Exercise induced hypoalgesia is elicited by isometric, but not aerobic exercise in individuals with chronic whiplash associated disorders.

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ABSTRACT

Background and aims:

Reduced pain sensitivity following exercise is termed exercise induced hypoalgesia (EIH). Preliminary evidence suggests that impairment of EIH is evident in individuals with whiplash associated disorders (WAD) following submaximal aerobic exercise. This study aimed to compare EIH responses to isometric and aerobic exercise in patients with chronic WAD and healthy controls and investigate relationships between EIH, conditioned pain modulation (CPM) and psychological factors in patients with chronic WAD.

Methods:

A cross sectional pre-post study investigated the effect of a single session of submaximal aerobic cycling exercise and a single session of isometric timed wall squat exercise on EIH in a group of participants with chronic WAD ($n = 21$) and a group of asymptomatic control participants ($n = 19$). Bivariate analyses between EIH and baseline measures of CPM and psychological features (fear of movement, pain catastrophization and posttraumatic stress symptoms) were also investigated.

Results:

The isometric wall squat exercise but not the aerobic cycling exercise resulted in EIH in both groups ($P < 0.023$) with no between-group differences ($P > 0.55$) demonstrated for either exercise. There were no significant associations measured between EIH (for either exercise performed), and CPM, or any of the psychological variables.

Conclusions:

This study showed that individuals with chronic WAD and mild to moderate pain and disability, and no evidence of dysfunctional CPM, demonstrated reduced pain sensitivity, both in the cervical spine and over the tibialis anterior following an isometric, timed wall squat exercise. Cycling exercise did not increase pain sensitivity.

Implications:

Individuals with chronic WAD and mild to moderate levels of neck pain and disability may experience less pain sensitivity both locally and remotely following an exercise program directed at non-painful muscles performing isometric exercises. Individuals cycling for thirty minutes at 75% of age-predicted heart rate maximum do not experience increased pain sensitivity.

Keywords:

Exercise-induced hypoalgesia, whiplash, isometric exercise, pain sensitivity, aerobic exercise, conditioned pain modulation

1. Introduction

Reduced pain sensitivity following exercise is termed exercise induced hypoalgesia (EIH) [1, 2] and is believed to result from activation of endogenous pain inhibitory processes [3]. In contrast to responses in healthy, pain-free individuals [4, 5], various painful conditions, such as fibromyalgia, demonstrate dysfunction of endogenous pain inhibitory processes that results in increased sensitivity to pain (reduced thresholds) following aerobic and isometric exercise [5, 6].

In chronic whiplash associated disorders (WAD), dysfunction in endogenous pain control have been demonstrated [7, 8]. Furthermore, preliminary evidence suggests that EIH is also impaired with submaximal (<75% of age-predicted maximal heart rate) or physiologically limited (<80% of heart rate corresponding to anaerobic threshold) cycling exercise resulting in hyper not hypoalgesia [9]. The reasons for impaired EIH in chronic WAD are unknown, but are likely multifactorial. Individuals with chronic WAD primarily present with regional neck pain, but their clinical presentation may also include pro-nociceptive features (e.g. sensory hypersensitivity presenting as reduced pressure and thermal pain thresholds) and various psychological features including pain catastrophization, posttraumatic stress symptoms and fear of movement/re-injury [10]. Psychological features have been demonstrated to influence endogenous analgesia, with recent research demonstrating that greater pain catastrophization predicts diminished EIH (as measured by temporal summation) in healthy pain-free individuals [11]. However, research in patient groups is lacking. The type of exercise performed may be another factor that influences EIH [12]. Isometric exercise of non-painful muscles reduces pain sensitivity in people with shoulder pain, but not in individuals with widespread pain conditions, such as in fibromyalgia [13]. The relationship of pro-nociceptive features, exercise type and psychological features to EIH has so far not been investigated in chronic WAD.

Endogenous analgesia in chronic WAD has previously been evaluated utilizing the Conditioned Pain Modulation Paradigm (CPM) [7, 8], whereby reduced endogenous pain inhibition has been demonstrated. It has been shown that EIH and CPM responses after exercise in healthy individuals are similar [14]. In addition, CPM has been demonstrated to predict EIH in healthy individuals [15]; but this relationship has so far not been investigated in a patient group. Further investigation of the relationship between CPM and EIH is warranted to determine if there are similar mechanisms underlying endogenous analgesia.

