2020

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This article was originally published as:
Muhsen, A., Moss, P., Gibson, W., Walker, B., Jacques, A., Schug, S. A., & Wright, A. (2020). The influence of a positive empathetic interaction on conditioned pain modulation and manipulation induced analgesia in people with lateral epicondylalgia. *Clinical Journal of Pain, Early View, Online First*.

Original article available here:
10.1097/AJP.0000000000000822

**The Clinical Journal of Pain Publish Ahead of Print**
**DOI:10.1097/AJP.0000000000000822**



# The influence of a positive empathetic interaction on conditioned pain modulation and manipulation induced analgesia in people with lateral epicondylalgia

**ORIGINAL ARTICLE**

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**Funding Sources**

The research was part of a PhD project that was funded by the Hashemite University, Jordan. The work was also supported by the School of Physiotherapy and Exercise Science at Curtin University.

## Abstract

**Objective:** Conditioned pain modulation (CPM) and manipulation induced analgesia (MIA) are two forms of endogenous analgesia. Many forms of analgesia can be influenced by the nature of the patient clinician interaction. The aim of this study was to evaluate the influence of an empathetic and supportive interaction on CPM and MIA in people with Lateral Epicondylalgia (LE).

**Methods**: In a double-blind, randomised, controlled trial, 68 participants with LE were assigned to two groups: the empathetic and neutral interaction groups. The interactions were carried out by a trained, professional role play actor, playing the part of a research assistant (RA). The RA actor spent 15min prior to CPM and MIA assessment interacting with the participants in an empathetic or neutral manner. Immediately after the interaction, a blinded assessor measured pressure pain threshold (PPT) at the symptomatic elbow and ipsilateral wrist during CPM and MIA testing. Linear mixed models were used to evaluate differences in CPM and MIA responses between the interaction groups.

**Results:** There was a significant difference in CARE scores between the groups ($p<0.001$), indicating that the intervention group experienced a more empathic interaction. Both groups showed a significant increase in PPT measures, indicative of a CPM and MIA analgesic response ($p<0.001$), however the analgesic responses were greater in the group that had experienced a supportive, empathetic interaction (post CPM, wrist: $p<0.001$; elbow: $p=0.001$), (post MIA wrist: $p=<0.001$; elbow: $p=0.001$).

**Discussion:** A single session of empathetic interaction positively influenced both CPM and MIA responses in people with LE.

## Keywords

Conditioned pain modulation, manipulation induced analgesia, empathy, therapeutic interaction, lateral epicondylalgia

The authors declare no conflict of interest.

## 1. Introduction

A positive therapeutic interaction involves an emotional bond between clinicians and their patients, and agreement about treatment goals and interventions. This is essential for the effective delivery of clinical care [1, 2]. It requires the clinician to connect positively with patients [3] through development of rapport [4], respect [5], empathy, trust [4], and collaboration [6]. A positive therapeutic interaction has been shown to improve patient engagement in therapy, patient satisfaction and treatment effectiveness [7, 8].

Previous research has identified key aspects of a positive therapeutic interaction [9]. Mistiaen and colleagues classified patient-clinician interactions into three main components: cognitive care, emotional care and procedural preparation [10]. Cognitive care involves enhancing the patient's expectations to produce a positive therapeutic outcome. Emotional care involves improving the perceived empathy of the clinician and so put patients at ease. This can encompass strategies such as continuous verbal support and reassurance [11], active listening [12], showing friendliness and warmth [13], encouraging a sense of control [14], using non-verbal strategies (eye contact, head nodding, smiling), and explaining questions clearly [15]. Procedural preparation deals with arrangements intended to facilitate therapeutic interventions such as information giving, procedural instructions, and relaxation [10]. Manipulating these components in experimental settings has been shown to influence patients' perceptions of their pain [10]. Mistiaen et al concluded however, that more research is necessary to distinguish the most influential of these components [10].

Nir and colleagues investigated the effect on conditioned pain modulation (CPM) of positive (likely placebo-inducing) and negative (likely nocebo-inducing) suggestions about the effects of an anaesthetic cream in healthy participants [16]. The placebo-induced group showed a reduction in pain, and therefore a CPM effect. In contrast, the nocebo-induced group demonstrated an increase in pain, therefore no CPM effect and in fact a hyperalgesic

response. A further study investigated the impact of verbally delivered positive or negative expectations on CPM analgesia [17]. Compared to the control group that received simple instructions, the nocebo-induced group demonstrated an increase in pain in response to the suggestion that cold application would be painful. In contrast, the placebo-induced group showed a reduction in the test stimulus pain as a result of a suggestion of decreased pain [17]. This highlights the importance of cognitive influences on CPM response.

The influence of cognitive factors on manipulation induced analgesia (MIA) has not been widely investigated. Bialosky and colleagues [18] studied the impact of expectation (positive, negative, neutral) of pain relief on the analgesic effect of lumbar spine manipulation. The positive expectation group was informed that lumbar manipulation, "is a very effective form of manipulation used to treat low back pain (LBP) and we expect it to reduce your perception of heat pain". The negative expectation group was given the opposite instruction, while the neutral group was informed that manipulation had, "an unknown effect" on heat pain perception. The negative expectation group showed a substantial increase in pain response during thermal sensitivity testing (i.e. a nocebo response), while no effect was observed on pain perception in the positive or neutral expectation groups. Expectation may therefore have an influence on MIA, although the effect does not appear to be as consistent as it is for CPM. Recent research has shown a significant positive correlation between the MIA response and CPM response suggesting that both forms of endogenous analgesia may share similar mechanisms [19]. However, to date, there have been no studies investigating the influence of an enhanced, empathetic interaction on CPM and MIA concurrently.

