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Original article

# Association between sympathoexcitatory changes and symptomatic improvement following cervical mobilisations in participants with neck pain. A double blind placebo controlled trial

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ABSTRACT

*Background:* sympathoexcitation observed with passive cervical mobilisations may imply activation of an endogenous pain inhibition system resulting in hypoalgesia. However, research is mostly in asymptomatic participants and there is very limited evidence of a relationship between sympathoexcitation and symptomatic improvement in people with clinical pain.
*Objective:* to investigate the effects of cervical mobilisations on the sympathetic nervous system in participants with neck pain, and to explore the relationship between symptomatic improvement and sympathoexcitation.
*Design:* double-blind randomised controlled trial.
*Method:* 40 participants with neck pain (aged 20–69 years, 25 female) were randomly allocated to either cervical mobilisations or motionless placebo. Skin conductance was measured before, during, and after intervention. After interventions were completed, their credibility was assessed. Participants were classified as responders or non-responders according to global symptom change.
*Results:* participants receiving mobilisations were more likely to be classified as responders (odds ratio: 4.33, $p = 0.03$) and demonstrated greater change in most outcome measures of sympathoexcitation from baseline to during the intervention but not from during to after the intervention. There was no association between sympathoexcitation and symptomatic improvement. Mobilisations and placebo were equally credible.
*Conclusions:* These findings suggest sympathoexcitatory changes may be caused by an orienting response unrelated to the activation of an endogenous pain inhibition system Alternatively, the observed lack of an association may be explained by the existence of various mechanisms for pain relief. This study used single outcome measures of sympathoexcitation and symptomatic improvement and other measures may reveal different things.
*ClinicalTrials.gov number:* M10/2016/095.

## 1. Introduction

Neck pain is highly prevalent, costly and disabling (Hoy et al., 2010, 2014). 90% of physiotherapists and chiropractors use cervical mobilisations - low velocity passive oscillatory movements (Sweeney and Doody, 2010; Blanpied et al., 2017), to treat people with neck pain (Carlesso et al., 2014).

The pain relieving effects of spinal mobilisations appear to be largely produced by a central nervous system mediated response (Schmid et al., 2008; Lascurain-Aguirrebeña et al., 2016) since changes occur both locally (La Touche et al., 2013; Salom-Moreno et al., 2014; Sterling et al., 2001) and distal (La Touche et al., 2013; Salom-Moreno et al., 2014; Vicenzino et al., 1996, 1998a) to the mobilisation site. This suggests an extrasegmental effect not limited to the mobilised level.

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Animal studies have found that mobilisations of the knee for hyperalgesia induced at the ankle cause a decrease in the activity of areas in the dorsal horn (Malisza et al., 2003a) and brain (Malisza et al., 2003b) associated with nociceptive transmission and processing. The hypoalgesic effects can be prevented by blocking 5-$HT_{1A}$ receptors at the spinal cord and attenuated by blocking α2-adrenergic receptors while no effect was found when opioid receptors were blocked. This suggests that mobilisations activate descending inhibitory serotonergic and noradrenergic pathways that inhibit ascending nociceptive transmission by acting on α2-adrenergic and 5-$HT_{1A}$ receptors (Skyba et al., 2003). This is in accordance with two studies in humans where the hypoalgesic effect of mobilisations to the elbow (Paungmali et al., 2004) and cervical spine (Zusman et al., 1989) was not affected by the administration of the opioid antagonist naloxone, suggesting non-opioid analgesia.

It has been postulated that the activation of the dorsal periaqueductal gray matter (dPAG) of the brain by the stimulation of spinal mechanoreceptors may be responsible for the centrally mediated response (Vicenzino et al., 1996; Kingston et al., 2014; Moutzouri et al., 2012; Villafane et al., 2014; Tsirakis and Perry, 2015; Perry et al., 2015; Wright, 1995; Hegedus et al., 2011; Souvlis et al., 2004; Wright and Grant, 2002). This is based on the fact that mobilisations have been shown to cause sympathoexcitation (Tsirakis and Perry, 2015; Piekarz and Perry, 2016; Chu et al., 2014), in some cases concurrently with hypoalgesia (La Touche et al., 2013; Sterling et al., 2001), and early animal work showed that electrical and chemical stimulation of the dPAG in rats produced analgesia and sympathoexcitation (Lovick et al., 1991; Reynolds, 1969).

