OPEN

The Association Between Conditioned Pain Modulation and Manipulation-induced Analgesia in People With Lateral Epicondylalgia

Ahmad Muhsen, MSc,† Penny Moss, PhD,* William Gibson, PhD,‡ Bruce Walker, DrPH,§ Angela Jacques, M.Biostats,*§ Stephan Schug, MD, FANZCA,‖ and Anthony Wright, PhD**

Objectives: Conditioned pain modulation (CPM) and manipulation-induced analgesia (MIA) may activate similar neurophysiological mechanisms to mediate their analgesic effects. This study assessed the association between CPM and MIA responses in people with lateral epicondylalgia.

Materials and Methods: Seventy participants with lateral epicondylalgia were assessed for CPM followed by MIA. A single assessor measured pressure pain thresholds (PPT) before, during, and after cold water immersion (10°C) of the asymptomatic hand and contralateral lateral glide (CLG) mobilization of the neck. For analyses, linear mixed models evaluated differences in CPM and MIA responses. Pearson partial correlations and regression analyses evaluated the association between CPM and MIA PPT.

Results: There was a significant increase (CPM and MIA, $P < 0.001$) in PPT from baseline during the interventions (CPM mean: 195.84 kPa for elbow and 201.87 kPa for wrist, MIA mean: 123.01 kPa for elbow and 126.06 kPa for wrist) and after the interventions (CPM mean: 126.06 kPa for elbow, 114.24 kPa for wrist, MIA mean: 123.50 kPa for elbow and 122.16 kPa for wrist). There were also significant moderate and positive partial linear correlations (r: 0.40 to 0.54, $P < 0.001$) between CPM and MIA measures, controlling for baseline measures. Regression analyses showed that CPM PPT was a significant predictor of MIA PPT ($P < 0.001$) and the models explained between 73% and 85% of the variance in MIA PPT.

Discussion: This study showed that CPM and MIA responses were significantly correlated and that the CPM response was a significant predictor of MIA response.

Key Words: conditioned pain modulation, lateral epicondylalgia, tennis elbow, manual therapy, manipulation-induced analgesia

(*Clin J Pain* 2019;35:435–442)

Conditioned pain modulation (CPM)[1] is one of the most extensively studied forms of endogenous analgesia (EA). It is based on the phenomenon of pain inhibiting pain[2,3] and involves a cortically mediated spinal-bulbo-spinal inhibitory pathway acting through inhibition of wide dynamic range neurons in the dorsal horn of the spinal cord.[2]

CPM response has been used as a reliable measure of EA efficiency.[4] A less efficient CPM response is associated with chronic pain states, implying dysfunctional pain modulatory mechanisms.[5]

Another form of EA is manipulation-induced analgesia (MIA).[6,7] This is the analgesic effect that is associated with manual therapy treatments. A recent systematic review provided evidence of increased pressure pain thresholds (PPT) after manual therapy, suggesting a clear analgesic effect.[8] Wright[6] suggested that MIA is a multifaceted phenomenon exerting its analgesic effects through several mechanisms, including descending pain modulation.

Vicenzino et al[9] showed a strong association between MIA following cervical lateral glide mobilization and measures of sympathoexcitation in people with chronic lateral epicondylalgia (LE). Similarly, changes in sympathetic nervous system function were significantly associated with CPM response in pain-free healthy individuals[10] and in patients with fibromyalgia.[11] This concurrent association of sympathetic responses with MIA and CPM suggests a role for central pain modulatory mechanisms in both forms of analgesia.[7,9]

Data from pharmacological studies also suggests that CPM and MIA share similar neurophysiological mechanisms. Systemic or local administration of an α1-adrenoceptor agonist,[12,13] systemic administration of a selective α2-adrenoceptor agonist,[12] or the 5-hydroxytryptamine 7 (5-HT7) receptor antagonist SB269970[14] inhibited CPM responses. Likewise, MIA was partially blocked by intrathecal injection of an α2-adrenergic receptor (AR) antagonist while 5-HT receptor antagonists completely blocked the analgesic effect of manual therapy.[15] Spinal blockade of gamma amino butyric acid or opioid receptors; however, did not affect the MIA response.[15] These data suggest that CPM and MIA responses are potentially mediated by descending serotonergic and noradrenergic pathways.

Reports on the association between different forms of EA are limited. The current available evidence shows that CPM is positively associated with exercise-induced analgesia.[16,17]

Received for publication November 1, 2018; revised December 25, 2018; accepted January 28, 2019.

From the *School of Physiotherapy and Exercise Science, Curtin University; §School of Health Professions, Murdoch University; ‖Discipline of Anaesthesiology, University of Western Australia, Perth; ‡School of Physiotherapy, University of Notre Dame Australia, Fremantle, WA, Australia; and †School of Physical and Occupational Therapy, The Hashemite University, Zarqa, Jordan.

This 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, Perth, Australia. The authors declare no conflict of interest.

Reprints: Anthony Wright, PhD, School of Physiotherapy and Exercise Science, Curtin University, GPO Box U1987, Perth, WA 6845, Australia (e-mail T.Wright@curtin.edu.au).

DOI: 10.1097/AJP.0000000000000696

However, to date there has been no study assessing the association between CPM and MIA. It is important to determine whether an association exists to gain some insight into the potential for both forms of EA to act through similar neurophysiological mechanisms.

The aim of this study was therefore to assess the association between the analgesic effects of CPM and MIA in people with LE. It was hypothesized that there would be a strong positive correlation between CPM response and MIA response.

