity tasks and cervical flexion/extension* - 5 (56)	Falla[52]	Samani et al.[58] Samani et al.[59] Falla et al.[52] Gizzi et al.[38] Madeleine et al.[55]	Falla et al.[52]	No change on upper trapezius activation during manual dexterity, cervical flexion/ extension tasks. LOW quality of evidence.[b,c]	Heterogeneity explained by the location of nociceptive stimuli, the task performed, and the intensity of the task.
Neck flexor muscles					
Upper trapezius/splenius capitis/ sternocleidomastoid/masseter - *Cervical movement and jaw clench* - 6 (91)	Falla et al.[52] Svensson et al.[35] Cagnie et al.[47]	Falla et al.[52] Gizzi et al.[38] Svensson et al.[35] Pasinato et al.[36] Cagnie et al.[47] Gizzi et al.[38]		No change on cervical flexor activation during cervical and jaw tasks. LOW quality of evidence.[b,c]	Heterogeneity explained by the location of nociceptive stimuli, the task performed, the muscle assessed, and the intensity of the task.
Neck extensor muscles					
Upper trapezius/splenius capitis/ sternocleidomastoid/masseter - *Cervical movement and jaw clench* - 4 (56)	Falla et al.[52] Cagnie et al.[46]	Falla et al.[52] Gizzi et al.[38] Svensson et al.[35] Cagnie et al.[46]		No change on cervical extensor activation during cervical and jaw tasks. LOW quality of evidence.[b,c]	Heterogeneity explained by the location of nociceptive stimuli, the task performed, the muscle assessed, and the intensity of the task.

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
NOTE. Certainty of evidence rated accordingly with GRADE (high, moderate, low, and very low). Reasons for rating down the quality of evidence: [a]study limitation (risk of bias); [b]publication bias; [c]imprecision; [d]inconsistency; [e]indirectness.

Table 3. Effects of experimentally induced pain in the upper trapezius muscle on redistribution of activity within upper trapezius and motor units discharge rates of upper trapezius - Summary of findings and certainty of evidence (GRADE).

Region stimulated *- Task* *- N studies (n part)*	*Upper trapezius redistribution of activity on the medial-lateral axis*			*Findings & certainty of evidence*	*Comments*
	Medial shift	*No changes*	*Lateral shift*		
Upper trapezius *- Shoulder abduction and flexion* - 5 (60)		Dideriksen[49] Falla[53] Falla[54] Falla[52] Madeleine[44]		No change in the redistribution of upper trapezius activation in the medial-lateral axis. **MODERATE** quality of evidence.[b]	Most of the evidence is from the same research group.
	Upper trapezius redistribution of activity on the cranio-caudal axis			**Findings & certainty of evidence**	**Comments**
	Cranial shift	*No changes*	*Caudal shift*		
Upper trapezius *- Shoulder abduction and flexion* - 5 (60)			Dideriksen[49] Falla[53] Falla[54] Falla[52] Madeleine[44]	Redistribution of activation towards the caudal region of the upper trapezius. **MODERATE** quality of evidence.[b]	Most of the evidence is from the same research group.
	Changes in discharge rate of upper trapezius motor units			**Findings & certainty of evidence**	**Comments**
	Decreased	*No change*	*Increased*		
Upper trapezius *- Shoulder abduction* - 1 (12)	Dideriksen[49] [cranial motor units]	Dideriksen[49] [caudal motor units]		Decrease in motor units' discharge rate depending of the upper trapezius region assessed. **LIMITED** evidence.	

Certainty of evidence rated accordingly with GRADE (high, moderate, low, very low). Reasons for rating down the quality of evidence: [a] Study limitation (risk of bias); [b] Publication bias; [c] Imprecision; [d] Inconsistency; [e] Indirectness.

Table 4. Main Findings and Quality of Evidence of the Effects of Experimentally Induced Pain in the Cervical Region on Kinematics