However, systematic reviews (Kingston et al., 2014; Hegedus et al., 2011) conclude whilst there is evidence of mobilisation induced sympathoexcitation in the pain-free, evidence is limited among symptomatic participants and call for further research with patients with pain. Four studies (La Touche et al., 2013; Sterling et al., 2001; Vicenzino et al., 1998a; Perry and Green, 2018) have assessed the sympathoexcitatory effects of spinal mobilisations in symptomatic participants, of these only one (Sterling et al., 2001) involved participants with neck pain. Whilst a positive correlation between sympathoexcitation and hypoalgesia has been reported (Vicenzino et al., 1998a), no study has assessed if such association extents to symptomatic improvement.

Changes in skin conductance (SC) are widely used as a measure of sympathetic nervous system (SNS) activity (Perry et al., 2015; Storm, 2008; Clark et al., 2018). Other measures have included cutaneous blood flux, respiratory rate and heart rate (Vicenzino et al., 1998a, 1998b; Win et al., 2015). Sweat glands are exclusively innervated by sympathetic sudomotor fibres and, in normal ambient temperature ranges, SC is highly correlated with SNS activity (Dawson et al., 2016). SC is composed of a slow-moving tonic and another fast changing wave of activity. The tonic response – skin conductance level (SCL), manifests as shifts in SC over a long period of time, whereas rapid skin conductance responses (SCR) occur over a few seconds either following external stimuli or spontaneously (Dawson et al., 2016; Benedek and Kaernbach, 2010a). Previous investigations into the effects of spinal mobilisations on the SNS (La Touche et al., 2013; Sterling et al., 2001; Vicenzino et al., 1998a; Perry and Green, 2018) have not separated the different contributors of the SC signal. Non-separation has been discouraged (Boucsein et al., 2012) since each component may be attributed to different brain processes (Braithwaite et al., 2014), requiring different interpretation. Separate analysis of SCRs allows the relationship between specific stimuli and SNS activity to be explored (Benedek and Kaernbach, 2010b). Whilst changes in SCL require a longer time to occur, changes in SCR are rapid and immediate, hence an association between a specific stimulus (e.g. commencement of mobilisations or placebo manual contact) and SNS response can be evaluated. Furthermore, since SCR amplitude is correlated with the amplitude of the sudomotor fiber activity (Storm, 2008; Benedek and Kaernbach, 2010b), size of the SCRs may be used as an index of SNS activity (Benedek and Kaernbach, 2010a).

The aim of this study was to investigate if cervical mobilisations cause changes in SCR and SCL response in people with neck pain, and to explore if such changes are associated with treatment success. It was hypothesized that there would be a difference in SC response measures between mobilisations and placebo, and that the response would be associated with treatment success.

## 2. Methodology

Following ethical approval (M10_2016_095), a double-blind parallel randomised controlled trial with a 1:1 allocation ratio was conducted (ClinicalTrials.gov record number: M10/2016/095). Data collection took place at a research laboratory between April and May 2018.

### 2.1. Participants

Data from a previous study (Lascurain-Aguirrebena et al., 2018) was used to perform the sample size calculation in G*Power software (version 3.1.9.2; http://www.gpower.hhu.de/). With statistical significance set at 0.05 and power at 80%, 40 subjects were required to detect an association between SC and treatment success, where those with a higher SC change secondary to the intervention (see %ΔSCL in section 2.5) were more likely to be classified as responders (odds ratio 3.45, moderate effect (Chen et al., 2010)). Participants with non-specific neck pain of any duration where cervical mobilisations were indicated according to pre-defined criteria (Lascurain-Aguirrebena et al., 2018) (Table 1) were recruited through a Physiotherapy clinic and local posters. Potential participants were excluded if they had sustained a whiplash injury, had or were awaiting neck surgery, had been diagnosed with an inflammatory disease or rheumatologic, orthopaedic or neurological spinal condition, or had any systemic, circulatory or skin condition that affected SC measurements (Fig. 1). Since expectation affects treatment outcome (Puentedura et al., 2012; Bishop et al., 2013) and instructional set can affect treatment expectation (Bialosky et al., 2014), participants were not informed of the presence of a placebo or sham intervention and were advised that the effectiveness of two different manual therapy interventions was being investigated.

### 2.2. Procedure

Following informed consent, participants' age, gender, body mass index, area of symptoms (left, right, bilateral) and time since onset of symptoms (classified as chronic if duration was >12 weeks, otherwise as acute/subacute (Blanpied et al., 2017; Treede et al., 2015)) were noted. Maximum and average pain intensity during the previous 24 h were recorded using a numeric pain rating scale (Hawker et al., 2011) (range 0–10), and participants completed the neck disability index (NDI) questionnaire (Andrade Ortega et al., 2010) (range 0–100). Participants were then asked to supine lie on a plinth. After a 10 min period of stabilisation (Perry et al., 2015), SC was measured continuously 2 min prior (baseline), during and 2 min after (post-treatment) the