It is clear that there is a strong overlap between areas of the brain involved in attentional and emotional modulation of pain and areas of the brain related to expectation, anticipation and emotional state [20, 21]. Areas such as anterior cingulate cortex, anterior insula and

orbitofrontal cortex appear to be important for regulating attention, emotional state and pain perception [20, 21].

This study therefore aimed to evaluate, in individuals with tennis elbow, the effect of a positive, supportive empathetic interaction, compared to a neutral interaction on a person's hypoalgesic response related to CPM and MIA. If the intervention produced similar changes in MIA and CPM response this would strengthen support for the suggestion that they share similar neurophysiological mechanisms. Tennis elbow was used as the clinical model for this study since evidence for the analgesic effect of cervical manual therapy in lateral epicondylalgia (LE) is well established [19, 22-24] and data have been published evaluating CPM analgesia in this condition [19, 25].

## 2. Materials and Method

### Study design

A randomised, controlled, between-group experimental design was used. Eligible participants were randomised to receive either an enhanced empathetic interaction (active) condition or a neutral interaction (control) condition in one single session.

### Randomisation

The randomisation sequence was computer-generated and held by a researcher who was not otherwise involved in the study. Group allocation for each participant was ascertained prior to the test session by the research assistant (RA) actor, who provided the interaction condition but did no testing. The primary investigator (AM), who completed all CPM and MIA testing, remained blind to group allocation.

### Participants

A group of 68 participants with LE, aged between 18 and 60 years, was voluntarily recruited from Perth, Western Australia between March 2017 and April 2018 through radio advertisements, adverts in physiotherapy clinics and a specialised online clinical trials

recruitment agency. Individuals aged 18 years or older who met the clinical criteria for diagnosis of LE as defined by Haker and Lundeberg [26] were included. Exclusion criteria included: evidence of neurological or radicular dysfunction; history of fracture/surgery in the forequarter (past 2 years); history of generalized arthritis; other significant chronic pain problems, recent steroid injection into the elbow (preceding month); specific contraindications to cold application; current use of antidepressants. To confirm that eligibility criteria were met, a thorough clinical examination of all participants was carried out by the primary investigator (AM) prior to commencing the study. All testing was carried out at the Physiotherapy Clinic, School of Physiotherapy and Exercise Science, Curtin University. Participants were asked to refrain from taking pain medications 24 hours prior to testing and to avoid any physiotherapy treatment and other physical treatments (e.g. chiropractic or acupuncture) on the testing day.

Curtin University Human Research Ethics Committee approved the study (HREC approval number: HRE2016-0175). On the testing day, all participants provided written informed consent prior to commencing testing. Each participant was provided with a $20 voucher to pay for travel and parking.

**Conditioned pain modulation (CPM) protocol**

CPM is based on the phenomenon of pain inhibiting pain and it is a commonly used test paradigm [19].

**Test stimulus**: Participants were seated with the affected forearm comfortably positioned in pronation on a table. PPT was then tested on three occasions at two sites over the wrist and elbow of the affected arm: at baseline prior to cold water immersion; at 1 minute during cold water immersion; and at 1 minute post immersion. At each time point, PPT was measured three times at each site with 10-15-second intervals between [23]. The mean PPT value at each site was used for analysis.

**Conditioning stimulus**: The Cold Pressor Test (CPT) was used as a conditioning stimulus to elicit a CPM response. The unaffected hand was submerged to 10 cm above the wrist crease in a water bath maintained at 10°C for a period of 2 minutes [19, 27]. The water bath contained a mix of water and ice and had a circulating pump and thermometer to ensure uniformity of water temperature at the skin.

**Manipulation induced analgesia (MIA) protocol**

MIA refers to the initial analgesic response induced by joint mobilisation techniques [19].

**Test stimulus**: PPT at the wrist and elbow test sites was used as the test stimulus. PPT was assessed at both sites before and immediately after the manual therapy stimulus (C5/6 cervical lateral glide (CLG)) [28]. Testing was performed with the participants lying supine on a plinth. The pain-free grip (PFG) and upper limb neurodynamic-radial nerve (ULND-RN) bias tests were also performed pre and post CLG to provide additional evidence of the MIA effect (described below).

**Mobilisation stimulus**: a grade III passive oscillatory, cervical lateral glide (CLG) of the C5/6 motion segment of the cervical spine was used to induce MIA [23, 29]. The participant lay supine with arms by their side and they were instructed to report if they felt any discomfort or pain during the mobilisation. In contrast to CPM, this mobilisation technique was intended to be painless [29]. The CLG mobilisation was performed for 60 seconds, and was repeated three times, with 60-second rest periods in between (5 minutes total) [23].