STUDY	N	COMPARISON	BODY REGION STIMULATED	TASK INVESTIGATED	OVERALL RISK OF BIAS	RESULTS	MAIN FINDINGS AND CERTAINTY OF EVIDENCE	COMMENTS
Gizzi et al[38]	8	HSI × ISO HSI × BASE	Splenius capitis	Multiplanar head movements	Some concerns	= Movement time = Distance traveled = Time to peak velocity = Maximal velocity	Inconsistent and limited evidence.	The large heterogeneity in the outcome measurements across studies do not allow to draw meaningful conclusions about the effects of experimentally induced pain in the cervical region on kinematics.
Madeleine et al[55]	10	HSI × BASE	Upper trapezius	Knife cutting task	Serious	↑ Work cycle duration		
Qu et al[56]	15	HSI × ISO HSI × BASE	C4/C5 interspinous ligament	Cervical flexion and extension	Some concerns	↑ Total C0/C1 motion during first-half range of extension ↓ Total C0/C1 and C2/C3 motion during second-half range of extension = Total C3/C4, C4/C5, C5/C6, and C6/C7 motion during extension = Total motion during flexion for all cervical joints		
Qu et al[57]	15	HSI × BASE	Upper trapezius or multifidus	Cervical flexion and extension	Moderate	↓ Total C3/C4 and C5/C6 motion during first-half range of flexion ↑ Total C1/C2, C3/C4, and ↓ total C2/C3 motion during second-half range of flexion = Total C4/C5 motion during flexion = Total motion during extension for all cervical joints		
Wang et al[61]	30	HSI × BASE	Multifidus	Repositioning after cervical flexion	Moderate	↑ Average absolute error of cervical joint repositioning ↑ Absolute error of C4/C5 repositioning = Absolute error of C0/C1, C1/C2, C2/C3, C3/C4, C5/C6, and C6/C7 repositioning		
Wiesinger et al[62]	38	HSI × BASE	Masseter	Jaw opening-close movement	Moderate	↑ Initial head extension ↑ Head movement amplitude		
Wiesinger et al[63]	21	HSI × BASE	Masseter	Jaw opening-close movement	Moderate	↑ Head movement amplitude		

Abbreviations: HSI, hypertonic saline injection; ISO, isotonic saline injection.

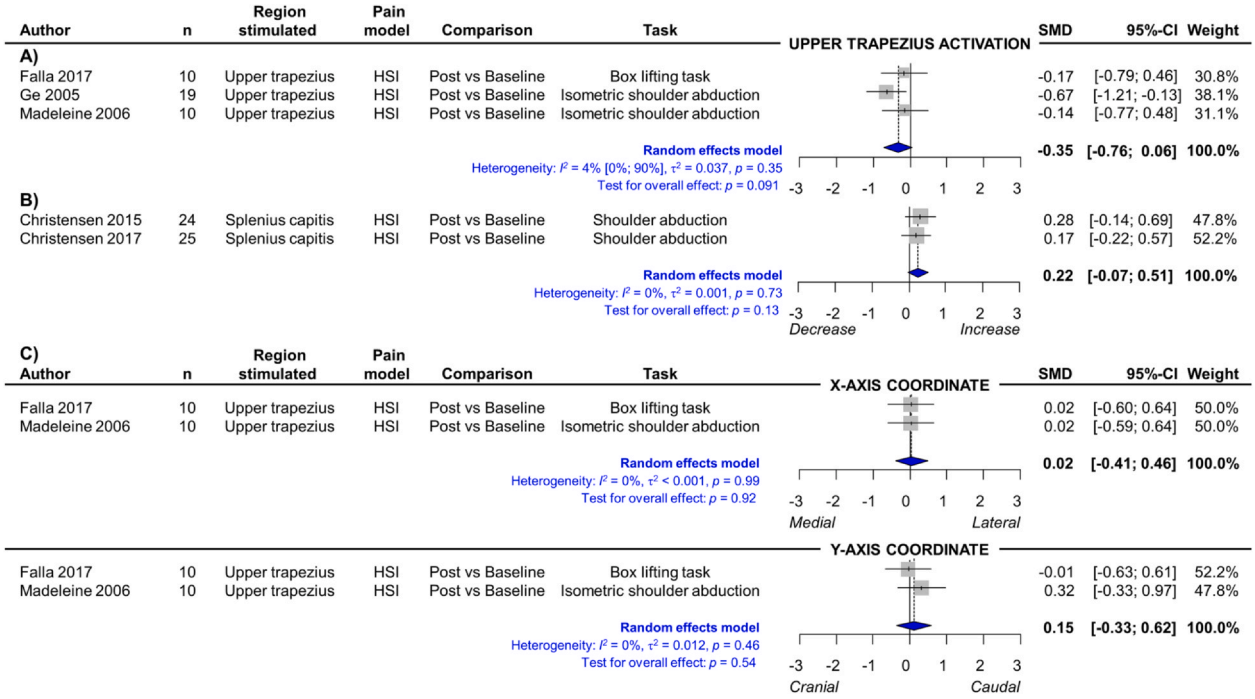

Figure 8. Forest plot with meta-analysis on EMG activity of the upper trapezius (**A** and **B**) and EMG centroid coordinates of the upper trapezius (**C**) when comparing post pain with baseline. Pain was induced in the upper trapezius (**A and C**) and splenius capitis (**B**). SMD and 95% confidence interval (95% CI) are reported. Centroid coordinates recorded with high-density surface EMG. Pain model: hypertonic saline injection (HSI). EMG, eletromyography.

the subacromial space[40] and found that there was no difference with BASE (–.02 [–.46; .42]).