**Table 1**
Inclusion criteria.

| |
|---|
| Primary complaint of neck pain |
| Non-traumatic history of onset |
| Mechanical in nature |
| Pain has a clear mechanical aggravating and easing positions or movements |
| Limited range of motion |
| Local provocation tests produce recognisable symptoms (e.g. localised upper, middle or lower neck passive side flexion) |
| No neurological deficit (either sensory or motor) or radicular pain |
| No signs of central hyperexcitability (e.g. widespread, non-anatomical/nonspecific distribution of pain; stimulus-independent spontaneous pain) |
| Referral to other health professional to exclude red flags not required |

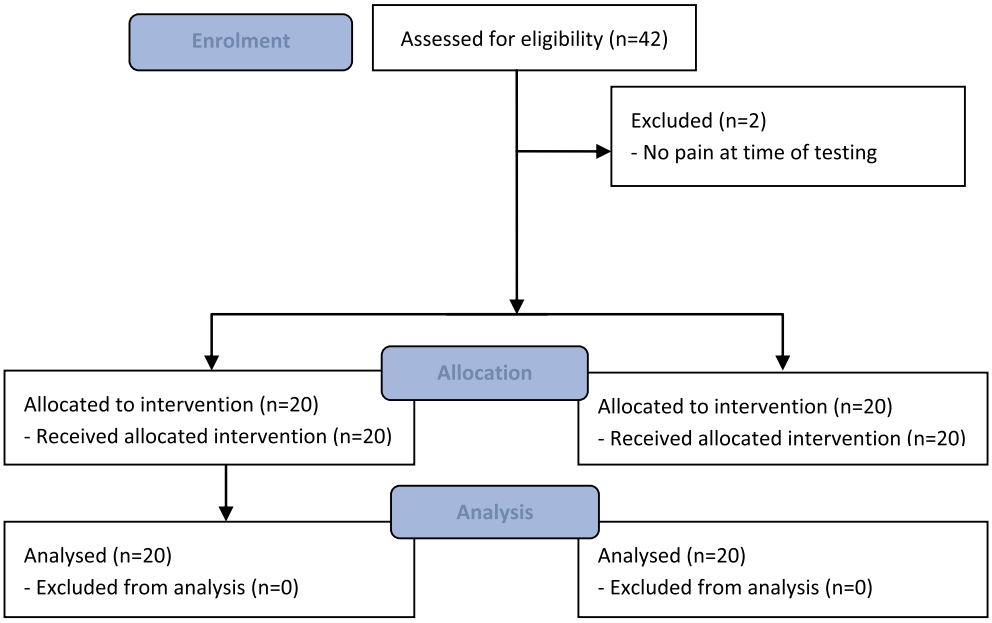


**Fig. 1.** CONSORT flow diagram.

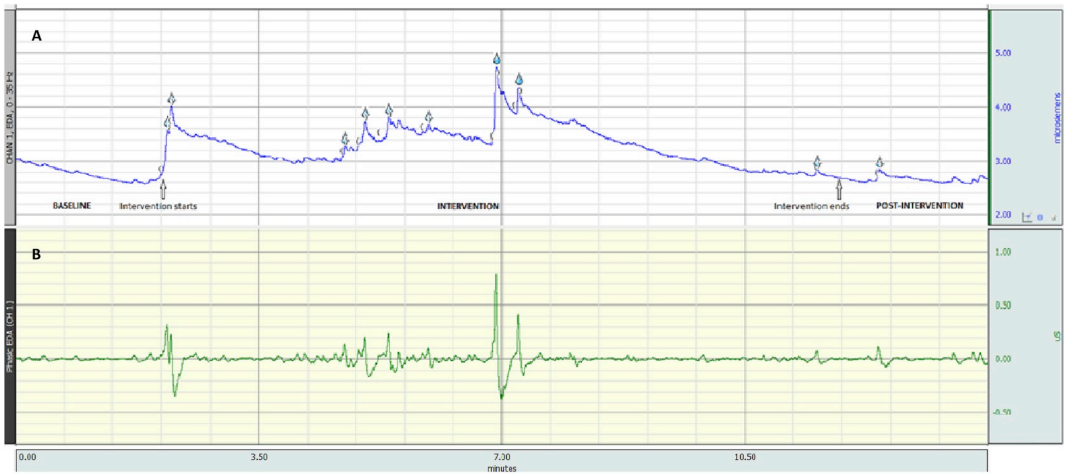


**Fig. 2.** Electrodermal activity of a typical participant (n = 1) treated with mobilisations. A) skin conductance. Water droplet represents peak of skin conductance response. Parenthesis represents start of skin conductance response. B) Skin conductance phasic activity (following application of 0.05 Hz high-pass filter to skin conductance signal) for calculation of skin conductance responses and skin conductance level.

intervention.