MATERIALS AND METHODS

Design

This was a quasiexperimental single-group, repeated measures study conducted in one testing session. Curtin University Human Research Ethics Committee approved the study (HREC approval number: HRE2017-0198-02). The study was prospectively registered with the Australia New Zealand Clinical Trials Registry (ANZCTR) (ID number: ACTRN12617000218392). On the study day, before the start of testing, all participants were given a detailed description of the study in the form of a participant information sheet and written informed consent was obtained.

Participants

Seventy volunteers with LE were recruited through radio advertisements, a specialized clinical trials recruitment agency, advertisements on social media, in sports clubs, and a range of musculoskeletal and sports physiotherapy clinics in Perth. LE was diagnosed based on the criteria established by Haker and Lundeberg.[18] Exclusion criteria included history of surgery or fracture, neurological dysfunction, and the presence of widespread arthritis.

Potential participants were initially contacted via phone. They were questioned about LE diagnosis and history of pain to ensure that they had unilateral elbow pain for a duration of at least 6 weeks. To further confirm that the eligibility criteria were met, a thorough clinical examination of the upper quarter, including the diagnostic tests described by Haker and Lundeberg[18] (pain on palpation and isometric muscle tests) was carried out by the primary investigator (A.M.) before commencing the study. All testing was conducted at the Physiotherapy Clinic, Curtin University. Participants were asked to avoid taking pain medications 24 hours before testing and to avoid any additional physical treatments (eg, physiotherapy, chiropractic, or acupuncture) on the testing day.

Quantitative Sensory Testing

Pressure Pain Threshold

PPT was measured using an electronic digital algometry (Somedic AB, Sweden). PPT has been shown to have a high intrarater reliability with excellent intraclass correlation coefficients (ICCs: 0.81 to 0.99) when measured at 4 different body sites,[19] and more particularly when used for assessment of pain in LE (ICC: 0.86).[20] 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 (A.M.).

All PPT measures were carried out by a single assessor (A.M.). The assessor identified the most tender point at the lateral aspect of the affected elbow and also identified a point on the posterior aspect of the wrist, 2 cm proximal to the wrist crease and marked these sites. For the CPM assessment protocol, a modified footswitch control was used to assess PPT so that participants could place one hand in the cold water and still respond to the pressure stimulus.[21] The algometer was applied perpendicularly over each marked site by the assessor (pressure application rate: 40 kPa/s). The participant was instructed to press the footswitch control when they perceived the pressure becoming painful. For the MIA protocol the participant lay supine on a plinth. A pressure algometer with a standard hand switch control was used for testing. Three PPT measurements were taken at each site (wrist and elbow) on the symptomatic side with 10 to 15 seconds intervals between each. Mean PPT values (kPa) were used in analysis.

Pain-free Grip (PFG)

Pain on gripping is a common feature of LE.[22] PFG refers to the amount of grip force that can be applied before the onset of pain.[23] PFG was measured with an electronic digital dynamometer (MIE; Medical Research Ltd) using standard methodology.[22] It is both a reliable (ICC: 0.97)[24] and valid[23] measure for use in patients with LE. The participant lay supine with the affected arm by their side, positioned in elbow extension and forearm pronation. They were then requested to squeeze the dynamometer handles until they first felt their lateral elbow pain, and then to stop the squeezing action. The force (N) exerted was recorded from the digital display. The PFG test was performed 3 times with 10 to 20 seconds rest intervals. The average value was used for analysis.

Upper Limb Neurodynamic Test With Radial Nerve Bias (ULNDT-RN)

The ULNDT-RN has been used to assess neural mobility of the upper limb.[25] Pain-free range of motion in the test is restricted in people with LE.[26] The participant's symptomatic arm was progressively positioned in scapular depression and protraction, elbow extension, internal rotation, forearm pronation, and wrist and finger flexion.[25] Scapular depression was sustained while performing the test. The arm was slowly moved into shoulder abduction and the participant was instructed to say "now" to indicate the onset of pain. The shoulder abduction range at the onset of pain was measured using an M180 twin axis electrogoniometer (Penny & Giles, UK) positioned over the anterior shoulder.[22] Three measures were obtained with 20 to 30 seconds intervals. The average of these readings was used for analysis.

Assessment Protocols

CPM Assessment Protocol

Test stimulus. PPT was used as the test stimulus and testing was carried out at the 2 marked locations (wrist and elbow) of the affected arm at baseline before cold water immersion, after 1 minute during hand immersion, and 1 minute after hand immersion (Fig. 1).

Conditioning stimulus. The cold pressor test (CPT) was used as a conditioning stimulus to elicit the CPM response. The unaffected hand was submerged 10 cm above the wrist crease in a cold water bath for a period of 2 minute, with temperature maintained at 10°C.[27] The water bath contained a mix of water and ice and had a circulating pump to ensure uniformity of water temperature at the skin. It was anticipated that the cold water immersion would induce an unpleasant, painful experience. Participants were therefore

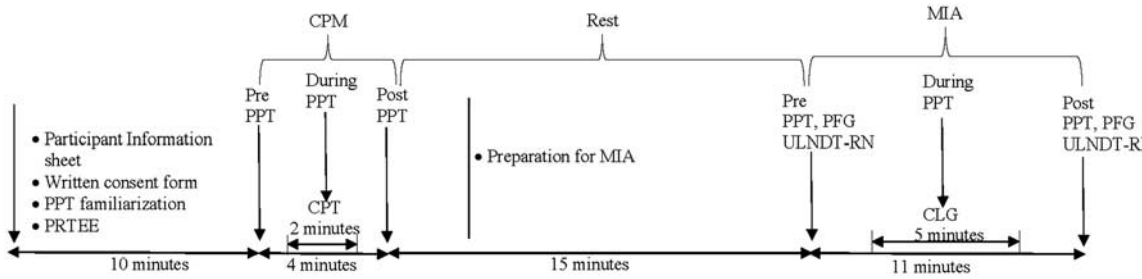

FIGURE 1. Test session timeline. CLG indicates cervical lateral glide mobilization; CPM, conditioned pain modulation; CPT, cold pressor test; MIA, manipulation-induced analgesia; PFG, pain-free grip; PPT, pressure pain threshold; PRTEE, Patient-rated Tennis Elbow Evaluation; ULNDT-RN, upper limb neurodynamic test-radial nerve.

asked to rate the painfulness of the stimulus on a Visual Analog Scale (VAS).