Only 1 study assessed EMG amplitude of the sternocleidomastoid and splenius capitis muscles during POST when pain was induced either in the masseter or splenius capitis.[35] The authors demonstrated no difference in the sternocleidomastoid activity POST compared with BASE (.05 [–.40; .50]), when participants were asked to maximally rotate their heads to the right. Additionally, no differences were found in EMG amplitude of the splenius and sternocleidomastoid for other conditions (maximal neck extension and jaw clench) when pain was induced in the masseter or splenius capitis muscles.

Two studies compared the centroid coordinates of the upper trapezius EMG amplitude map during POST compared with BASE when pain was induced in the upper trapezius.[42,44] The pooled mean effects indicated no significant differences in either x-axis or y-axis (Fig 8C).

Only 1 study assessed upper trapezius muscle timing during POST when pain was induced in the upper trapezius.[35] The authors showed no differences in the mean time to reach the peak EMG amplitude during POST compared with BASE (–.09 [–.53; .35]).

One study compared cervical kinematics during POST compared with BASE[38] and found no differences in the movement time, distance traveled, time to peak velocity, and maximal velocity during multiplanar head movements.

Discussion

This systematic review demonstrates that experimental pain induced in the neck, shoulder, and orofacial regions of healthy individuals results in decreased or unchanged muscle activation. Specifically, meta-analyses showed reduced upper trapezius activation during upper limb movements when pain was induced in the upper trapezius, splenius capitis, and supraspinatus. A caudal shift of activation within the upper trapezius was also observed when pain was induced in the upper trapezius. None of these adaptations persisted after pain had resolved. The other neuromuscular and kinematic features examined showed limited or conflicting evidence. These findings further our understanding of how the central nervous system adapts to acute neck and shoulder pain.

Regardless of muscle, pain location, and task, in most cases, experimental pain resulted in a decrease or no change of muscle activation, and very infrequently resulted in increased muscle activation. In contrast, when pain is experimentally induced in the lumbar region, muscle activation sometimes increases with pain.[23] These differences suggest that the central nervous system may adopt different strategies in response to experimental spinal pain induced in the lumbar or cervical region, possibly because of their different structure and function. For instance, increased muscle activation during lumbar pain may be a strategy to limit further injury by increasing stiffness and limiting movement. Instead, since activation of the trapezius increases during shoulder flexion and abduction,[64–66] a reduced upper trapezius activity when pain is induced in the trapezius or neck muscles might be an attempt to unload painful tissues.[16,67] Since reduced upper trapezius activation was observed during shoulder flexion-abduction tasks, but not during manual dexterity or cervical flexion-extension tasks, this review confirms the

task-specificity of motor adaptation to pain observed when pain was induced in the lumbar region.[23]

The neuromuscular adaptations identified in this systematic review were dependent on the location of the nociceptive stimulation. Activation of the upper trapezius during shoulder flexion-extension tasks decreased when pain was induced in the upper trapezius, splenius capitis, and supraspinatus, while no change was found when pain was induced in the subacromial space. A possible reason for this location-specific adaptation is that larger decreases are observed when pain is induced in the muscle itself or close to the spine, as opposed to further away from the muscle. This is also supported by the fact that effect sizes were larger when pain was induced in the trapezius (Fig 4A) or in the splenius capitis (Fig 4B), compared with the supraspinatus (Fig 4C). It should be noted that the lack of effect following injection of the subacromial space may also be due to differences in the tissue injected (muscle vs nonmuscle). However, previous research has found consistent adaptations of muscle activation when pain was induced in noncontractile tissues,[68] and differences in effect size between splenius capitis, upper trapezius, and supraspinatus still support a role of spatial location in determining the size of the neuromuscular adaptation. Decreased muscle activity in the painful contracting muscles[35,69] and an effect of pain location on neuromuscular adaptations[35,69,70] are in accordance with previous literature on experimental pain induced in limb muscles. While 2 studies[49,71] demonstrated similar motor adaptation when pain was induced in the cranial or caudal region of the trapezius, the regions stimulated were only approximately 5 cm apart. In this review, the pain location spanned from the spine to the acromion, therefore, the effect of pain location on neuromuscular adaptation was more apparent.

Pain location did not appear to determine the extent or direction of the adaptation of cervical muscles. In keeping with the pain adaptation theory,[72] it would be expected that during a movement, pain induced in the agonist muscle would result in decreased activation of the agonist muscle and increased activation of the antagonist muscle. This was, however, not observed in the current review where most cervical muscles demonstrated no significant changes in activation during pain. The results from an individual study[52] also directly contradict this notion since the predominant pattern was of decreased muscle activation regardless of pain location or the muscle's role as an agonist or antagonist. Differences between the location-dependent motor adaptation to pain observed for the upper trapezius and the absence of such a behavior in neck muscles are currently unclear and may be due to several reasons from biomechanical constraints of the tasks to specific characteristics of the tissues injected.