After measures of SC had been completed, participants were asked to rate their perceived treatment effect using the Global Rating of Change Scale (GROC). This is a 15 point scale where change is rated from −7 (a very great deal worse), through 0 (no change), to +7 (a great deal better) (Tseng et al., 2006) and is widely used to assess treatment effectiveness in neck pain (Tseng et al., 2006; Griswold et al., 2015; Izquierdo Perez et al., 2014; Masaracchio et al., 2013). It has good face and construct validity and high reliability (Kamper et al., 2009). The credibility of the interventions was assessed by participants rating their agreement with the following statement: "I am confident that this treatment can alleviate my complaint" with a 5 point Likert scale (from "strongly disagree" to "strongly agree") (Licciardone and Russo, 2006) immediately after intervention but still lying supine and before assessment with GROC.

All data collection took place in the afternoon (to account for diurnal variations in SC (Dawson et al., 2016)) in a noise attenuated room (O'Leary et al., 2007), and temperature and humidity were maintained constant (Buckingham, 2008; Vetrugno et al., 2003) to avoid their confounding effects on SC.

### 2.3. Electrodermal activity

SC was measured with a system (MP36R, Biopac systems Inc, CA) that provided exosomatic measures using a constant applied voltage of 0.5 V (Buckingham, 2008; Ogorevc et al., 2013). The standard error of measurement (relative to the mean) for SC has been reported to be 4.6% (Perry et al., 2011). Silver/silver chloride electrodes with an isotonic electrode contact gel comprised of 0.5% saline in a neutral base were attached bilaterally to participants' 2nd and 3rd fingers (O'Leary et al., 2007; Bowler et al., 2017). Electrodes were attached to the distal phalanges because a larger number of active sweat glands provide a higher amplitude of SCL and SCRs signals (Dawson et al., 2016). Skin at the electrode site was prepared by cleaning it with warm water, and the use of alcohol or abrasion was avoided in order not to affect the natural resistive/conductive properties of the skin (Dawson et al., 2016; Buckingham, 2008). SC was collected at a frequency of 1000 Hz (Desmarais et al., 2011) and filtered with a 0–35 Hz band-pass filter

(Piekarz and Perry, 2016). Data was then downsampled to 100 Hz and smoothed with a 1 s median smoothing function for the removal of artefacts. The phasic component of SC was extracted using a 0.05 Hz high-pass filter, and SCRs were identified as those over a threshold of 0.03 μS (microsiemens); SCRs with an amplitude of < 10% of the maximum for that subject were rejected (Braithwaite et al., 2014) (Fig. 2). Amplitude of the SCR was computed as the difference in SC between the onset and peak of the SCR, and SCL was obtained by averaging SC excluding SCRs (Benedek and Kaernbach, 2010b). Three time intervals of interest were identified: 2 min baseline (pre-intervention), during intervention (10 min) and 2 min post-intervention. For each interval SCL (Clark et al., 2018; Dawson et al., 2016) and frequency of SCR (Braithwaite et al., 2013, 2014; Buckingham, 2008) were calculated. In addition, the maximum amplitude SCR during and post intervention, and the time elapsed to 50% of all SCRs during the intervention were calculated. Data analysis was performed using Biopac Acqknowledge (Biopac systems Inc, CA) and Matlab (MathWorks Inc., Natick, MA) softwares.

### 2.4. Interventions

Participants were randomly allocated (simple randomisation, 1:1 allocation ratio) to either passive cervical mobilisations or placebo. After all baseline data had been collected, the treating therapist opened an opaque sealed envelope (one for each participant) which had been prepared in advance by a third party and contained the treatment allocation of that participant (Doig and Simpson, 2005). All participants lay supine for the 10 min intervention duration. The mobilisation group received 10 min of segmental grades II-III unilateral postero-anterior and antero-posterior oscillatory mobilisations following the movement plane of the cervical zygapophyseal joints (downslope or upslope) (McNair et al., 2007; Dewitte et al., 2014) directed at painful and/or hypomobile cervical motion segments according to the Physiotherapist's clinical examination. This involved both active and passive movement testing, and localization of vertebral segments that reproduced participant's symptoms. C5-C7 bilaterally were most frequently mobilised. For the placebo group, the Physiotherapist positioned their hands as for mobilisations but without performing the oscillation (La Touche et al., 2013). Both groups had minimal and similar therapist-patient interaction during the intervention, such as asking about symptom reproduction and discomfort, as this can affect treatment outcome (Riley et al., 2015a, 2015b). Both interventions were delivered by the same Physiotherapist who had 15 years' experience in musculoskeletal Physiotherapy.