MIA Assessment Protocol

Test stimulus. PPT was the test stimulus. PPT was measured at both test sites (wrist and elbow) at baseline, during (at the start of the third minute of mobilization) and immediately after the mobilization stimulus. Testing was performed with the participants lying supine on a plinth. The PFG test and ULNDT-RN bias test were also performed before and after mobilization to provide additional measures of the MIA effect (Fig. 1).

Mobilization stimulus. A grade III passive oscillatory, contralateral lateral glide (CLG) mobilization of the C5/C6 motion segment of the cervical spine was used to induce MIA, as this technique has previously been shown to induce a short-term MIA response in people with LE.[9,22,28] The participant lay supine with their arms by their side. The therapist cradled the occiput and neck above the C5/C6 cervical segment and applied a grade III passive oscillatory accessory glide directed towards the unaffected upper limb. In contrast to CPM this stimulus should be painless[29] so participants were instructed to report if they felt any discomfort during the mobilization. The CLG stimulus was performed for 60 seconds, and was repeated 3 times, with 60 seconds rest periods (5 min total). It was anticipated that the CLG mobilization would induce a pleasant, relaxing experience. Participants were therefore asked to rate the pleasantness of the stimulus on a VAS.

Questionnaire

Tennis Elbow–specific Assessment Instrument

The Patient-rated Tennis Elbow Evaluation (PRTEE), a condition-specific assessment instrument, was used to measure pain (5 items) and functional disability levels (10 items) during daily activities, work, and sports over the preceding week on a scale of 0 to 10.[30] Responses were aggregated to give an overall score from 0 (no pain or disability) to 100 (worst possible pain and disability). PRTEE is a reliable[31,32] and valid[33] measure for evaluation of pain and function in people with LE.

Procedure

After clinical examination and eligibility criteria were confirmed, each participant was asked to attend for CPM and MIA assessment protocols in a single session. The CPM assessment protocol was conducted first followed by the MIA assessment protocol with a rest period of 15 minutes between to control for any carryover effect. This time interval was determined based on findings from an initial pilot study. All instructions were standardized (Fig. 1).

Data Analysis

Sample Size Calculation

Sample size calculations were determined using Stata/IC (version 15.0: StataCorp LLC, TX). The aim of the study was to evaluate the correlation between PPT measures obtained during the MIA and CPM assessment protocols. As there is no current literature that quantifies the correlation between MIA and CPM effects we estimated that the correlation coefficient between PPT measures for these variables would be 0.35, just above the cut-off for a moderate correlation (Cohen 1992). In determining our sample size we set α at 0.05 and power at 0.80 to detect a correlation coefficient of 0.35. The minimum required sample size for a one-sample correlation test was 62. Allowing for potential drop-outs, we recruited 70 participants.

Statistical Analysis

Data were analyzed using Stata/IC (version 15.0: StataCorp LLC). For all analyses, $P < 0.05$ was considered statistically significant. Descriptive statistics for demographic data were based on frequency distributions for categorical variables and means and SD or medians and interquartile ranges for continuous variables, depending on normality.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data were transformed using natural logarithms (PPT) or square roots (PFG and ULNDT-RN).

Linear mixed models with random participant effects were used to test within intervention (CPT and the mobilization stimulus) differences in PPT over time, relative to baseline at the wrist and elbow test sites.

Pearson partial correlation coefficients and linear regression models were used to examine associations between CPM and MIA PPT measures at the wrist and elbow sites, controlling for baseline CPM and MIA PPT values, which were identified as potential confounders. The strength of the partial correlations were interpreted according to the guidelines defined by Cohen: (small: $0.10 \le r \le 0.29$; medium: $0.30 \le r \le 0.49$; large: $0.50 \le r \le 1.0$). The adjusted coefficient of determination (adjusted R^2) was used to measure the proportion of variance explained by variables in the linear regression models.

RESULTS

Sample Description

A total of 70 participants met the eligibility criteria and participated in the study. All volunteers completed both the

TABLE 1. Descriptive Summaries for the Research Sample

Demographics (n [%])	Sample (N = 70)
Gender	
F	24 (34.3)
M	46 (65.7)
Elbow tested	
L	33 (47.1)
R	37 (52.9)
Age	46.20 (10.6)
Duration (median [IQR])	0.67 (0.42-1.5)
PRTEE	38.73 (16.4)

Level of significance, $P < 0.05$. Data were summarized as mean (SD) unless otherwise specified.

F indicates female; L, left; M, male; PRTEE, Patient-rated Tennis Elbow Evaluation Questionnaire; R, right.

CPM and MIA assessment protocols and were included in the analysis. Characteristics of the participants are summarized in Table 1. A Consort diagram of participant numbers is provided in the Figure 2.