The aims of this study were:

1. To compare EIH responses to isometric and aerobic exercise in patients with chronic WAD and healthy controls
2. To determine if there is a differential response of exercise type on EIH
3. To investigate relationships between EIH and CPM in patients with chronic WAD
4. To investigate relationships between EIH and psychological factors in patients with chronic WAD.

It was hypothesized that healthy controls would demonstrate EIH following both types of exercise, and EIH would not occur in chronic WAD. It was also anticipated that a lower CPM response and higher scores on the psychological measures would be associated with impaired EIH.

2. Methods

A cross sectional pre-post study investigated the effect of a single session of aerobic exercise and a single session of isometric exercise on EIH in a group of participants with chronic WAD and a group of asymptomatic control participants.

2.1 Participants

Individuals with WAD were eligible to participate if they presented with Whiplash Grade II (neck pain but no fracture/dislocation of the neck and no neurological deficit [16]) of at least 3 months but less than 10 years duration and were aged between 18-65 years. Individuals were excluded if they had known or suspected serious spinal pathology (e.g. metastatic, inflammatory or infective diseases of the spine); confirmed fracture or dislocation at the time of injury; nerve root compromise (at least 2 of the following signs: weakness/reflex changes/sensory loss associated with the same spinal nerve); spinal surgery in the previous 12 months; history or presentation of psychosis, bipolar disorder, organic brain disorder or severe depression; were taking anti-depressant or anti-convulsant medication; or who answered 'yes' to *any* of the 7 questions on the PAR-Q physical activity screening questionnaire [17].

Healthy control participants were eligible to participate if they did not have a history of WAD or recent (within the previous 12 months) musculoskeletal pain and did not answer 'yes' to any questions on the PAR-Q.

2.2 Procedure

Volunteers who met the inclusion criteria were invited to attend two testing sessions: one to perform submaximal aerobic bicycle exercise; and a second to complete an isometric exercise. These sessions were scheduled 5-10 days apart. Participants were asked to refrain from analgesics for 48 hours prior to testing and to refrain from exercise, nicotine, alcohol and caffeine for 12 hours prior to testing. Participant information was provided at the initial testing session, and participants provided informed consent before completing the baseline questionnaire and resting physical measures (Fig. 1). Participants waited ten minutes prior to commencing exercise to avoid the testing protocols influencing exercise [18, 19]. During this time, resting heart rate and blood pressure measures were collected and appropriate warnings and precautions were provided. Participants then completed an aerobic or isometric exercise session, immediately followed by post-exercise testing. The order of testing was kept constant within each testing session, both prior to and following exercise (Fig. 1). Ethical clearance for this study was granted by the institutional Medical Research Ethics Committee.

Figure 1: Flow Diagram of Study Procedure

Legend: PPT = Pressure Pain Threshold; CPT = Cold Pain Threshold; HPT = Heat Pain Threshold; CPM = Conditioned Pain Modulation; BP = Blood Pressure; HR = Heart Rate

2.3 Exercise Sessions

2.3.1 Aerobic exercise

Participants completed a standardised, submaximal bicycle ergometer test [20]. Prior to starting the test, the rating of perceived exertion (RPE) scale was explained to participants [21] and 75% of age-predicted maximum heart rate was calculated ($.75 \times (220 - \text{age in years})$). The participant started to cycle at 25W and the power output was increased by 25W every minute until attainment of 75% of age-predicted maximum heart rate. The participant continued to cycle at this power output for a total duration of 30 minutes [20]. The Aerobic Power Index test has been shown to be reliable for healthy populations and populations with chronic medical conditions, and enables completion of a standardised, 30 minute aerobic exercise session [22]. Heart rate, RPE and blood pressure were recorded each minute during the increase in power output and then once every 3 minutes until the end of the exercise session.

2.3.2 Isometric exercise

Participants completed a wall squat. Participants stood upright with their back against the wall, feet parallel and shoulder-width apart, and hands by their sides. A goniometer was aligned with the lateral epicondyle of the femur. Participants were then asked to lower their back down the wall until a knee joint angle of approximately 100° was reached. Participants were asked to maintain this contraction until fatigued or for a maximum of 3 minutes [23]. Heart rate, RPE and blood pressure were assessed each minute.