Group allocation was concealed to the participant and outcome assessor until all data collection had been completed.

### 2.5. Data analysis

Differences between groups in the credibility scale were assessed using an independent samples T test. A Mann-Whitney test was used to assess differences in the categorical distribution of GROC between groups. In addition, GROC was used to classify participants according to treatment success. Those reporting feeling “somewhat better” or greater where classified as successful whereas all others (“slightly better” or “worse”) were classified as unsuccessful (Cook et al., 2014). Differences between groups with regards to treatment success were assessed using a binary logistic regression. To control for the possible confounding effects of participant characteristics on treatment success, demographic and clinical characteristics were previously tested for an association with treatment outcome through parametric tests (Cleland et al., 2007), however none were found and therefore the logistic regression did not require adjusting.

There were no differences between sides for any of the SC outcome measures and therefore an average of both sides was computed (Perry and Green, 2018). Within group differences in SC were assessed with paired T tests except from the change in SCR maximum amplitude which was tested with a Wilcoxon Signed Rank test because of the non-normal distribution of this variable when subgrouped into participants receiving placebo or mobilisations. For a between group comparison, to account for between participants differences in skin conduction, SCL for each period was normalised by calculating percentage change (Piekarz and Perry, 2016; Desmarais et al., 2011) (%ΔSCL). Percentage changes from baseline to intervention, from intervention to post-intervention, and from baseline to post-intervention were calculated. Since 75% of participants did not show any SCRs during baseline, changes in SCRs frequency between periods were assessed in absolute terms (ΔSCR frequency). Normality and the presence of outliers were assessed with histograms and normality statistics (Learman et al., 2014). Outliers are common when measuring SC (Chu et al., 2014; Jowsey and Perry, 2010); %ΔSCL and ΔSCR frequency data were winsorized (1–3 values depending on variable) to the nearest value (Reifman et al., 2010; Terry et al., 2012; Wheelock et al., 2016) and time to largest SCR log transformed (Meisingset et al., 2016) to obtain a normal distribution.

Differences between groups in %ΔSCL, ΔSCR frequency and SCR amplitude were tested using ANCOVAs, with the outcome of interest as dependent variable, intervention group as independent factor and the relevant baseline value as covariate. Differences between groups in the time to 50% of all SCRs was assessed using independent samples T tests. The relationship between treatment success and %ΔSCL and ΔSCR frequency either during or post intervention was assessed using separate binary logistic regressions. In the regression model, the interaction with treatment group was also studied in order to determine if the intervention received affected such association i.e. if an association existed when all participants were considered regardless of intervention or if this association depended on the intervention received. The relationship between %ΔSCL and ΔSCR was assessed with a linear regression.

## 3. Results

Participants' characteristics are shown in Table 2. Within and between group changes in SC are shown in Tables 3 and 4. There were no significant differences between groups ($p = 0.586$) in treatment expectation (credibility scale). The median for all participants was 4, i.e. responding “agree” to the statement made in the credibility scale.

### 3.1. Effect of intervention on skin conductance level

The mobilisation group showed a greater %ΔSCL from baseline to during the intervention and from baseline to post-intervention. No significant differences between groups were noted from during to post-intervention (Table 4).

### 3.2. Effect of intervention on skin conductance responses

The mobilisation group showed greater ΔSCR frequency from

**Table 2**
Participants characteristics at baseline. Values are mean ± SD or number of cases.

| | Mobilisation | Placebo |
|---|---|---|
| Age (years) | 41 ± 14 | 47 ± 10 |
| BMI | 24.4 ± 3.5 | 24.5 ± 3.9 |
| Gender (F/M) | 12/8 | 13/7 |
| Acute-subacute/chronic | 1/19 | 5/15 |
| NDI score | 22 ± 8 | 24 ± 11 |
| Area of pain (Bilateral/Right/Left) | 14/6/0 | 14/5/1 |
| Maximum pain | 6.2 ± 2.2 | 5.3 ± 1.9 |
| Average pain | 4.2 ± 1.8 | 3.5 ± 1.8 |