CPM and MIA Effects

Participants demonstrated a significant increase in PPT measured at wrist and elbow sites during and immediately after the CPM and MIA stimuli ($P < 0.001$). There was also a significant improvement in the secondary outcome measures of PFG and ULNDT-RN immediately after the CLG mobilization (Table 2).

The CPT stimulus rated highly on the pain VAS (mean: 8.10, SD: 1.3), while conversely the CLG stimulus rated highly on a pleasantness VAS (mean: 8.16, SD: 1.4), indicating that they induced markedly different sensations. There were significant differences between the CPM and MIA responses

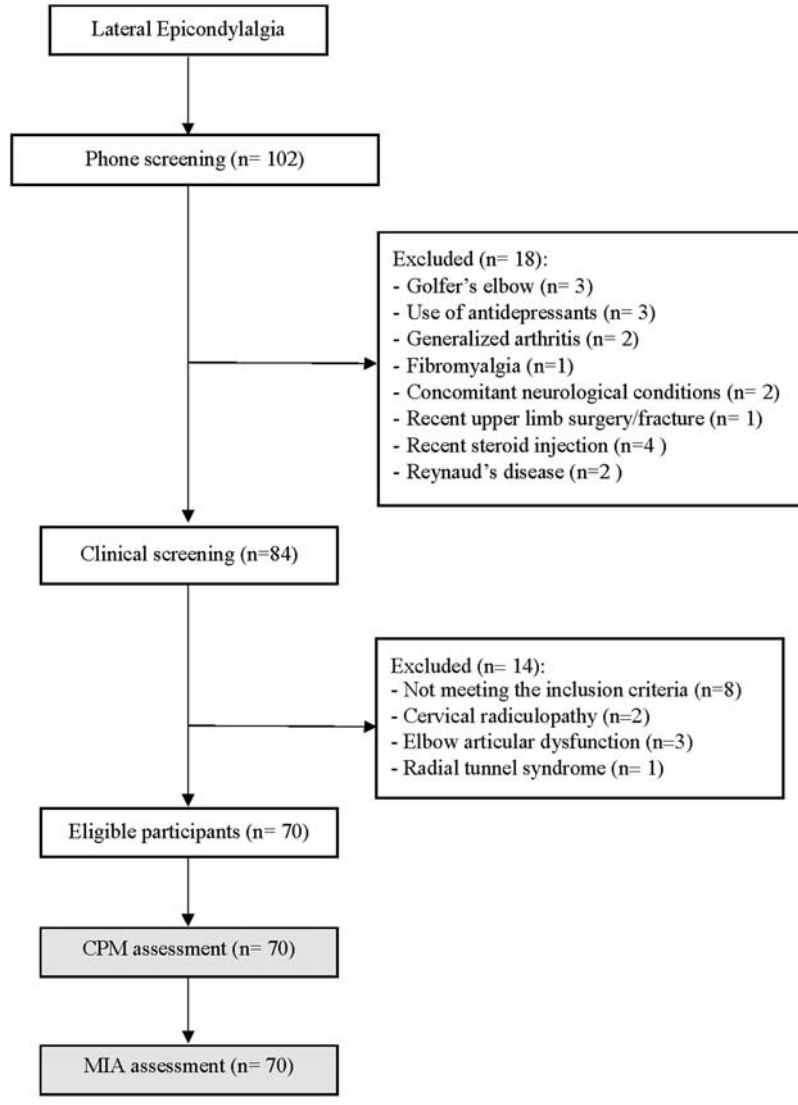

FIGURE 2. Consort diagram. Flow of participants during the recruitment process. CPM indicates conditioned pain modulation; MIA, manipulation-induced analgesia.

measured at both sites during the cold pressor and cervical lateral glide stimuli ($P < 0.001$), with larger increases in PPT measured during CPM. The average increase from baseline in PPT during CPM was 195.84 kPa at the elbow and 201.87 kPa at the wrist. During MIA the average increase at the elbow was 123.01 kPa and at the wrist it was 126.06. However, no differences were detected between the stimuli at either test site immediately after the cold pressor and mobilization stimuli (Wrist: $P = 0.569$, elbow: $P = 0.839$, mean increase after CPM: 126.06 kPa for elbow, 114.24 kPa for wrist and after MIA 123.50 kPa for elbow, 122.16 kPa for wrist) (Fig. 3).

Correlation Between MIA and CPM Effects

The partial correlation values (controlling for baseline PPT values) for the association between PPT measures for MIA and CPM at each assessment time point are presented in the Table 3. The Pearson partial correlation coefficient (r) values showed statistically significant, moderate ($r > 0.3$) positive partial correlations (r: 0.40 to 0.54, $P < 0.001$) between CPM and MIA PPT values. The regression analysis showed that CPM PPT values are a significant predictor of MIA PPT values ($P < 0.001$) measured at both sites over different time points. The adjusted R^2 values ranged between 0.73 and 0.85, indicating that between 73% and 85% of the variance in MIA PPT values was explained by CPM PPT values (Table 3).

DISCUSSION

This is the first study to investigate the association between CPM and MIA. There was a significant increase in PPT at both test sites (wrist and elbow) during and immediately after the CPT and the cervical lateral glide mobilization, indicating an analgesic response to both stimuli. There were significant differences between the CPM and MIA PPT values during the cold water immersion and CLG mobilization, with the CPT stimulus producing a more pronounced analgesic effect during the intervention. However, no difference was seen between CPM and MIA responses in the period following the interventions. PPT did not increase as much during the CLG mobilization but the increase was maintained during the later mobilization period, whereas it decreased substantially following the CPT stimulus. This suggests that the analgesic effect experienced by individuals after the intervention is similar for the cervical mobilization and the cold water immersion. There was also a significant association between the CPM and MIA responses (controlling for baseline variability) and the level of CPM response explained > 73% of the variance in MIA response.