Compared with the cervical region, motor adaptations due to pain induced in orofacial and shoulder regions were less consistent, although this could be due to the smaller number of studies retrieved. As discussed previously, upper trapezius activation decreased minimally or did not change when pain was induced in the supraspinatus and subacromial space, respectively, and no studies assessed changes in the upper trapezius with orofacial pain. Two individual studies documented no changes in neck muscle activation with orofacial pain, with the exception of a decreased sternocleidomastoid activation during jaw clenching. These results suggest that experimental pain in the orofacial and shoulder regions results in minimal adaptation of cervical neuromuscular strategies, although this needs to be confirmed in future studies.

This systematic review identified that motor adaptation did not outlast pain duration. When compared with other systematic reviews, motor adaptation that outlasts pain duration has been identified in some, but not all, studies that induced experimental pain in the low back,[23] and motor evoked potentials were consistently reduced after pain resolution in hand and face muscles.[22] Adaptations outlasting pain duration have also been reported at the knee, both for the population of recruited motor units[73] and regional muscle activation.[70] It is currently unclear why neuromuscular activation strategies are restored immediately after experimental neck pain, whereas motor adaptation is not always resolved when pain is induced in other body regions.

Inconsistent alterations in cervical kinematics were also observed in this review albeit based on limited evidence. Recent reviews have identified kinematic performance of a task is mostly unaltered in the presence of acute experimental pain[20,23] and only reduced lumbar spine range of motion was evident with lumbar pain.[23] It has been suggested the redistribution of activity within and between muscles likely results in gross maintenance of task performance, but quality may be negatively affected.[16,20] Overall, in the present review, it was not possible to draw specific conclusions on cervical kinematics adaptations to pain, given the heterogeneity of tasks and variables assessed.

Systematic reviews on clinical populations with neck and shoulder pain highlight heterogeneity of neuromuscular activation across muscles and tasks. Similar to this review, individuals who have experienced whiplash injuries with moderate/severe symptoms[74] tend to have decreased upper trapezius activation, although the increased sternocleidomastoid activation observed in clinical population was not replicated by the experimental pain studies included in this review. Conversely, systematic reviews on people with neck pain[75] and in musicians with musculoskeletal disorders[76] display no clear evidence of altered activation of the upper trapezius, and individuals with shoulder impingement tend to have increased upper trapezius activation,[77] although no differences in upper trapezius muscle activation during a shoulder flexion/abduction task were observed in swimmers with unilateral shoulder pain compared with healthy controls.[15] With respect to the regional activation, a caudal redistribution of trapezius activation similar to that induced by experimental pain was observed in women with fibromyalgia.[54] The observed differences between muscle activation strategies

in clinical populations and those induced by experimental pain are likely to depend on several factors, including study design, task performed, pain location, pain duration, and psychological factors.

The findings of this systematic review present some limitations. All studies included in this review utilized injections to induce experimental pain, which elicits tonic pain. Future studies should investigate whether the findings on cervical neuromuscular adaptations to experimental pain also apply to other experimental models, particularly movement-evoked pain models, which may more closely reflect clinical neck pain. Recent research has shown that movement-evoked pain models may induce different neuromuscular adaptations compared with tonic pain.[78,79] Furthermore, a limited number of studies explored cervical kinematic adaptations to experimental pain, and there were significant inconsistencies across them in terms of the task, location of the nociceptive stimulus, and outcomes measured. Thus, future studies should explore kinematic alterations in the cervical region induced by experimentally induced pain. Last, it is important to note that our main results predominantly apply to young adults, as only 3 studies recruited participants with an average age higher than 30 years.

In conclusion, this systematic review demonstrates that experimental pain induced in the neck region results in decreased or unchanged, but not increased, muscle activation. Activation of the upper trapezius decreased in response to pain, especially when pain was induced in, or more proximal to the upper trapezius muscle. In addition, a redistribution of muscle activation within the trapezius muscle was observed when pain was induced in the upper trapezius, however, none of these adaptations persisted after pain had ceased. The location of nociceptive stimulation, task performed, and intensity of the task partly explains the other limited and conflicting neuromuscular and kinematics adaptations assessed. Collectively, the findings highlight pertinent factors that can influence motor adaptation to experimental pain and reveal some consistent neuromuscular adaptations to experimental pain. These findings further our understanding of how the central nervous system adapts to acute experimental cervical, shoulder, and orofacial pain, but these adaptations are only partially representative of muscle activation patterns observed in clinical populations.

Disclosure

The authors have no conflict of interest to declare. No funding was received for this research.

Author contributions

HVC, **VD**, **DF**, and **AG**: Conceptualization. **HVC**, **VD**, and **DF**: Methodology. **HVC** and **CO**: Investigation. **HVC**: Formal analysis and data curation. **HVC**, **CO**, and **AG**: Writing—original draft. **HVC**, **CO**, **VD**, **DF**, and **AG**: Writing—review and editing.

Appendix A. Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2024.104660.