**Table 3**
Within group differences in SC: SCL; SCR frequency; maximum amplitude SCR.

| Mean (SD) | | | | Within group p value | | |
|---|---|---|---|---|---|---|
| | Baseline | During | Post | Baseline to during | Baseline to post | During to post |
| SCL (microsiemens) | | | | | | |
| Mobilisations | 2.22 (1.63) | 2.89 (1.7) | 2.97 (1.63) | < **0.000** | **0.001** | 0.389 |
| Placebo | 3.08 (2.16) | 3.31 (2.65) | 3.05 (2.41) | 0.254 | 0.860 | **0.007** |
| SCR frequency (per minute) | | | | | | |
| Mobilisations | 0.33 (0.78) | 1.01 (0.89) | 0.99 (0.97) | **0.001** | **0.006** | 0.921 |
| Placebo | 0.43 (0.67) | 0.64 (0.71) | 0.63 (0.78) | 0.163 | 0.290 | 0.953 |
| SCR maximum amplitude (microsiemens) | | | | | | |
| Mobilisations | 0.2 (0.12) | 0.46 (0.31) | 0.39 (0.31) | **0.018** | 0.463 | **0.048** |
| Placebo | 0.38 (0.46) | 0.63 (0.41) | 0.42 (0.31) | **0.017** | 0.345 | 0.139 |

Bold signifies the p value is less than 0.05.

baseline to during the intervention but not from during to post-intervention or baseline to post-intervention. They showed a greater time to 50% of all SCRs during intervention. No differences were noted in the maximum amplitude (μS) SCR during intervention or post-intervention (Table 4).

Regardless of intervention, there was an association between %ΔSCL and ΔSCR frequency from baseline to during the intervention (R (Hoy et al., 2014) = 0.23; p = 0.02), from during to post-intervention (R (Hoy et al., 2014) = 0.36; p < 0.001) and from baseline to post-intervention (R (Hoy et al., 2014) = 0.4; p < 0.001).

### 3.3. Symptomatic improvement and relationship with changes in skin conductance

There was a significant difference (P = 0.028) between groups in the reported symptomatic improvement; medians in the GROC scale following mobilisation and placebo were 12.5 and 9 respectively, equivalent to feeling “moderately/quite a bit better” and “a tiny bit better” respectively (Fig. 3). 65% in the mobilisation group and 30% in the placebo group were classified as responders (odds ratio: 4.33, 95% IC: 1.15–16.32; p = 0.03).

There were no associations between symptomatic improvement and %ΔSCL from baseline to during intervention (p = 0.248; interaction with intervention p = 0.885), from during to post-intervention (p = 0.836; interaction with intervention p = 0.403) and baseline to post intervention (p = 0.394, interaction with intervention p = 0.63). Neither were there associations between symptomatic improvement and ΔSCR frequency from baseline to during intervention (p = 0.612, interaction with intervention p = 0.099), from during to post-intervention (p = 0.707, interaction with intervention p = 0.48) and from baseline to post-intervention (p = 0.946, interaction with intervention p = 0.335).

## 4. Discussion

This is the first study to explore the association between mobilisations induced SNS changes and symptomatic relief in neck pain. Cervical mobilisations were more effective in reducing short-term symptoms than placebo. This is in accordance with a previous study (Lascurain-Aguirrebena et al., 2018) in participants with the same selection criteria. Treatment credibility results suggest participants remained blind to treatment allocation throughout the study and had the same expectation of improvement regardless of intervention, hence differences in the effects between groups may be attributed to the mechanical or physiological effects. Mobilisations caused a significant increase in SC suggestive of sympathoexcitation when compared to placebo. In the mobilisation group we noted increased SCL during and after the intervention and increased frequency of SCRs during the intervention. The observed increase in SCL during the intervention (41%) is greater than that observed by Sterling et al. (Sterling et al., 2001) in participants with neck pain. A greater increase in SC in our study may have been caused by the type of mobilisation used or a longer treatment duration, although direct comparison is difficult since outcome measures used differ between our study and theirs (this study separated the phasic and tonic components of SC, whereas Sterling et al. (Sterling et al., 2001) calculated the average of the raw SC). Nevertheless sympathoexcitation appears to be a consistent finding in participants with neck pain, and in other symptomatic (La Touche et al., 2013; Vicenzino et al., 1998a) and asymptomatic (Tsirakis and Perry, 2015; Piekarz and Perry, 2016; Chiu and Wright, 1996) populations following spinal mobilisations.

We found no association between any of the studied outcome measures of SC (%ΔSCL or ΔSCR frequency in any time period) and symptomatic improvement. This was the contrary to our hypothesis given the findings of Vicenzino et al. (Vicenzino et al., 1998a). There are several factors that may have contributed to this.