This study, therefore, showed an intact CPM response in people with LE, in accordance with recent research findings of preserved CPM response reported for other chronic musculoskeletal conditions such as chronic back pain,[34] patellofemoral pain,[35] and long-term trapezius myalgia.[36] The CPM response found in this LE sample was similar to that observed in pain-free healthy populations,[21,37] suggesting unaltered endogenous inhibitory mechanisms in LE. However, a study by Lim et al[38] reported an impaired CPM response in people with LE when compared with healthy controls. The difference in the CPM responses reported in both studies may be explained by variations in the testing parameters used. Although Lim et al[38] used contact thermal heat to elicit CPM the current study protocol used the CPT as a conditioning stimulus, which has been found to induce a more pronounced

TABLE 2. Mixed Regression Models for CPM and MIA Responses (Predicted Marginal Means): Overall Differences Between Time Points

Test/ Measurements	Mean Pretreatment	95% CI Pretreatment	Mean During Treatment	95% CI During Treatment	Mean Posttreatment	95% CI Posttreatment	P (Before-During)	P (Before-After)
CPM wrist PPT	540.60	494.18-587.02	742.47	696.05-788.88	654.84	608.42-701.25	**< 0.001**	**< 0.001**
CPM elbow PPT	275.82	256.85-296.19	465.95	433.91-500.36	396.71	369.42-426.00	**< 0.001**	**< 0.001**
MIA wrist PPT	534.48	491.02-577.94	664.13	620.67-707.59	657.60	614.14-701.06	**< 0.001**	**< 0.001**
MIA elbow PPT	310.54	283.60-337.48	433.55	406.61-460.49	434.04	407.10-460.98	**< 0.001**	**< 0.001**
PFG	198.24	174.65-221.82			245.80	222.21-269.38		**< 0.001**
ULNDT-RN	13.35	11.87-14.84			20.76	19.28-22.25		**< 0.001**

Bold values indicate statistical significance.

CI indicates confidence interval; CPM, conditioned pain modulation; MIA, manipulation-induced analgesia; PPT, pressure pain thresholds; PFG, pain-free grip; ULNDT-RN, upper limb neurodynamic test with radial nerve bias.

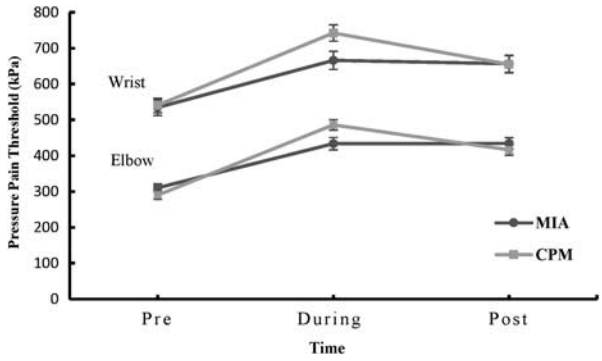

FIGURE 3. Differences in pressure pain threshold values between CPM and MIA over time (mean ± SEM). CPM indicates conditioned pain modulation; MIA, manipulation-induced analgesia.

analgesic effect.[39] In pain-free healthy controls Lim et al[38] reported a 19.02 (±27.49) to 24.75 (±26.21) percentage increase in PPT during thermal pain compared with a 35.80 (±26.26) percentage increase reported by Locke et al[21] during CPT. There may be a weaker CPM effect in response to contact thermal heat relative to CPT and this may provide a reason for the less efficient CPM effect.[38] These data suggest that there was an efficient CPM response in the current cohort.

Consistent with earlier studies evaluating the analgesic effects of cervical manual therapy,[9,22,40,41] this study showed a significant immediate increase in PPT at the elbow and improvements in PFG and ULNDT-RN after the CLG mobilization. This is the first study to report a positive increase in PPT values over the ipsilateral wrist in LE indicating an extrasegmental effect of the CLG mobilization. A similar pattern of MIA response was reported[42] locally at the knee and remotely at the ipsilateral heel after knee joint mobilization.

The increase in PPT during the CPT was significantly greater than during the CLG, suggesting a stronger initial analgesic response associated with the noxious cold conditioning stimulus compared with the nonpainful mobilization stimulus. Participants rated the CPT stimulus as inducing a relatively high level of pain but they conversely rated the CLG mobilization as a highly pleasant sensation. Despite these differences in the nature of the stimuli and the fact that the CPT stimulus elicited a very marked increase in PPT during the 2 minute immersion period, both interventions showed very similar increases (~120 kPa) in PPT in the period after intervention.

There are few studies investigating the association between different forms of EA, although an association between CPM and exercise-induced analgesia has been demonstrated.[16,17] A previous study[43] reported an enhanced CPM response with the addition of a mobilization stimulus in patients with knee osteoarthritis but the authors did not examine the association between CPM and MIA. The current study appears to be the first to investigate this association between CPM and MIA in people with musculoskeletal pain, demonstrating a significant, positive association between PPT measures at the wrist and elbow sites both during and following the CPT and CLG stimuli. This suggests that those individuals who show a significant analgesic response to the cold pressor stimulus also show a positive analgesic response to the mobilization treatment. Regression analysis showed that a significant proportion of the variance in MIA response could be explained by the CPM response. These findings suggest that while the nature of the 2 stimuli is quite distinct there are clear associations between the analgesic responses induced by both stimuli. This suggests that they may activate similar neurophysiological mechanisms.