References

1. Zimmer Z, Fraser K, Grol-Prokopczyk H, Zajacova A: A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. Pain 163(9):1740-1750, 2022. https://doi.org/10.1097/j.pain.0000000000002557

2. Hartvigsen J, Davidsen M, Hestbaek L, Sogaard K, Roos EM: Patterns of musculoskeletal pain in the population: a latent class analysis using a nationally representative interviewer-based survey of 4817 Danes. Eur J Pain 17(3):452-460, 2013. https://doi.org/10.1002/j.1532-2149.2012.00225.x

3. Safiri S, Kolahi A-A, Hoy D, *et al.* Global, regional, and national burden of neck pain in the general population, 1990-2017: systematic analysis of the Global Burden of Disease Study 2017. BMJ 368:m791, 2020. https://doi.org/10.1136/bmj.m791

4. Lucas J, van Doorn P, Hegedus E, Lewis J, van der Windt D: A systematic review of the global prevalence and incidence of shoulder pain. BMC Musculoskelet Disord 23(1):1073, 2022. https://doi.org/10.1186/s12891-022-05973-8

5. Häggman-Henrikson B, Liv P, Ilgunas A, *et al.* Increasing gender differences in the prevalence and chronification of orofacial pain in the population. Pain 161(8):1768-1775, 2020. https://doi.org/10.1097/j.pain.0000000000001872

6. James SL, Abate D, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1789-1858, 2018. https://doi.org/10.1016/S0140-6736(18)32279-7

7. Dieleman JL, Cao J, Chapin A, *et al.* US health care spending by payer and health condition, 1996-2016. JAMA 323(9):863-884, 2020. https://doi.org/10.1001/jama.2020.0734

8. Gorasso V, Van der Heyden J, De Pauw R, *et al.* The health and economic burden of musculoskeletal disorders in Belgium from 2013 to 2018. Popul Health Metr 21(1):4, 2023. https://doi.org/10.1186/s12963-023-00303-z

9. Hurwitz EL, Randhawa K, Yu H, Côté P, Haldeman S: The Global Spine Care Initiative: a summary of the global burden of low back and neck pain studies. Eur Spine J 27(S6):796-801, 2018. https://doi.org/10.1007/s00586-017-5432-9

10. Falla D, Farina D: Neuromuscular adaptation in experimental and clinical neck pain. J Electromyogr Kinesiol 18(2):255-261, 2006. https://doi.org/10.1016/j.jelekin.2006.11.001

11. Tsang SMH, Szeto GPY, Lee RYW: Altered spinal kinematics and muscle recruitment pattern of the cervical and thoracic spine in people with chronic neck pain during

functional task. J Electromyogr Kinesiol 24(1):104-113, 2013. https://doi.org/10.1016/j.jelekin.2013.10.011

12. Boudreau SA, Falla D: Chronic neck pain alters muscle activation patterns to sudden movements. Exp Brain Res 232(6): 2011-2020, 2014. https://doi.org/10.1007/s00221-014-3891-3

13. Hsu W-L, Chen CPC, Nikkhoo M, *et al.* Fatigue changes neck muscle control and deteriorates postural stability during arm movement perturbations in patients with chronic neck pain. Spine J 20(4):530-537, 2020. https://doi.org/10.1016/j.spinee.2019.10.016

14. Alsultan F, De Nunzio AM, Rushton A, Heneghan NR, Falla D: Variability of neck and trunk movement during single- and dual-task gait in people with chronic neck pain. Clin Biomech 72:31-36, 2020. https://doi.org/10.1016/j.clinbiomech.2019.11.019

15. Hidalgo-Lozano A, Calderón-Soto C, Domingo-Camara A, Fernández-de-las-Peñas C, Madeleine P, Arroyo-Morales M: Elite swimmers with unilateral shoulder pain demonstrate altered pattern of cervical muscle activation during a functional upper-limb task. JOSPT 42(6):552-558, 2012. https://doi.org/10.2519/jospt.2012.3875

16. Hodges PW, Tucker K: Moving differently in pain: a new theory to explain the adaptation to pain. Pain 152:S90, 2011.

17. Fillingim RB: Individual differences in pain: understanding the mosaic that makes pain personal. Pain 158(Suppl 1):S11, 2017.