**Table 4**
Between group differences in SC: SCL; SCR frequency; maximum amplitude SCR; time to 50% of all SCRs during intervention.

| | Mean (95% CI) | | p value[b] |
|---|---|---|---|
| | Mobs | Placebo | |
| %ΔSCL baseline to during intervention | 40.62 (27.39–53.84) | 5.31 (−7.91–18.53) | **0.001** |
| %ΔSCL during to post-intervention | 4.95 (−2.61–12.51) | −4.52 (−12.0.8–3.04) | 0.082 |
| %ΔSCL baseline to post-intervention | 45.26 (25.76–64.77) | 5.56 (−13.95–25.06) | **0.007** |
| ΔSCR frequency[a] baseline to during intervention | 0.59 (0.34–0.85) | 0.23 (0.03–0.48) | **0.048** |
| ΔSCR frequency[a] during to post-intervention | 0.06 (−0.29–0.42) | −0.09 (−0.45–0.26) | 0.539 |
| ΔSCR frequency[a] baseline to post-intervention | 0.64 (0.26–1) | 0.23 (−0.15–0.6) | 0.124 |
| Maximum amplitude (μS) SCR during intervention | 0.95 (0.71–1.19) | 0.71 (0.49–0.93) | 0.148 |
| Maximum amplitude (μS) SCR post intervention | 0.47 (0.17–0.77) | 0.4 (0.1–0.7) | 0.737 |
| Time (mins) to 50% of all SCRs during intervention | 4.5 (2.99–6.02) | 2.23 (1.36–3.1) | **0.018** |

[a] Skin conductance responses per minute.
[b] Between group comparison.

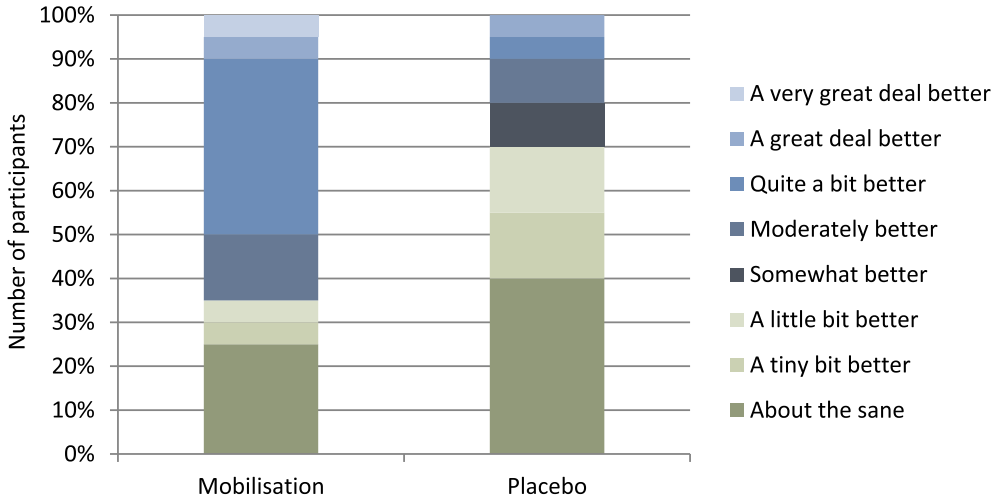


**Fig. 3.** Participant perceived improvement (GROC scale).

The original model of mobilisation induced pain relief attributed the effects to several mechanisms including changes in peripheral structures, activation of descending inhibitory systems, segmental pain inhibition and psychological influences (Wright, 1995; Souvlis et al., 2004; Wright and Grant, 2002; Wright et al., 1995). Therefore, a relationship between sympathoexcitation (thought to occur concurrently with the activation of a descending inhibitory system) and symptomatic improvement may be difficult to establish, given the fact that symptomatic relief may be attributed to a multifaceted process that includes not only the activation of descending inhibition. It is of note that, unlike Vicenzino et al. (Vicenzino et al., 1998a), who mobilised the cervical spine in participants with epicondylalgia, our mobilisations were directed at the symptomatic area. This may have modified the chemical environment of peripheral nociceptors or influence other peripheral sources of symptoms such as muscle or fascia and contribute to pain relief by means other than the activation of endogenous pain inhibition.

Alternatively the observed sympathoexcitatory changes may be considered components of the orienting response (Bradley, 2009), which would also explain the lack of an association with symptomatic relief. An orienting response is a sudden shift of attention to a new, unpredictable or unexpected stimulus, which permits its evaluation and, if necessary, adopting appropriate behavioural action (Friedman et al., 2009). During an orienting response, the presentation of novel, non-aversive and significant stimuli (in this case tactile or painful) cause sympathoexcitatory changes observable through %ΔSCL and presence of SCRs (Dawson et al., 2016; Bradley, 2009); a large SCR response is observed with the first stimulus, which gradually decreases and eventually vanishes due to habituation (Boucsein et al., 2012; Vetrugno et al., 2003). We found no differences between groups in the maximum amplitude SCR, a measure of the magnitude of the initial SNS response (Benedek and Kaernbach, 2010a; Sequeira et al., 2009), suggesting that both interventions provide a similar initial sympathoexcitatory stimulation. However, the significant differences in the frequency of SCR during intervention may suggest that the ever-changing stimuli provided by mobilisations (variation in force, mobilisation level, side, and pain reproduction) are capable of providing a novel stimulus for a longer duration than placebo. Time to 50% of all SCRs during the intervention was shorter in the placebo group, suggesting earlier habituation to the stimulus. Once the stimulus was removed (post-intervention) no differences in SCR between groups were detected.