One potential implication of this in the clinical setting is that measuring CPM response could be a useful predictor of the likelihood that an individual would respond positively to a course of joint mobilization treatments. CPM testing should be further evaluated as a possible predictor of response to manual therapy treatment over a longer treatment period and in different musculoskeletal conditions, reflective of normal clinical practice. An improved understanding of manual therapy analgesia may also lead to more appropriate and more effective treatment.

Recent imaging studies in humans suggest similarities in the cortical activity accompanying CPM and MIA. La Cesa et al[44] utilized functional magnetic resonance imaging and reported activity in several cortical structures in response to cold water hand immersion. These regions included medial areas of the postcentralgyrus bilaterally, the secondary somatosensory cortex (S2), posterior areas of the insular cortex, regions of the cingulate cortex and the cerebellum. Cortical activity has also been shown in other areas during CPM such as thalamus, medulla, amygdala,[45] supplementary motor area, and prefrontal cortex.[46] Previous research has also[47] found that MIA is associated with immediate changes in functional cortical connectivity of S1, posterior insular cortex, posterior cingulate cortex, and the periaqueductal gray region in experimentally induced low back pain. Other brain areas such as S2, premotor, and supplementary areas, amygdala, insula, anterior cingulate cortex, thalamus,[48] anterior cerebellum, and frontal cortex were

TABLE 3. Partial Correlations (Controlling for Baseline PPT Values) and Regression Models for CPM PPT and MIA PPT at Different Time Points

CPM PPT vs. MIA PPT	Partial Correlation Coefficient	Regression Coefficient (B)	SE (B)	95% CI (B)	Adjusted R^2	*P* (Partial Correlation)	*P* (B)	*P* (F-test)
CPM PPT wrist during vs. MIA PPT wrist during treatment	0.44	0.55	0.14	0.28-0.82	0.82	**< 0.001**	**< 0.001**	**< 0.001**
CPM PPT elbow during vs. MIA PPT elbow during treatment	0.45	0.47	0.11	0.24-0.70	0.73	**< 0.001**	**< 0.001**	**< 0.001**
CPM PPT wrist after vs. MIA PPT wrist after treatment	0.40	0.43	0.12	0.19-0.68	0.85	**< 0.001**	**0.001**	**< 0.001**
CPM PPT elbow after vs. MIA PPT elbow after	0.54	0.47	0.09	0.29-0.65	0.82	**< 0.001**	**< 0.001**	**< 0.001**

Bold values indicate statistical significance.
CI indicates confidence interval; CPM, conditioned pain modulation; MIA, manipulation-induced analgesia; PPT, pressure pain thresholds.

also active during manual therapy.[49] These data suggest that both CPM and MIA are mediated by similar cortical structures, which supports the hypothesis of overlapping cortical and descending neuronal networks being responsible for both forms of analgesia.

There is also evidence suggesting that CPM and MIA are mediated by serotonergic and noradrenergic neuronal networks. In a group with diabetic neuropathy CPM effect was improved in patients with less efficient CPM by the selective serotonin (5-hydroxytryptamine: 5-HT) and noradrenaline (NA) reuptake inhibitor, duloxetine.[50] In a recent animal study blockade of α2-AR through α2-AR antagonists, spinal atipamezole, or subcutaneous yohimbine, abolished the CPM response in intact animals, but it was augmented in spinally injured animals after intrathecal administration of a norepinephrine-reuptake inhibitor, reboxetine, or systemic injection of the norepinephrine-reuptake inhibitor and μ-opioid receptor agonist, tapentadol.[51] Some studies in humans have shown that CPM-induced analgesia is not affected by naloxone (an opioid antagonist)[52–54] suggesting a nonopioid form of analgesia. However, other studies have demonstrated that naloxone partially[45] or completely reverses CPM analgesia.[55,56] Therefore, the current evidence on the involvement of opioid pathways in CPM analgesia is inconclusive.

In contrast, in human studies, administration of naloxone does not block MIA,[57–59] suggesting that nonopioid mechanisms are likely to be involved. In addition, a study in rats[60] showed that knee joint mobilization decreased paw pressure hyperalgesia induced by joint inflammation. Utilizing this model, Skyba et al[15] reported that intrathecal administration of the α2-AR antagonist, yohimbine, partially blocked and the 5-HT receptor antagonists, methysergide and NAN-190 completely blocked the analgesic effect of joint mobilization. They also showed that intrathecal administration of naloxone did not block the MIA response. They concluded that spinal serotonergic and noradrenergic receptors linked to descending serotonergic and noradrenergic neurons play a key role in mediating MIA. These data suggest that CPM and MIA involve activation of serotonergic and noradrenergic neurons in the central nervous system to mediate their effects. There appears to be some variation between the 2 forms of EA in terms of the degree to which the analgesic effect is blocked or reversed by naloxone. The finding of moderate positive correlations between CPM and MIA suggest that there would be considerable value in conducting further studies in a suitable animal model to determine similarities and differences in the neurophysiological mechanisms responsible for both forms of analgesia.

In summary, the present study showed that the CPT and CLG stimuli both induced an analgesic response. CPM and MIA responses were of similar magnitude (post-intervention) and were significantly correlated in a population with LE. This suggests that there is a considerable overlap between both forms of EA and that they may share similar neurophysiological mechanisms, potentially involving descending serotonergic and noradrenergic neurons. Assessment of CPM may have some value as potential predictor of clinical response to manual therapy treatment. Further research is required to understand the detailed similarities and differences between the neurophysiological mechanisms responsible for both forms of analgesia.

ACKNOWLEDGMENTS

The authors thank all of the participants who contributed their time to the study.