18. Petrini L, Arendt-Nielsen L: Understanding pain catastrophizing: putting pieces together. Front Psychol 11:603420, 2020. https://doi.org/10.3389/fpsyg.2020.603420

19. Diatchenko L, Fillingim RB, Smith SB, Maixner W: The phenotypic and genetic signatures of common musculoskeletal pain conditions. Nat Rev Rheumatol 9(6):340-350, 2013. https://doi.org/10.1038/nrrheum.2013.43

20. Bank PJM, Peper CE, Marinus J, Beek PJ, van Hilten JJ: Motor consequences of experimentally induced limb pain: a systematic review: Motor consequences of experimental limb pain. Eur J Pain 17(2):145-157, 2013. https://doi.org/10.1002/j.1532-2149.2012.00186.x

21. Sanderson A, Wang SF, Elgueta-Cancino E, *et al.* The effect of experimental and clinical musculoskeletal pain on spinal and supraspinal projections to motoneurons and motor unit properties in humans: a systematic review. Eur J Pain 25(8):1668-1701, 2021. https://doi.org/10.1002/ejp.1789

22. Rohel A, Bouffard J, Patricio P, *et al.* The effect of experimental pain on the excitability of the corticospinal tract in humans: a systematic review and meta-analysis. Eur J Pain 25(6):1209-1226, 2021. https://doi.org/10.1002/ejp.1746

23. Devecchi V, Falla D, Cabral HV, Gallina A: Neuromuscular adaptations to experimentally induced pain in the lumbar region: systematic review and meta-analysis. Pain 164(6):1159-1180, 2023. https://doi.org/10.1097/j.pain.0000000000002819

24. Deeks JJ, Higgins JP, Altman DG, *et al.* Analysing data and undertaking meta-analyses. In: Julian PT, Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019. pp 241-284.

25. Li T, Higgins JPT, Deeks JJ: Collecting data. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019. pp 109-141.

26. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71, 2021. https://doi.org/10.1136/bmj.n71

27. Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 349:g7647, 2015. https://doi.org/10.1136/bmj.g7647

28. Devecchi V, Falla D, Cabral HV, Gallina A: Neuromuscular adaptations to experimentally induced pain in the lumbar region: protocol for a systematic review and meta-analysis. System Rev 10(1):1-270, 2021. https://doi.org/10.1186/s13643-021-01831-1

29. Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898, 2019. https://doi.org/10.1136/bmj.l4898

30. Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919, 2016. https://doi.org/10.1136/bmj.i4919

31. Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64(4):383-394, 2011. https://doi.org/10.1016/j.jclinepi.2010.04.026

32. Rosenthal R: Meta-Analytic Procedures for Social Research. SAGE Publications; 1991

33. Balshem H, Helfand M, Schünemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64(4):401-406, 2011. https://doi.org/10.1016/j.jclinepi.2010.07.015

34. Landis JR, Koch GG: The measurement of observer agreement for categorical data. Biometrics 33(1):159-174, 1977. https://doi.org/10.2307/2529310

35. Svensson P, Wang K, Sessle BJ, Arendt-Nielsen L: Associations between pain and neuromuscular activity in the human jaw and neck muscles. Pain 109(3):225, 2004.

36. Pasinato F, Santos-Couto-Paz CC, Zeredo JLL, Macedo SB, Corrêa ECR: Experimentally induced masseter-pain changes masseter but not sternocleidomastoid muscle-related activity during mastication. J Electromyogr Kinesiol 31:88-95, 2016. https://doi.org/10.1016/j.jelekin.2016.09.007

37. Christensen SW, Hirata RP, Graven-Nielsen T: The effect of experimental neck pain on pressure pain sensitivity and axioscapular motor control. J Pain 16(4):367, 2015.

38. Gizzi L, Muceli S, Petzke F, Falla D: Experimental muscle pain impairs the synergistic modular control of neck muscles. PloS One 10(9):0137844, 2015. https://doi.org/10.1371/journal.pone.0137844

39. Christensen SW, Hirata RP, Graven-Nielsen T: Bilateral experimental neck pain reorganize axioscapular muscle coordination and pain sensitivity. Eur J Pain 21(4):681-691, 2017. https://doi.org/10.1002/ejp.972

40. Dupuis F, Sole G, Wassinger CA, *et al.* The impact of experimental pain on shoulder movement during an arm elevated reaching task in a virtual reality environment. Physiol Rep 9(18):e15025, 2021. https://doi.org/10.14814/phy2.15025

41. Bandholm T, Rasmussen L, Aagaard P, Diederichsen L, Jensen BR: Effects of experimental muscle pain on shoulder-abduction force steadiness and muscle activity in healthy subjects. Eur J Appl Physiol 102(6):643-650, 2008. https://doi.org/10.1007/s00421-007-0642-1

42. Falla D, Cescon C, Lindstroem R, Barbero M: Muscle pain induces a shift of the spatial distribution of upper trapezius muscle activity during a repetitive task: a mechanism for perpetuation of pain with repetitive activity? Clin J Pain 33(11):1006, 2017.

43. Ge H-Y, Arendt-Nielsen L, Farina D, Madeleine P: Gender-specific differences in electromyographic changes and perceived pain induced by experimental muscle pain during sustained contractions of the upper trapezius muscle. Muscle Nerve 32(6):726-733, 2005. https://doi.org/10.1002/mus.20410

44. Madeleine P, Leclerc F, Arendt-Nielsen L, Ravier P, Farina D: Experimental muscle pain changes the spatial distribution of upper trapezius muscle activity during sustained contraction. Clin Neurophysiol 117(11):2436-2445, 2006. https://doi.org/10.1016/j.clinph.2006.06.753

45. Ashton-Miller JA, McGlashen KM, Herzenberg JE, Stohler CS: Cervical muscle myoelectric response to acute experimental sternocleidomastoid pain. Spine 15(10):1006, 1990.