2.4 Outcome Measures

2.4.1 Baseline Questionnaires

Age, gender, level of education, motor vehicle crash (MVC) information and compensation status were collected at baseline. The PAR-Q [17] was administered to screen for readiness to undertake physical activity. Following successful completion of the PAR-Q, the following questionnaires were completed: 1. numerical pain rating (0-10 scales) of average pain intensity over the a) past 24 hours and b) past week [24]; 2. the Neck Disability Index (NDI), a valid and reliable measure of neck pain related disability [25]; 3. the Pain Catastrophizing Scale (PCS) [26], and 4. the Tampa Scale of Kinesiophobia (TSK), a 17-item checklist that measures fear of movement/(re)injury [27]. The symptom severity scale (i.e. questions 22 to 38) of the Posttraumatic Stress Diagnostic Scale (PDS) which is designed to assist in the diagnosis of PTSD [28] was also completed by participants with WAD.

2.4.2 Primary Outcome Measure

Pressure pain thresholds were measured using a pressure algometer with a probe size of 1cm² and application rate of 40kPa/s (Somedic AB, Hörby, Sweden). PPTs were measured at mid cervical spine (C5), providing a measure of local pain sensitivity, and over the tibialis anterior (muscle belly), a distal site over uninjured tissues, providing a measure of remote pain sensitivity. These sites have previously been used in investigations of chronic WAD [29, 30]. The participants were asked to push a button when the sensation changed from one of pressure alone to one of pressure and pain. Triplicate readings were taken at each site and the mean values used for analysis. These measures were taken prior to and following each exercise. *Exercise induced hypoalgesia* was determined to have occurred when the post-exercise PPTs were greater than the pre-exercise PPTs. Pressure pain thresholds were limited to 500kPa in the neck region, and 1000kPa over the tibialis anterior muscle as a result of an inability to maintain a consistent rate of application.

2.4.3 Secondary Outcome Measures

Thermal Pain Thresholds: Heat and cold pain thresholds were measured over the mid-cervical spine using the Thermostat system (Somedic AB, Hörby, Sweden). The temperature was pre-set to increase/decrease at a rate of 1°C/s from a baseline of 30°C to a maximum of 50°C/8°C to prevent any possible tissue damage. Subjects were instructed to press a switch when the heat/cold sensation first became painful (heat pain threshold (HPT) or cold pain threshold (CPT)) [31, 32]. Triplicate recordings were taken and the mean values used for analysis.

Conditioned Pain Modulation (CPM): The test stimulus utilized was 'contact heat' (HPT) delivered centrally over the mid-cervical spine. Perceived pain during HPT testing was measured using a 10cm visual analogue scale (VAS_{HPT}) immediately following HPT assessment. The conditioning stimulus was cold water (cold pressor test). The participant's non-dominant hand was immersed in water, which was thermostatically controlled, with the temperature kept constant at 2-3°C. Pain threshold was determined by asking the participant to raise his/her dominant hand the moment he/she began to feel any pain/ discomfort. The time in seconds, that passed between the immersion and the raising of that hand was recorded as the cold pressor pain threshold [33]. Participants were instructed to keep the immersed hand in the cold water for as long as possible, and withdraw it from the water when no longer tolerable. Cold pressor pain tolerance was defined as the total time, in seconds, that the participant's hand was immersed in water minus the pain-threshold time [33]. Tolerance time had an imposed ceiling time of 120 seconds, at which time the task was discontinued. Participants rated the intensity of their pain during this task on a 10cm VAS, initially after the first 5 seconds, then at 15 second intervals until their hand was removed or until the ceiling time was reached. The peak pain intensity rating was recorded, together with the average pain intensity

score. HPT was measured again 30 seconds (HPT30) after hand withdrawal from the cold water. CPM was calculated by subtracting HPT from HPT30 [34].

2.5 Statistical Analysis

Sample size for the primary outcome was established *a priori* based on previous research on sensory hypersensitivity to pressure pain thresholds in individuals with WAD [35]. Utilising the variable of smallest within-participant effect size (PPT at Tibialis Anterior, effect = 0.69 at 80% power, $p < 0.05$), a sample size of 17 participants with chronic WAD and 17 controls was indicated in order to obtain the desired study power of 0.80 and significance level of 0.05. All data were analyzed via scatterplots, boxplots and Kolmogorov–Smirnov statistics to evaluate normality. Normally distributed data are reported as means and standard deviations (SD) in the text. Otherwise, data are reported as median and interquartile range (IQR). Statistical analyses were run in SPSS Statistics (Version 22; IBM, Armonk, NY, USA).

Parametric tests were utilized to examine group differences for normally distributed data (age and percentage predicted heart rate maximum), whilst non-parametric tests (Mann-Whitney U tests) were used to investigate between-group differences for exercise performance, and baseline physical and questionnaire/psychological measures.