**Pressure pain threshold (PPT)**

PPT has been shown to have a high intra-rater reliability with excellent intra-class correlation coefficients (ICCs: 0.81-0.99) when measured at 4 different body sites [30], and more particularly when used for assessment of pain in LE (ICC 0.86) [23]. During pilot testing

ICCs of 0.991 and 0.986 at the wrist and elbow, respectively, were demonstrated for repeated PPT measures by the assessor in the current study (AM).

All PPT measures were carried out by a single assessor (AM). The assessor identified the most tender point at the lateral aspect of the affected elbow and a point on the posterior aspect of the wrist, 2 cm proximal to the wrist crease. These sites were marked. A digital pressure algometer (SOMEDIC, Sweden) was used, with standard instructions and settings ($1cm^2$ tip, 40kPa/sec slope). For the MIA protocol the participant lay supine on a plinth and a standard hand switch control was used. For the CPM assessment protocol, the participant was in sitting and a modified footswitch control was used [19, 31]. Mean PPT values (kPa) of three measurements were used in analysis.

**Pain free grip (PFG)**

Pain on gripping is a common feature of LE [32]. Pain free grip (PFG) is the amount of grip force that can be applied prior to the onset of pain [32]. PFG was measured with an electronic digital dynamometer (MIE, Medical Research Ltd.) using standard methodology [19, 32]. It is both a reliable (ICC 0.97) [25] and valid measure for use in patients with LE. The participant lay supine and was requested to squeeze the dynamometer handles until they first felt their lateral elbow pain, and then to stop the squeezing action. The PFG test was performed three times with 10-20 second rest intervals and the average value was used for analysis.

**Upper limb neurodynamic test with radial nerve bias (ULNDT-RN)**

The upper limb neurodynamic test with radial nerve bias (ULNDT-RN) has been used to assess neural mobility of the upper limb [33]. Pain-free range in this test has been shown to be restricted in people with LE [34]. The participant was positioned in supine and their symptomatic arm progressively moved into shoulder abduction following a standard protocol, until the participant indicated the onset of pain [19, 23]. The shoulder abduction range at the

onset of pain was measured. Three measures were obtained with 20-30 second intervals and the average of these readings was used for analysis.

**Tennis Elbow specific assessment questionnaire**

All participants were also asked to complete the Patient Rated Tennis Elbow Evaluation (PRTEE). This questionnaire measures pain (5 items) and functional disability levels (10 items) during activities over the preceding week on a scale of 0-10 [35]. It is a reliable and valid [35-37] measure for evaluation of pain and function in people with LE.

**Experimental conditions: enhanced and neutral interactions**

Enhanced and neutral interaction conditions were provided by a female professional role play actor portraying the role of a research assistant (RA Actor). The interaction was delivered at two time-points during the study: for 15 minutes at the start of the session, before the CPM assessment protocol; and for 15 minutes during the rest period before the MIA test protocol. The RA actor remained in the room throughout the experiment but undertook some administrative activities and did not directly interact with the participant when the primary researcher was present in the room to undertake testing.

**Enhanced empathetic interaction condition**: For the enhanced interaction the RA actor engaged in a very positive, supportive and empathic interaction with the participant. This included many of the elements identified by Mistiaen and colleagues as cognitive care [10]. Her interaction was carefully controlled to include features that were likely to enhance the perception of empathy. The RA actor was very positive and enthusiastic about the participant's assistance with the project and supportive about the participant's LE condition. She established good rapport with the participant through use of positive communication strategies and body language. This included: assuming an open posture, maintaining appropriate eye contact, head nodding, being friendly and warm, using the person's name, listening to them without interruption, showing an interest in their life and interests, asking

about the impact of LE on them. The RA actor also used appropriate disengagement to smoothly transition the discussion from one topic to another or to initiate procedural activities as required.

**Neutral interaction condition**: For the neutral interaction the RA actor limited her engagement with the participant. She initially spent 5 minutes on normal, business-like interactions with the participant, greeting the participant and briefly advising them about the study without being particularly positive, supportive, or enthusiastic. The actor's interaction was carefully controlled so as not to include features that were likely to enhance empathy (i.e. none of the above). There was then a 10-minute interval during which the participant was asked to rest and the RA actor completed some administrative tasks and minimized interaction with the participant. The RA actor did not initiate conversation but politely and concisely answered any questions that were asked. She made minimal eye-contact, adopted a closed body position, showed more interest in her laptop or phone and concerned herself with her administrative tasks. In the 15 minute rest period before the MIA testing protocol was conducted there was only a short discussion and only minimal interaction with the RA actor as before.

**Intervention Fidelity**

In preparation for the study, the actor was given a detailed script explaining the key attitudes and behaviors that should be portrayed during each period of time on each testing day. The professional role play actor then underwent a comprehensive coaching session in which they were trained to perform the enhanced empathetic and neutral interactions by the research team, including a simulation expert.

The actor's adherence to experimental procedures was audited by a member of the research team during randomly selected testing sessions, to ensure intervention fidelity. These

observations confirmed that there was a clear difference in actor interactions between the enhanced and neutral groups.