46. Cagnie B, O'Leary S, Elliott J, Peeters I, Parlevliet T, Danneels L: Pain-induced changes in the activity of the cervical extensor muscles evaluated by muscle functional magnetic resonance imaging. Clin J Pain 27(5):392, 2011.

47. Cagnie B, Dirks R, Schouten M, Parlevliet T, Cambier D, Danneels L: Functional reorganization of cervical flexor activity because of induced muscle pain evaluated by muscle functional magnetic resonance imaging. Man Ther 16(5):470-475, 2011. https://doi.org/10.1016/j.math.2011.02.013

48. Castelein B, Cools A, Parlevliet T, Cagnie B: The influence of induced shoulder muscle pain on rotator cuff and scapulothoracic muscle activity during elevation of the arm. J Should Elbow Surg 26(3):497-505, 2017. https://doi.org/10.1016/j.jse.2016.09.005

49. Dideriksen JL, Holobar A, Falla D: Preferential distribution of nociceptive input to motoneurons with muscle units in the cranial portion of the upper trapezius muscle. J Neurophysiol 116(2):611-618, 2016. https://doi.org/10.1152/jn.01117.2015

50. Diederichsen LP, Winther A, Dyhre-Poulsen P, Krogsgaard MR, Nørregaard J: The influence of experimentally induced pain on shoulder muscle activity. Exp Brain Res 194(3):329-337, 2009. https://doi.org/10.1007/s00221-008-1701-5

51. Falla D, Farina D, Graven-Nielsen T: Experimental muscle pain results in reorganization of coordination among trapezius muscle subdivisions during repetitive shoulder flexion. Exp Brain Res 178(3):385-393, 2007. https://doi.org/10.1007/s00221-006-0746-6

52. Falla D, Farina D, Dahl MK, Graven-Nielsen T: Muscle pain induces task-dependent changes in cervical agonist/antagonist activity. J Appl Physiol 102(2):601-609, 2007. https://doi.org/10.1152/japplphysiol.00602.2006

53. Falla D, Arendt-Nielsen L, Farina D: Gender-specific adaptations of upper trapezius muscle activity to acute nociceptive stimulation. Pain 138(1):217, 2008.

54. Falla D, Andersen H, Danneskiold-Samsøe B, Arendt-Nielsen L, Farina D: Adaptations of upper trapezius muscle activity during sustained contractions in women with fibromyalgia. J Electromyogr Kinesiol 20(3):457-464, 2010. https://doi.org/10.1016/j.jelekin.2009.07.002

55. Madeleine P, Lundager B, Voigt M, Arendt-Nielsen L: Shoulder muscle co-ordination during chronic and acute experimental neck-shoulder pain. An occupational pain study. Eur J Appl Physiol Occup Physiol 79(2):127-140, 1999. https://doi.org/10.1007/s004210050486

56. Qu N, Lindstrøm R, Graven-Nielsen T, Hirata RP: Experimental cervical interspinous ligament pain altered cervical joint motion during dynamic extension movement. Clin Biomech 65:65-72, 2019. https://doi.org/10.1016/j.clinbiomech.2019.04.002

57. Qu N, Lindstrøm R, Hirata RP, Graven-Nielsen T: Origin of neck pain and direction of movement influence dynamic cervical joint motion and pressure pain sensitivity. Clin Biomech 61:120-128, 2019. https://doi.org/10.1016/j.clinbiomech.2018.12.002

58. Samani A, Holtermann A, SØGaard K, Madeleine P: Experimental pain leads to reorganisation of trapezius electromyography during computer work with active and passive pauses. Eur J Appl Physiol 106(6):857-866, 2009. https://doi.org/10.1007/s00421-009-1083-9

59. Samani A, Fernández-Carnero J, Arendt-Nielsen L, Madeleine P: Interactive effects of acute experimental pain in trapezius and sored wrist extensor on the electromyography of the forearm muscles during computer work. Appl Ergon 42(5):735-740, 2011. https://doi.org/10.1016/j.apergo.2010.11.008

60. Sole G, Osborne H, Wassinger C: Electromyographic response of shoulder muscles to acute experimental subacromial pain. Man Ther 19(4):343-348, 2014. https://doi.org/10.1016/j.math.2014.03.001

61. Wang X, Qu N, Wang Y, Dong J, Jiao J, Wu M: Effects of experimental pain on the cervical spine reposition errors. BMC Musculoskelet Disord 23(1):259, 2022. https://doi.org/10.1186/s12891-022-05170-7