Mean PPTs measured prior to exercise were subtracted from those measured post-exercise. A positive value indicated the presence of exercise induced hypoalgesia (EIH). A random intercept model was constructed to evaluate the effect of exercise type (isometric/aerobic) on PPTs (for both the cervical spine and tibialis anterior regions) and to determine if these effects varied by study group (WAD/controls). The fixed effects of time (pre/post exercise), exercise type (isometric/aerobic) and study group (WAD/controls) were included in the model. Age was included as a covariate. Interactive effects of time with exercise type (time * exercise), time with group (time * group) and time with exercise with group (time * exercise * group) were examined. Where significant effects of fixed factors were observed, pairwise comparisons using Bonferroni corrections for multiple comparisons were performed to investigate specific between group or between exercise differences. P -values less than .05 were considered significant for all the above analyses.

To address the secondary aims of the study, bivariate analyses between percentage change in EIH [(post-exercise PPT minus pre-exercise PPT)/pre-exercise PPT] and baseline physical and psychological measures were performed using Spearman's rho. Bonferroni corrections for multiple comparisons were performed. As such, P -values less than .001 were considered significant for correlation analyses.

3. Results

3.1 Participants: Demographics

Of the 21 individuals with WAD (age = 44.5 ± 10.5 yrs, 55% female), 18 completed the wall squat and 17 completed the bicycle test. Of the 19 healthy controls (age = 37.4 ± 10.8 yrs, 74% female), 17 completed the wall squat and 17 completed the bicycle test. All participants who did not perform both tests failed to attend the second exercise session. No reason for their withdrawal was provided. The control participants were significantly younger ($t_{38} = -.21, P=.04$). There was no significant gender difference between groups ($\chi^2 = 2.41, P=.31$).

The majority of participants with WAD (66%) presented with symptoms of greater than 2 years duration (Median [interquartile range]: 5 years [4,6]) and had received various types of conservative treatment (physiotherapy 94%; massage therapy 53%; chiropractic 29%; acupuncture 29% and laser therapy 6%). Prior to the commencement of the study, individuals were taking various medications for symptom relief (non-steroidal anti-inflammatory 35%; over the counter analgesics 24%; opioids 12%; muscle relaxants 12%; anti-anxiety medication 12%, and neuropathic pain medication 6%). Individuals refrained from taking medication in the 24-48 hours prior to study participation. Seven participants had an ongoing compensation claim.

Participants with WAD presented with significantly higher levels of disability (Mann Whitney U: $Z = 12.5, P = .000$) and fear of movement (Mann Whitney U: $Z = -3.15, P = .002$) than control participants, with no significant difference in pain catastrophization (Mann Whitney U: $Z = -1.35, P = .18$). The WAD group exhibited mild-to-moderate 24 hour pain (VAS = 2.9 ± 1.8) and pain over the last week (VAS = 3.4 ± 1.8); mild to moderate levels of disability (Median [IQR]: NDI = 20% [16,31]; controls = 0% [0,1]); moderate levels of fear of movement (TSK = 41 [34,44]; controls = 31 [25,36]); low levels of pain catastrophization (PCS = 12 [2,19]; controls = 3 [1,13]) and low levels of posttraumatic stress symptoms (PDS symptom severity score = 10 [5,16]).

3.2 Baseline Participant Characteristics: Physical Features

Participants with WAD demonstrated significantly reduced PPTs at the cervical spine and tibialis anterior compared to the healthy controls (Mann Whitney U: $Z < -2.24, P < .025$) (Table 1). Compared with control participants, participants with WAD also demonstrated significantly elevated cold pain thresholds (Mann Whitney U: $Z = -2.01, P = .045$), and reduced cold pressor threshold/tolerances (Mann Whitney U: $Z < -2.01, P < .045$). There was no difference between groups in peak or average reported pain levels during the cold pressor test (Mann Whitney U: $Z < -1.21, P > .06$). There were no differences in heat pain thresholds (Mann Whitney U: $Z = -1.36, P = .18$) or CPM (difference in HPTs measured before and after cold water immersion) (Mann Whitney U: $Z = -.11, P = .91$) between WAD and healthy controls, suggesting that there was no evidence of dysfunctional CPM in the WAD sample.

There were no significant group differences in resting heart rate or blood pressure ($P > .31$) between WAD participants and healthy controls (Table 2).