**Procedure**

All participants attended a single test session where they underwent a CPM assessment protocol followed by a MIA assessment protocol, with either an enhanced or a neutral therapeutic interaction as described above. A rest period of 15 minutes was provided between the CPM and MIA test protocols (Figure 1). Both CPM and MIA assessment protocols were performed by the same primary investigator (AM), who was blinded to the intervention group of each participant. Interactions between this assessor and all participants were kept as neutral and standardised as possible.

Following completion of the experiment, participants were thanked for their participation and received a debriefing session from the primary investigator, in the presence of the RA actor, to explain the purpose of the study and the role of the RA actor in both experimental conditions. Any questions were also answered.

**Empathetic interaction outcome measure**

At the end of the testing session, and in the absence of the RA actor, all participants were asked by the main investigator to complete the Consultation and Relational Empathy (CARE) Measure [38] to rate the overall interaction they experienced with the RA actor. The CARE measure includes 10 items rated on a 5 point scale (poor=1, excellent=5) that were summed to give a total score out of 50. A maximum of 2 'does not apply' responses were permitted and these were substituted by the mean average score of other responses [38]. The CARE Measure has been validated for assessment of empathetic interaction in primary [39] and secondary care [40], and in rehabilitation settings [41]. It has been shown to have a high reliability (Cronbach's $\alpha$=0.92) and excellent validity (mean r=0.85) compared to other measures of empathy [38].

**Actor Evaluation**

The RA actor was also required to rate how well she was able to deliver an enhanced or neutral interaction session as appropriate for each participant, using a quality of session scale: (0-10; unsatisfactory to excellent).

**Sample Size calculation**

Sample size calculations were conducted using Stata/IC (version 15.0: StataCorp LLC, TX). Based on data from a large clinical trial comparing corticosteroid injections and physiotherapy management of lateral epicondylalgia [42], the minimal clinically important difference (MCID) in PPT at the elbow was considered to be 88kPa (personal communication) [43]. In determining the sample size, we used a more conservative difference value of 50kPa (just above half of the MCID) because we anticipated that the effect of the psychological intervention evaluated in this study might be more subtle than the influence of a corticosteroid injection. Using this value with a pooled standard deviation of 73.22kPa the sample size calculation indicated a required sample size of 68 (34 per group).

**Statistical analysis**

Data were analysed using Stata/IC (version 15.0: StataCorp LLC, TX). For all analyses, $p<0.05$ was considered statistically significant. Descriptive statistics were based on frequency distributions for categorical data (i.e. sex and elbow tested) and means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous data (age, duration CARE, RA actor rating and PRTEE), depending on normality. Univariate group comparisons between intervention groups included $\chi^2$ and Fisher exact tests for categorical comparisons, and independent t-tests or Mann-Whitney U tests for continuous outcomes.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data were transformed using natural logarithms or square root transformations.

Generalised linear mixed models with log or identity link functions, as appropriate, and with random subject effects were used to calculate the overall differences (relative to baseline) between time points (all participants) and between groups over time for CPM and MIA outcomes (i.e. PPT, PFG and ULNDT-RN). The initial model calculated predicted marginal means adjusted for the CARE score, RA quality of session rating and sex to determine overall differences between time points (all participants). A further model determined predicted marginal means adjusted for CARE score, RA quality of session rating and sex and evaluated differences between the enhanced and neutral interaction groups over time. The respective marginal means, 95% confidence intervals (CI), and p-values of these differences were calculated.

Number needed to treat (NNT) analysis was also performed for each interaction group to compare CPM and MIA effect using an online NNT calculator [44]. We defined a difference of 50kPa (the value used in our sample size calculations) between the pre and post PPT measures obtained for CPM and MIA protocols as a clinically positive outcome.

## 3. Results

A total of 68 participants met the eligibility criteria and participated in the study. There were no drop-outs. All participants received the intended interaction intervention for their group (n=34 per group), and all data were analysed. Characteristics of the participants are summarised by group in Table 1.

**Demographics**

There were no significant group differences in the characteristics of participants in each of the experimental groups (i.e. affected elbow tested (p=0.097), age (p=0.950) and duration of tennis elbow condition (p=0.738). Although there were more females in the enhanced interaction group, the sex difference did not reach significance (p=0.112). There was also no statistically significant difference between groups for PRTEE scores (p=0.203). The mean

PRTEE score was 37.1 points (SD=17.7) for the neutral interaction group and 42.5 points (SD=17.1) for the enhanced interaction group.

**Empathetic interaction outcome measures**

There was a significant difference in the CARE Measure score ($p<0.001$) between groups, with the enhanced interaction group reporting higher RA actor empathy: neutral (27.5/50, SD=12.6), enhanced (43.8/50, SD=7.2). The RA rating of the quality of the sessions was close to significant ($p=0.052$) suggesting more effective delivery of the enhanced interaction sessions, although the average scores for both groups were high (8.8/10, SD 1.5 compared with 8.0/10, SD 1.7) suggesting that the professional actor believed that overall the sessions were delivered appropriately.

**Between-time points (all participants)**

**CPM and MIA response**

The differences in PPT between time-points for all participants are presented in Table 2. Both interaction groups demonstrated a significant analgesic effect (increase in PPT) at both wrist and elbow sites for CPM: baseline to during CPM ($p<0.001$) and baseline to immediately post CPM ($p<0.001$). They also showed a significant analgesic effect for MIA: baseline to post MIA ($p<0.001$).