REFERENCES

1. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain*. 2010;14:339.
2. Le Bars HD, Dickenson HA, Besson HJ-M. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain*. 1979;6:283–304.
3. Reinert A, Treede R-D, Bromm B. The pain inhibiting pain effect: an electrophysiological study in humans. *Brain Res*. 2000;862:103–110.
4. Kennedy LD, Kemp IH, Ridout SCD, et al. Reliability of conditioned pain modulation: a systematic review. *Pain*. 2016;157:2410–2419.
5. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain*. 2015;156(suppl 1): S24–S31.
6. Wright A. Hypoalgesia post-manipulative therapy: a review of a potential neurophysiological mechanism. *Man Ther*. 1995;1: 11–16.
7. Wright A, Vicenzino B. Cervical mobilisation techniques, sympathetic nervous system effects and their relationship to analgesia. In: Shacklock M, ed. *Moving in on Pain*. Melbourne: Butterworth-Heinemann; 1995:164–173.
8. Voogt L, de Vries J, Meeus M, et al. Analgesic effects of manual therapy in patients with musculoskeletal pain: a systematic review. *Man Ther*. 2015;20:250–256.
9. Vicenzino B, Collins D, Benson HAE, et al. An investigation of the interrelationship between manipulative therapy-induced hypoalgesia and sympathoexcitation. *J Manipulative Physiol Therap*. 1998;21:448–453.
10. Chalaye P, Devoize L, Lafrenaye S, et al. Cardiovascular influences on conditioned pain modulation. *Pain*. 2013;154: 1377–1382.
11. Chalaye P, Lafrenaye S, Goffaux P, et al. The role of cardiovascular activity in fibromyalgia and conditioned pain modulation. *Pain*. 2014;155:1064–1069.
12. Sanada T, Kohase H, Makino K, et al. Effects of alpha-adrenergic agonists on pain modulation in diffuse noxious inhibitory control. *JMed Dental Sci*. 2009;56:17–24.
13. Makino K, Kohase H, Sanada T, et al. Phenylephrine suppresses the pain modulation of diffuse noxious inhibitory control in rats. *Anesth Analg*. 2010;110:1215–1221.
14. Bannister K, Lockwood S, Goncalves L, et al. An investigation into the inhibitory function of serotonin in diffuse noxious inhibitory controls in the neuropathic rat. *Eur J Pain*. 2017;21:750–760.
15. Skyba DA, Radhakrishnan R, Rohlwing JJ, et al. Joint manipulation reduces hyperalgesia by activation of monoamine receptors but not opioid or GABA receptors in the spinal cord. *Pain*. 2003;106:159–168.
16. Lemley JK, Hunter KS, Bement HMK. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. *Med Sci Sports Exerc*. 2015;47:176–184.
17. Vaegter HB, Handberg G, Jørgensen MN, et al. Aerobic exercise and cold pressor test induce hypoalgesia in active and inactive men and women. *Pain Med*. 2015;16:923–933.
18. Haker E, Lundeberg T. Acupuncture treatment in epicondylalgia: a comparative study of two acupuncture techniques. *Clin J Pain*. 1990;6:221–226.
19. Waller R, Straker L, O'Sullivan P, et al. Reliability of pressure pain threshold testing in healthy pain free young adults. *Scand J Pain*. 2015;9:38–41.
20. Fernández-Carnero J, Fernández-De-Las-Peñas C, De La Llave-Rincón A, et al. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: a blinded, controlled study. *Clin J Pain*. 2009;25: 555–561.
21. Locke D, Gibson W, Moss P, et al. Analysis of meaningful conditioned pain modulation effect in a pain-free adult population. *J Pain*. 2014;15:1190–1198.
22. Vicenzino B, Collins D, Wright A. The initial effects of a cervical spine manipulative physiotherapy treatment on the