TABLE 1: Group Baseline Physical Characteristics

Measure	WAD (n=21) Median [IQR]	Controls (n=19) Median [IQR]
PPT C5 (kPa)	256 [150,342]	367 [242,500]*
PPT TibAnt (kPa)	372 [249,513]	521 [351,711]*
HPT (°C)	46.1 [45.3,48.4]	47.8 [45.9,49.0]
CPT (°C)	13.9 [8,21.7]	8 [8,14.5]*
Cold Press Thr (secs)	4.9 [2.7,7.4]	6.5 [5.2,9.4]*
Cold Press Tol (secs)	23.5 [9.9, 101.5]	52.7 [28.8,120]*
Cold Press Peak (secs)	8 [7.4, 9.1]	7.8 [6.5, 8.8]
Cold Press Avg (VAS/10)	7.3 [5.7,8.1]	6.3 [5.5,7.5]
CPM (°C)	0.47 [-.67,2.4]	0.4 [0,1.2]

Legend: WAD = whiplash associated disorder; TibAnt = tibialis anterior; C/HPT = cold/heat pain threshold; Cold Press Thr/Tol/Avg = Cold Pressor Threshold/Tolerance/Average; VAS = Visual Analog Scale; CPM = Conditioned Pain Modulation (difference in HPTs after cold water immersion); IQR = interquartile range; kPa = kilopascals; * $P < 0.05$

3.3 Exercise Performance

Compared to WAD participants, healthy control participants performed the wall squat for a longer duration (Mann Whitney U: $Z = -2.05$, $P = 0.04$), and had higher levels of power output (Mann Whitney U: $Z = -2.58$, $P = .01$) during the bicycle exercise (Table 2). Both groups performed the exercises at the same relative intensity (percentage of predicted heart rate maximum during bicycle test: $t_{30} = -1.61$, $P = .12$; RPE during wall squat: $t_{32} = .39$, $P = .71$).

TABLE 2: Group Exercise Results for Isometric (Wall Squat) and Aerobic (Bicycle) Exercise

	WAD Median [IQR] Mean (SD)	Controls Median [IQR] Mean (SD)
Bicycle Test	n=17	n=17
Avg power output (W)	62.8 [47.3,76.8]	81.7 [70.8,99.2]*
% predicted 75%HRmax	0.94 (.04)	0.91 (.07)
Resting HR (bpm)	77 (9)	72 (12)
Resting Blood Pressure (mmHg)	126/78 (13/9)	123/81 (13/11)
Isometric Wall Squat	n=18	n=17
Time (secs)	106 [43,180]	152 [122,180]*
Peak RPE wall	5 [3,9]	6 [5,8]
Resting HR (bpm)	76 (13)	78 (12)
Resting Blood Pressure (mmHg)	128/84 (21/17)	126/84 (15/11)

Legend: WAD = whiplash associated disorder; HRmax = maximum heart rate; W = watts; RPE = rated perceived exertion; IQR = interquartile range; SD = standard deviation;

* $P < 0.05$ (Mann Whitney U or independent t-test)

3.4 The Effect of Exercise Type on EIH

3.4.1 Tibialis Anterior

There was a significant interaction between exercise type and time indicating that a change in PPTs following exercise varied significantly between isometric and aerobic exercise types (time * exercise: $F_{2,88.46} = 3.23$, $P = 0.044$) (Figure 2). This differential effect of exercise type on change in PPTs was not significantly different between groups (time * exercise * group: $F_{2,88.39} = .49$, $P = 0.61$). There was no effect of age ($F_{1,37.10} = 2.49$, $P = .12$). PPTs were significantly increased following the wall squat exercise ($P = 0.001$), however there were no significant changes following the bicycle test ($P = 0.17$).

Figure 2: Tibialis Anterior Pressure Pain Threshold Box Plots Demonstrating Medians and Interquartile Range for Each Group and Exercise.

3.4.2 Cervical Spine

There was a significant interaction between exercise type and time indicating that change in PPTs following exercise varied significantly between isometric and aerobic exercise types (time * exercise: $F_{2,90.33} = 6.08$, $P = 0.003$) (Figure 3). This differential effect of exercise type on change in PPTs was not significantly different between groups (time * exercise * group; $F_{2,90.32} = .57$; $P = 0.57$). There was no effect of age ($F_{1,35.33} = 2.66$, $P = .11$). PPTs were significantly increased following the wall squat exercise ($P = 0.015$), however there were no significant changes following the bicycle test ($P = 0.96$).

Figure 3: Cervical Spine Pressure Pain Threshold Box Plots Demonstrating Medians and Interquartile Range for Each Group and Exercise.