**PFG and ULNDT-RN**

PFG and ULNDT-RN were used as secondary evidence of MIA effect (Table 2). There was a significant increase in PFG ($p<0.001$) and ULNDT-RN ($p<0.001$) following the CLG mobilisation.

**Group x time interaction effects**

**CPM and MIA response**

Table 3 shows that there were significant group x time interaction effects for PPT at both test sites during CPM (wrist: $p<0.001$; elbow: $p<0.001$), post CPM (wrist: $p<0.001$; elbow:

p=0.001) and post MIA (wrist: p<0.001; elbow: p=0.001). In each case, a greater increase in PPT (higher levels of analgesia) was observed for the enhanced interaction group compared to the neutral group.

**PFG and ULNDT-RN**

There were no significant group x time interaction effects for change in PFG (p=0.293) or ULNDT-RN (p=0.971). (Table 3).

**Number needed to treat (NNT)**

Table 4 shows that there were a greater number of positive outcomes (> 50kPa increase in PPT) for the enhanced interaction group, compared to the neutral interaction group. The lowest NNT was for MIA effect at the elbow, indicating a greater influence of the enhanced interaction for this measure, which may be relevant for LE treatment.

## 4. Discussion

All participants demonstrated a significant analgesic response (as measured by PPT) at both the elbow and the wrist sites for both CPM and MIA. There was also a significant difference in PPT between groups over time, with the enhanced empathetic interaction group demonstrating higher levels of analgesia compared to the neutral interaction group, again for both CPM and MIA. In addition, there was a higher number of positive outcomes (> 50 kPa increase in PPT) for the enhanced empathetic interaction group. There was however no difference in PFG or ULNDT-RN values between groups.

Participants' evaluation of the session clearly distinguished the enhanced and neutral interaction conditions. The enhanced interaction group scored higher on the CARE measure as compared to the neutral interaction group. This higher score is an indication that the positive and empathetic interactions of the RA actor when dealing with the participants in the enhanced interaction group were effective and the interaction with the enhanced group was clearly distinct from the neutral group. The neutral group rating of 27.5/50 suggests a mid-

range rating of the interaction with approximately half the participants rating the session negatively and approximately half rating it positively.

The RA actor rating of the effective delivery of the interaction sessions approached significance (p=0.052) with a rating for the enhanced interaction group of 8.8/10 indicating that the actor felt they had delivered the enhanced interaction better than the more limited, neutral interaction (8/10). The relatively high score on the actor evaluation measure for both groups however suggests that overall the two different types of interaction were appropriately and adequately delivered.

A number of recent studies have highlighted the importance of psychological influences on CPM response. Gougeon and colleagues [45] studied the role of empathy in influencing CPM during three experimental conditions: pain, self-observation, and spouse-observation. Both the self-observation and spouse-observation conditions showed significant CPM effects, even in the absence of a painful conditioning stimulus [45]. Whilst that study investigated the impact of participants' empathy on CPM in response to emotional triggers, the current study examined the effect of an empathetic interaction initiated by a care provider on CPM responses, which has not been previously investigated. This study therefore provides new data in relation to the effect of manipulating the empathetic and cognitive care component of the interaction on CPM response.

A recent study by Fuentes and colleagues [12] manipulated the therapist-patient interaction (enhanced or limited) to investigate the pain relieving effect of a single session of interferential current (IFC) (sham or active) on low back pain. Compared to other groups, the group that received active IFC with an enhanced interaction experienced the most significant pain relief on a numerical pain rating scale. There was also a significant increase in PPT for both sham and active groups when combined with an enhanced interaction [12]. The authors concluded that enhanced interactions positively influenced clinical outcomes when combined

with active IFC in the treatment of LBP. Fuentes and colleagues manipulated the enhanced interaction through verbal and nonverbal behaviors and empathy, and measured expectancy, but they did not evaluate the degree of empathy experienced during the therapeutic interaction [12]. The current study however specifically manipulated the degree of empathy experienced during the interaction and assessed the interaction using the CARE Measure. The use of a trained professional actor helped to ensure a clear distinction between the types of interaction.

A recent study demonstrated a positive association between CPM response and MIA response in a cohort of people experiencing LE [19]. This suggests that these forms of hypoalgesia may share similar mechanisms. The current study provides further evidence to support this proposed overlap between the MIA and CPM responses, in that both phenomena were enhanced by a positive, supportive interaction. Further research is warranted to explore potential links between these two forms of endogenous analgesia.

**Clinical implications**

We used the NNT analysis to compare the influence of the interactions on CPM and MIA effects. An NNT value of 2.13 for PPT change at the elbow following MIA is a useful indication of the added value of empathetic interaction (relative to the neutral interaction) to potentially reduce pain in musculoskeletal practice. The extent to which it is possible to achieve these potential benefits in the clinical setting is unpredictable but certainly warrants further study.

The results of this study suggest that a patient's perception of a clinician as being empathetic and supportive may be associated with improvement in objective analgesic response. Clinicians are often encouraged to be more empathetic as part of a client-centred approach. This concept is based on evidence from the business sphere, where clients will be more satisfied with the service they receive if they have an enhanced interaction with the service

provider [7, 8]. Our findings therefore provide further evidence to support the use of an enhanced interaction with patients to reduce their pain in any clinical encounter.