pain and dysfunction of lateral epicondylalgia. *Pain*. 1996;68: 69–74.
23. Paungmali A, O'Leary S, Souvlis T, et al. Hypoalgesic and sympathoexcitatory effects of mobilization with movement for lateral epicondylalgia. *Phys Ther*. 2003;83:374–383.
24. Smidt N, van Der Windt DA, Assendelft WJ, et al. Interobserver reproducibility of the assessment of severity of complaints, grip strength, and pressure pain threshold in patients with lateral epicondylitis. *Arch Phys Med Rehabil*. 2002;83: 1145–1150.
25. Butler DS. *The Sensitive Nervous System*. Adelaide: Noigroup Publications; 2000.
26. Yaxley GA, Jull GA. Adverse tension in the neural system. A preliminary study of tennis elbow. *Aust J Physiother*. 1993;39:15–22.
27. Hoffken O, Ozgul O, Enax-Krumova E, et al. Evoked potentials after painful cutaneous electrical stimulation depict pain relief during a conditioned pain modulation. *BMC Neurol*. 2017;17:167.
28. Vicenzino B, Neal R, Collins D, et al. The displacement, velocity and frequency profile of the frontal plane motion produced by the cervical lateral glide treatment technique. *Clin Biomech (Bristol, Avon)*. 1999;14:515–521.
29. Vicenzino B, Cartwright T, Collins D, et al. An investigation of stress and pain perception during manual therapy in asymptomatic subjects. *Eur J Pain*. 1999;3:13–18.
30. Macdermid J. Update: the Patient-Rated Forearm Evaluation Questionnaire is now the Patient-Rated Tennis Elbow. *Evaluation*. 2005;18:407–410.
31. Overend TJ, Wuori-Fearn JL, Kramer JF, et al. Reliability of a Patient-rated Forearm Evaluation Questionnaire for patients with lateral epicondylitis. *J Hand Ther*. 1999;12:31–37.
32. Rompe JD, Overend TJ, Macdermid JC. Validation of the Patient-rated Tennis Elbow Evaluation Questionnaire. *J Hand Ther*. 2007;20:3–11.
33. Vincent JI, Macdermid JC, King GJ, et al. Validity and sensitivity to change of patient-reported pain and disability measures for elbow pathologies. *J Orthop Sports Phys Ther*. 2013;43: 263–274.
34. Gerhardt A, Eich W, Treede R-D, et al. Conditioned pain modulation in patients with nonspecific chronic back pain with chronic local pain, chronic widespread pain, and fibromyalgia. *Pain*. 2017;158:430–439.
35. Rathleff M, Stephenson A, Mellor R, et al. Adults with patellofemoral pain do not exhibit manifestations of peripheral and central sensitization when compared to healthy pain-free age and sex matched controls—An assessor blinded cross-sectional study. *PLoS One*. 2017;12:e0188930.
36. Leffler A-S, Hansson P, Kosek E. Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. *Eur J Pain*. 2002;6:149–159.
37. Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. *Neurosci Lett*. 2005;380:209–213.
38. Lim WEC, Sterling M, Vicenzino B. Chronic lateral epicondylalgia does not exhibit mechanical pain modulation in response to noxious conditioning heat stimulus. *Clin J Pain*. 2017;33: 932–938.
39. Oono Y, Nie H, Matos RL, et al. The inter- and intra-individual variance in descending pain modulation evoked by different conditioning stimuli in healthy men. *Scand J Pain*. 2011;2:162–169.
40. Fernández-Carnero J, Fernández-de-Las-Peñas C, Cleland JA. Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia. *J Manipulative Physiol Ther*. 2008;31:675–681.
41. Maduro de Camargo V, Alburquerque-Sendín F, Bérzin F, et al. Immediate effects on electromyographic activity and pressure pain thresholds after a cervical manipulation in mechanical neck pain: a randomized controlled trial. *J Manipulative Physiol Ther*. 2011;34:211–220.
42. Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. *Man Ther*. 2007;12: 109–118.
43. Courtney CA, Steffen AD, Fernández-De-Las-Peñas C, et al. Joint mobilization enhances mechanisms of conditioned pain modulation in individuals with osteoarthritis of the knee. *J Orthop Sports Phys Ther*. 2016;46:168–176.
44. La Cesa S, Tinelli E, Toschi N, et al. fMRI pain activation in the periaqueductal gray in healthy volunteers during the cold pressor test. *Magn Reson Imaging*. 2014;32:236–240.
45. Sprenger C, Bingel U, Büchel C. Treating pain with pain: supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain*. 2011;152:428–439.
46. Piché M, Arsenault M, Rainville P. Cerebral and cerebrospinal processes underlying counterirritation analgesia. *J Neurosci*. 2009;29:14236–14246.
47. Gay CW, Robinson ME, George SZ, et al. Immediate changes following manual therapy in resting state functional connectivity as measured by magnetic resonance imaging (fMRI) In subjects with induced low back pain. *J Manipulative Physiol Ther*. 2014;37:614–627.
48. Sparks C, Cleland JA, Elliott JM, et al. Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *J Orthop Sports Phys Therapy*. 2013;43:340–348.
49. Boendermaker B, Meier ML, Luechinger R, et al. The cortical and cerebellar representation of the lumbar spine. *Hum Brain Mapp*. 2014;35:3962–3971.
50. Yarnitsky D, Granot M, Nahman-Averbuch H, et al. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain*. 2012;153:1193–1198.
51. Bannister K, Patel R, Goncalves L, et al. Diffuse noxious inhibitory controls and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. *Pain*. 2015;156:1803–1811.
52. Edwards RR, Ness TJ, Fillingim RB. Endogenous opioids, blood pressure, and diffuse noxious inhibitory controls: a preliminary study. *Percept Mot Skills*. 2004;99:679–687.
53. Hermans L, Nijs J, Calders P, et al. Influence of morphine and naloxone on pain modulation in rheumatoid arthritis, chronic fatigue syndrome/fibromyalgia, and controls: a double-blind, randomized, placebo-controlled, cross-over study. *Pain Pract*. 2018;18:418–430.
54. Peters LM, Schmidt JMA, Van Den Hout AM, et al. Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). *Pain*. 1992;50:177–187.
55. Pertovaara A, Kemppainen P, Johansson G, et al. Ischemic pain nonsegmentally produces a predominant reduction of pain and thermal sensitivity in man: a selective role for endogenous opioids. *Brain Res*. 1982;251:83–92.
56. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. *Eur J Pharmacol*. 1990;182:347–355.
57. Vicenzino B, O'Callaghan J, Kermode F, et al. No influence of naloxone on the initial hypoalgesic effect of spinal manual therapy. Proceedings of the 9th World Congress on Pain. *Prog Pain Res Manag*. 2000;16:1039–1044.
58. Zusman M, Edwards BC, Donaghy A. Investigation of a proposed mechanism for the relief of spinal pain with passive joint movement. *J Man Med*. 1989;4:58–61.
59. Paungmali A, O'Leary S, Souvlis T, et al. Naloxone fails to antagonize initial hypoalgesic effect of a manual therapy treatment for lateral epicondylalgia. *J Manipulative Physiol Ther*. 2004;27:180–185.
60. Sluka KA, Wright A. Knee joint mobilization reduces secondary mechanical hyperalgesia induced by capsaicin injection into the ankle joint. *Eur J Pain*. 2001;5:81–87.