SCL is considered to reflect an overall level of SNS arousal (Boucsein et al., 2012; Braithwaite et al., 2014; Buckingham, 2008) and has been shown to increase in response to external stimuli and attention to internal information processing (Dawson et al., 2016). The longer lasting and changing proprioceptive and nociceptive (if pain is reproduced) stimuli provided by mobilisations and its associated emotions (expectation, fear of pain etc) may be responsible for the increased SCL. Fear of pain has been shown to cause increased SCL in participants with spinal pain (Glombiewski et al., 2015). Changes in SC have been associated with several emotions including anxiety, fear, suspense or relief (Kreibig, 2010), all of which may be provoked by the therapist-patient interaction during an intervention involving cervical mobilisations. The relationship between emotional responses and SC is such that sweat gland activity in the palms and fingers (and hence %ΔSCL) has been termed “emotional sweating” (Storm, 2008; Sequeira et al., 2009; Asahina et al., 2015), thought to be predominantly controlled by the anterior cingulated cortex (Vetrugno et al., 2003). It is of note that participants with neck pain demonstrate increased SC responses when watching a video that involves neck movements, and that SC responses are positively correlated with scores of kinesiophobia (La Touche et al., 2018).

%ΔSCL may have also been affected by the occurrence of several consecutive SCRs due to repetitive stimulation, where following a SCR, SCL does not have enough time to return to baseline values before a subsequent SCR is produced (Dawson et al., 2016). Hence, increased SCL in the mobilisations group may also be explained by the number of SCRs provoked by the intervention. We noted a positive correlation between %ΔSCL and ΔSCR frequency in all tested time periods.

It has also been suggested that mobilisations may mechanically stimulate the sympathetic trunk and paravertebral ganglia due to proximity to the cervical joints being mobilised (Kingston et al., 2014; Slater et al., 1994). Since we mobilised both sides of the cervical spine, we are unable to determine if the ΔSC were part of a generalised response or the occurrence of specific bilateral neck responses, although previously Sterling et al. (Sterling et al., 2001) reported no effect of treatment side, and the observed pattern of sympathoexcitation is more suggestive of the aforementioned phenomena.

This study supports previous reports of mobilisation induced sympathoexcitation. Changes in SC were not associated with symptomatic improvement. This may be explained by the existence of various mechanisms for pain relief or the occurrence of an orienting response. Whilst direct stimulation of dPAG has been shown to cause sympathoexcitation (Benarroch, 2012), this is also the case for the stimulation of the amygdala, hippocampus, anterior cingulate and frontal cortex (Vetrugno et al., 2003; Mangina and Beuzeron-Mangina, 1996). Further research is required to ascertain the nature of the sympathoexcitatory changes observed and their relevance in mobilisations induced symptomatic relief.

## 5. Study limitations

We used GROC to assess symptomatic improvement and its association with changes in SC. It is possible that GROC may have not been sensitive and specific enough to detect differences between participants. The use of further outcome measures of sympathoexcitation (e.g blood flux), symptomatic improvement and nociceptive function such us pain during specific neck movements or pressure pain threshold, could have aided the understanding of the neurophysiological mechanisms responsible for symptomatic change. This study was limited in the use of a single outcome measure of SNS function and symptomatic improvement.

Although the majority of participants had chronic neck pain, the sample also included a few acute/subacute patients. Mechanisms of mobilisations may differ between these groups and hinder the possibility of detecting an association between symptomatic improvement and a single mechanism.

## 6. Conclusion

Cervical mobilisations were immediately effective at reducing symptoms in participants with neck pain. When compared to placebo, they produced significant increase in SC, however changes were not associated with symptomatic relief. It is possible that SC changes may be secondary to an orienting response unrelated to the activation of a central nervous system mediated pain inhibition system. Alternatively, the observed lack of an association may be explained by the limitations of the study discussed above.

## Conflicts of interest

None.

## Ethical approval

The study received the approval of the University of the Basque Country Research Ethics Committee.

## Funding

None.

## Clinical trials registry

ClinicalTrials.gov record number: M10/2016/095.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2019.05.001.

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