**Limitations**

There are several potentially limiting factors in this study that need to be taken into consideration. First, there was a difference in the sex balance between the groups, with the enhanced interaction group having more females (63.6%) than the neutral interaction group (45.5%). This might explain the lower baseline PPT threshold values recorded for this group, as females tend to have lower PPT values than males [46-48]. However, statistically the group sex difference was not significant (p=0.112) and sex was also controlled for in the analysis. A baseline evaluation of each individuals CPM and MIA responsiveness was not carried out and so we do not know if there was any inherent difference between the groups in their capacity to exhibit a CPM or MIA response. Random assignment to the test groups should have minimized the influence of individual variations but without a baseline measurement we cannot confirm this. Whilst there was a clear difference in PPT measures between groups this was not reflected in any distinction between the PFG or ULNDT-RN measures for the MIA testing protocol. It may be that a larger participant cohort or a more sustained intervention might be required to see differences in these measures.

Although interacting for 15 minutes prior to CPM and MIA protocols was sufficient to induce increased analgesic responses in people with LE, it remains unclear whether higher levels of analgesia or a positive effect on PFG and ULNDT-RN would have been achieved with a longer enhanced interaction. Equally, only the immediate analgesic responses of CPM and MIA were measured. Although in this study we investigated the degree of CPM and MIA induced by a short term interaction, it would be useful to gather more information on the pattern of CPM and MIA responses gathered over longer follow-up periods. The current study used an additional person to provide the enhanced or neutral interaction, in order to

benefit from the expertise of a professional actor. However, this person did not deliver any treatment. Future studies could consider ways to train experienced clinicians to deliver neutral or enhanced interaction as an integrated component of the therapeutic interaction.

**Conclusion**

The current study showed that a single session of enhanced, supportive, empathetic interaction positively influenced CPM and MIA analgesic responses in people with LE. Results also showed that both interaction groups demonstrated analgesia during the CPM and MIA protocols. Our previous research has shown a positive association between CPM and MIA responses in the same clinical condition [19]. It has therefore been suggested that CPM and MIA may share similar neurophysiological mechanisms when activating endogenous descending pain inhibitory systems [19]. Further research is recommended into the effect of a longer period of enhanced empathetic intervention on MIA, and into the specific mechanisms through which CPM and MIA exert their effects.

**Acknowledgements**

The authors thank all of the participants who contributed their time to the study. They would also like to thank Sharon Thomas and Role Players on Demand for their contribution to the research.

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**Figure Legends**

**Figure 1:** Consort diagram for participant flow though recruitment and study procedure.

**Figure 2:** Study procedure. PPT: pressure pain threshold, CPM: conditioned pain modulation, CPT: cold pressor test, PRTEE: patient rated tennis elbow evaluation, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test- radial nerve, CLG: cervical lateral glide.

**Table 1:** Descriptive summaries for the research sample by intervention groups.
Data are presented as mean and standard deviation (SD) unless otherwise specified*

| | | **Neutral n=34** ***Mean (SD)*** | **Enhanced n=34** ***Mean (SD)*** | **p** |
|---|---|---|---|---|
| Sex n (%)* | F | 15 (44.1) | 21 (61.8) | 0.112 |
| | M | 19 (55.9) | 13 (38.2) | |
| Elbow tested n (%)* | L | 8 (23.5) | 14 (41.2) | 0.097 |
| | R | 26 (76.5) | 20 (58.8) | |
| Age (years) | | 50.8 (11.2) | 50.6 (9.6) | 0.950 |
| Duration (years) median, (IQR)* | | 0.6 (0.3, 2.1) | 0.5 (0.3, 2.0) | 0.738 |
| PRTEE | | 37.1 (17.7) | 42.5 (17.1) | 0.203 |
| CARE Measure | | 27.5 (12.6) | 43.8 (7.2) | **<0.001** |
| RA rating of rapport (1-10 scale) | | 8.0 (1.7) | 8.8 (1.5) | 0.052 |

F: female, M: male, L: left, R: right. IQR: interquartile range, PRTEE: patient rated tennis elbow evaluation, CARE: consultation and relational empathy measure, RA: research assistant. Level of significance, $p<0.05$

**Table 2:** Linear mixed models for CPM and MIA responses: predicted marginal means adjusted for the CARE Measure, RA actor rating and sex: overall differences between time points (all participants).

| Test/ Measurement | Mean pre CPM MIA | Mean during CPM | Mean post CPM/ MIA | 95%CI (mean) pre CPM/MIA | 95%CI (mean) during CPM | 95% CI (mean) post CPM/ MIA | p pre-during CPM | p pre-post CPM/MIA |
|---|---|---|---|---|---|---|---|---|
| CPM Wrist PPT | 383.63 | 470.63 | 425.76 | 354.15 - 413.11 | 434.85 - 506.42 | 393.27 - 458.25 | **<0.001** | **<0.001** |
| CPM Elbow PPT | 254.00 | 338.94 | 289.82 | 235.91 - 272.09 | 315.53 - 362.36 | 269.52 - 310.11 | **<0.001** | **<0.001** |
| MIA Wrist PPT | 399.08 | | 454.33 | 365.75 - 432.42 | | 416.64 - 492.01 | — | **<0.001** |
| MIA Elbow PPT | 275.47 | | 342.54 | 253.85 - 297.09 | | 320.92 - 364.17 | — | **<0.001** |
| PFG | 177.68 | | 209.77 | 160.44 - 194.92 | | 192.53 - 227.01 | — | **<0.001** |
| ULNDT-RN | 13.32 | | 18.74 | 11.78 - 14.87 | | 17.20 - 20.29 | — | **<0.001** |