62. Wiesinger B, Häggman-Henrikson B, Hellström F, *et al.* Does induced masseter muscle pain affect integrated jaw-neck movements similarly in men and women? Eur J Oral Sci 124(6):546-553, 2016. https://doi.org/10.1111/eos.12315

63. Wiesinger B, Haggman-Henrikson B, Eklund A, *et al.* Multimodal sensory stimulation of the masseter muscle reduced precision but not accuracy of jaw-opening movements. Front Neurosci 13:01083, 2019. https://doi.org/10.3389/fnins.2019.01083

64. Guney-Deniz H, Harput G, Toprak U, Duzgun I: Relationship between middle trapezius muscle activation and acromiohumeral distance change during shoulder elevation with scapular retraction. J Sport Rehab 28(3):266-271, 2019. https://doi.org/10.1123/jsr.2018-0131

65. Wattanaprakornkul D, Halaki M, Boettcher C, Cathers I, Ginn KA: A comprehensive analysis of muscle recruitment patterns during shoulder flexion: an electromyographic study. Clin Anat 24(5):619-626, 2011. https://doi.org/10.1002/ca.21123

66. Wolff WL, Heinemann CM, Lipps DB: The influence of idiopathic chronic neck pain on upper trapezius and sternocleidomastoid muscle activity and elasticity during

functional reaching: a cross-sectional study. J Biomech 141:111223, 2022. https://doi.org/10.1016/j.jbiomech.2022.111223

67. Merkle SL, Sluka KA, Frey-Law LA: The interaction between pain and movement. J Hand Ther 33(1):60-66, 2020. https://doi.org/10.1016/j.jht.2018.05.001

68. Tucker KJ, Hodges PW: Motoneurone recruitment is altered with pain induced in non-muscular tissue. Pain 141(1-2):151-155, 2009. https://doi.org/10.1016/j.pain.2008.10.029

69. van den Hoorn W, Hodges PW, van Dieën JH, Hug F: Effect of acute noxious stimulation to the leg or back on muscle synergies during walking. J Neurophysiol 113(1):244, 2015. https://doi.org/10.1152/jn.00557.2014

70. Gallina A, Salomoni SE, Hall LM, Tucker K, Garland SJ, Hodges PW: Location-specific responses to nociceptive input support the purposeful nature of motor adaptation to pain. Pain 159(11):2192-2200, 2018. https://doi.org/10.1097/j.pain.0000000000001317

71. Falla D, Arendt-Nielsen L, Farina D: The pain-induced change in relative activation of upper trapezius muscle regions is independent of the site of noxious stimulation. Clin Neurophysiol 120(1):150-157, 2009. https://doi.org/10.1016/j.clinph.2008.10.148

72. Lund JP, Donga R, Widmer CG, Stohler CS: The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 69(5):683-694, 1991. https://doi.org/10.1139/y91-102

73. Tucker K, Larsson AK, Oknelid S, Hodges P: Similar alteration of motor unit recruitment strategies during the anticipation and experience of pain. Pain 153(3):636-643, 2012. https://doi.org/10.1016/j.pain.2011.11.024

74. Daenen L, Nijs J, Raadsen B, Roussel N, Cras P, Dankaerts W: Cervical motor dysfunction and its predictive value for long-term recovery in patients with acute whiplash-associated disorders: a systematic review. J Rehabil Med 45(2):113-122, 2013. https://doi.org/10.2340/16501977-1091

75. Castelein B, Cools A, Bostyn E, Delemarre J, Lemahieu T, Cagnie B: Analysis of scapular muscle EMG activity in patients with idiopathic neck pain: a systematic review. J Electromyogr Kinesiol 25(2):371-386, 2015. https://doi.org/10.1016/j.jelekin.2015.01.006

76. Overton M, Du Plessis H, Sole G: Electromyography of neck and shoulder muscles in instrumental musicians with musculoskeletal pain compared to asymptomatic controls: a systematic review and meta-analysis. Musculoskelet Sci Pract 36:32-42, 2018. https://doi.org/10.1016/j.msksp.2018.04.001

77. Struyf F, Cagnie B, Cools A, *et al.* Scapulothoracic muscle activity and recruitment timing in patients with shoulder impingement symptoms and glenohumeral instability. J Electromyogr Kinesiol 24(2):277-284, 2014. https://doi.org/10.1016/j.jelekin.2013.12.002

78. Bergin M, Tucker K, Vicenzino B, Hodges PW: "Taking action" to reduce pain-Has interpretation of the motor adaptation to pain been too simplistic? PLoS One 16(12):e0260715, 2021. https://doi.org/10.1371/journal.pone.0260715

79. Gallina A, Abboud J, Blouin JS: A task-relevant experimental pain model to target motor adaptation. J Physiol 599(9):2401-2417, 2021. https://doi.org/10.1113/jp281145