CPM: conditioned pain modulation, MIA: manipulation induced analgesia, 95% CI: 95% confidence interval, PPT: pressure pain threshold, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test-radial nerve bias. Level of significance, $p<0.05$.

**Table 3:** Linear mixed models for CPM and MIA responses: predicted marginal means adjusted for CARE, RA actor rating and sex: differences between enhanced and neutral interaction groups over time.

| Test/ Measurement | Interaction group | Mean pre CPM/ MIA | Mean during CPM | Mean post CPM/ MIA | 95%CI (mean) pre CPM | 95%CI (mean) during CPM | 95% CI (mean) post CPM/ MIA | p pre-during CPM | p pre-post CPM/MIA |
|---|---|---|---|---|---|---|---|---|---|
| CPM Wrist PPT | Enhanced | 361.02 | 479.45 | 424.54 | 315.69 - 406.34 | 419.78 - 539.12 | 371.54 - 477.53 | **<0.001** | **<0.001** |
| | Neutral | 405.28 | 462.19 | 426.93 | 355.94 - 454.61 | 406.12 - 518.26 | 375.04 - 478.83 | | |
| CPM Elbow PPT | Enhanced | 239.61 | 350.92 | 290.53 | 211.99 - 267.23 | 311.72 - 390.12 | 257.66 - 323.39 | **<0.001** | **0.001** |
| | Neutral | 268.35 | 327.01 | 289.11 | 237.83 - 298.87 | 290.37 - 363.65 | 256.44 - 321.78 | | |
| MIA Wrist PPT | Enhanced | 374.75 | | 449.31 | 323.53 - 425.96 | | 388.23 - 510.38 | _ | **<0.001** |
| | Neutral | 422.29 | | 459.11 | 366.46 - 478.12 | | 398.52 - 519.70 | | |
| MIA Elbow PPT | Enhanced | 260.50 | | 345.88 | 225.11 - 295.90 | | 310.49 - 381.27 | _ | **0.001** |
| | Neutral | 290.44 | | 339.21 | 255.05 - 325.83 | | 303.82 - 374.60 | | |
| PFG | Enhanced | 156.18 | | 184.77 | 127.88 - 184.48 | | 156.47 - 213.07 | _ | 0.293 |
| | Neutral | 199.17 | | 234.77 | 170.87 - 227.47 | | 206.47 - 263.07 | | |
| ULNDT-RN | Enhanced | 12.52 | | 17.92 | 9.99 - 15.04 | | 15.39 - 20.45 | _ | 0.971 |
| | Neutral | 14.13 | | 19.56 | 11.60 - 16.65 | | 17.03 - 22.09 | | |

CPM: conditioned pain modulation, MIA: manipulation induced analgesia, 95%CI: 95% confidence interval, PPT: pressure pain threshold, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test-radial nerve bias. Level of significance, $p<0.05$

**Table 4:** Number need to treat analysis (NNT)

| Measurement of analgesia (PPT) | Empathetic interaction (no. of positive outcomes*) | Neutral interaction (no. of positive outcomes*) | NNT |
|---|---|---|---|
| CPM Wrist | 14 | 8 | 5.67 |
| CPM Elbow | 16 | 9 | 4.86 |
| MIA Wrist | 21 | 13 | 4.25 |
| MIA Elbow | 28 | 12 | 2.13 |

PPT: pressure pain threshold, CPM: conditioned pain modulation, MIA: manipulation induced analgesia. *An outcome was considered positive if there was an increase in PPT of 50kPa or more.

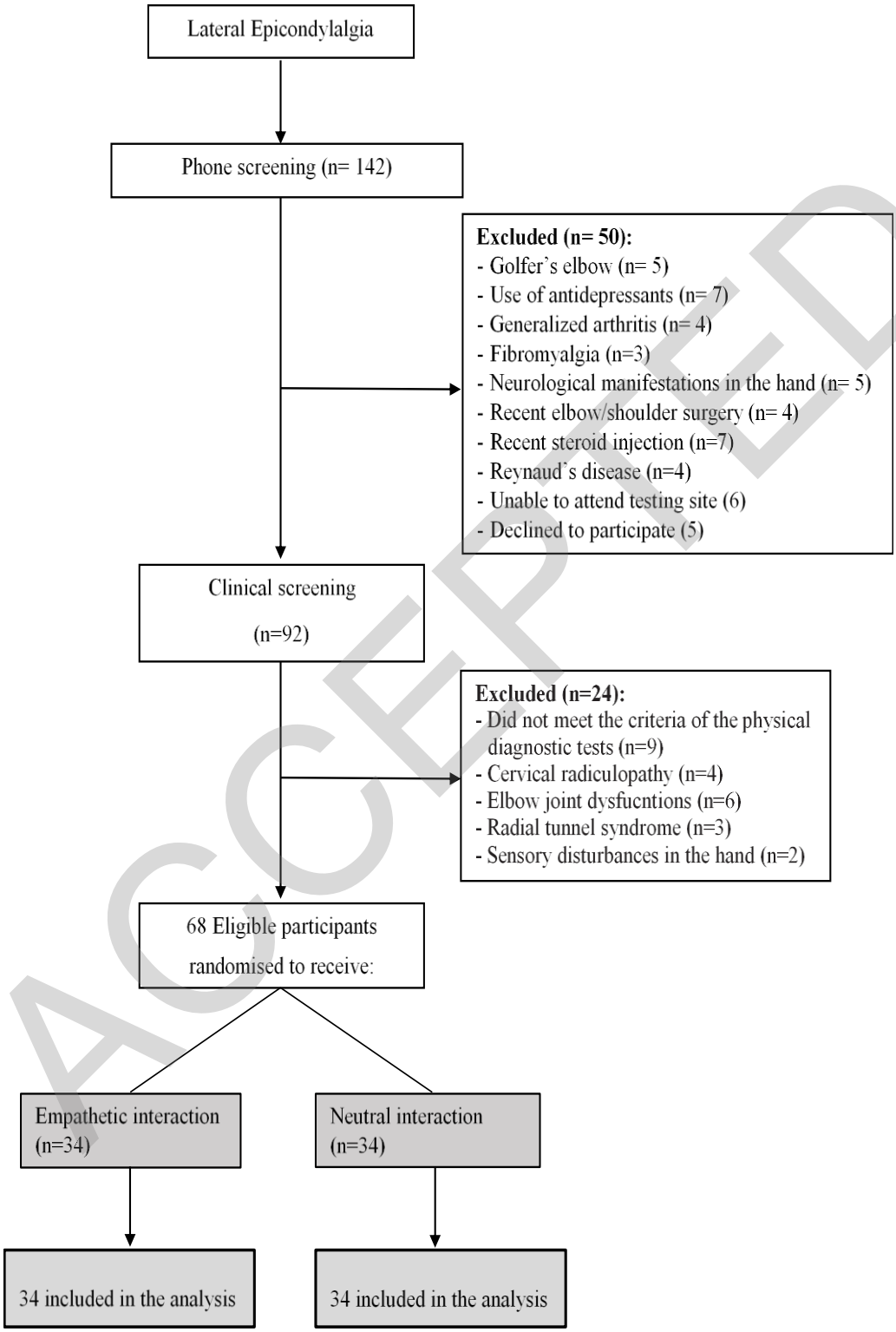


**Figure 1:** Consort diagram for participant flow though recruitment and study procedure.

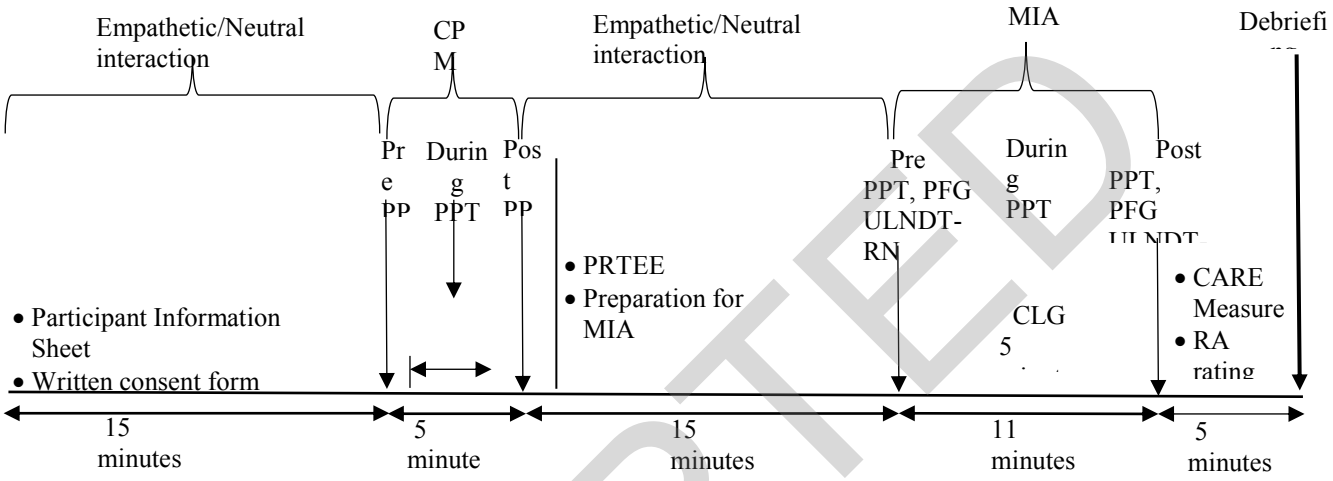


**Figure 2:** Study procedure. PPT: pressure pain threshold, CPM: conditioned pain modulation, CPT: cold pressor test, PRTEE: patient rated tennis elbow evaluation, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test- radial nerve, CLG: cervical lateral glide.