3.4.3 Relationship between Baseline Variables and EIH

There were no significant correlations demonstrated between the percentage change in EIH measured at baseline and the percentage change in CPM for either anatomical location (tibialis anterior or cervical spine) in either group (WAD or controls) (Table 3).

There were no significant associations between percentage change in EIH (at either anatomical location) and any of the psychological variables measured at baseline for either group (WAD or controls), or for posttraumatic stress symptom severity in the WAD group (Table 3).

TABLE 3: Spearman's rho Correlations between Percentage Change in EIH and Baseline Variables

		% change in CPM		PCS		TSK		PDS Symptoms
		WAD	HC	WAD	HC	WAD	HC	WAD
% change in EIH (Tib Ant)	Correlation Coefficient	.38	-.01	.02	.22	-.02	-.14	.21
	Sig. (2-tailed)	.10	.98	.94	.39	.94	.59	.42
% change in EIH (C5)	Correlation Coefficient	.08	-.11	-.01	.06	-.11	.06	.06
	Sig. (2-tailed)	.76	.68	.97	.82	.66	.08	.82

Legend: EIH = Exercise Induced Hypoalgesia; Tib Ant = tibialis anterior;
 CPM = Conditioned Pain Modulation (difference in HPTs after cold water immersion);
 PCS = Pain Catastrophization Scale; TSK = Tampa Scale of Kinesiophobia;
 PDS Symptoms = Symptoms Score of Post Traumatic Stress Diagnostic Scale

There were no significant correlations demonstrated between percentage change in EIH (for the cervical spine or tibialis anterior), and any of the physical variables (thermal pain thresholds, cold pressor threshold/tolerance/peak) measured at baseline for either group (WAD or controls).

4. Discussion

The aim of this study was to investigate EIH in individuals with WAD, compare two different exercise types and investigate relationships between EIH, CPM and psychological factors. The isometric wall squat exercise but not the aerobic cycling exercise resulted in EIH in both groups with no between-group differences demonstrated for either exercise. EIH measured at either the cervical spine or lower limb, was not associated with CPM or psychological measures.

After whiplash injury, approximately 50% of individuals will develop chronic pain and disability with 20-30% of these experiencing ongoing moderate to severe symptoms [36]. The WAD participants in this study reported mild to moderate levels of pain and disability. Compared with healthy controls, participants with WAD demonstrated significantly reduced local and remote pressure pain thresholds, increased cold pain sensitivity, and cold pressor thresholds/tolerances. This generalised hyperalgesia likely indicates augmented central nociceptive processing and these results are consistent with previous research demonstrating the presence of generalised hyperalgesia in chronic WAD [37, 38]. Thus, the WAD participants in this study seem to be representative of the WAD population, albeit with milder baseline levels of pain and disability than previously reported.

EIH was demonstrated over the cervical spine and tibialis anterior for both WAD and healthy control groups following the isometric exercise but not after the aerobic bicycle exercise. The induction of EIH following the isometric wall squat exercise is consistent with prior research in other painful conditions (e.g. shoulder pain), where isometric exercise of a non-painful muscle (e.g. quadriceps) resulted in reduced pressure sensitivity of the painful (e.g. infraspinatus) region [13]. However, the

results of the aerobic cycling exercise are in contrast to a recent study where impaired EIH was found in individuals with chronic WAD after performing a submaximal bicycle exercise at the same intensity as the present study, however for a duration of only 4 minutes [9]. Our WAD group did not have impaired EIH (in the cervical spine or tibialis anterior), nor did they demonstrate EIH following 30 minutes of cycling exercise. A recent meta-analytic review concluded that larger effect sizes for EIH are found with longer duration (>10 minute) of exercise in healthy individuals [12]. Our study also included males and females, in contrast to the female only recruitment by Van Oosterwijck et al. (2012). It has been shown that females demonstrate greater EIH [14]. Thus, the previous findings of impaired EIH in WAD [9] may have resulted from participants not exercising long enough to induce EIH, with the differences between studies possibly resulting from reduced EIH demonstrated in our participants as a result of the gender mix. Another possible explanation for the contrasting findings may be that the WAD participants in the previous study reported higher baseline levels of pain (mean VAS: 5/10) than those of our study (mean VAS: 2.9/10). This is consistent with research demonstrating that EIH is reduced in chronic musculoskeletal pain patients with higher levels of clinical pain and associated pain sensitivity [39]. As the results of our study are in agreement with those reported for individuals with chronic milder low back pain [40, 41], it may suggest that baseline levels of pain and disability are associated with EIH. Overall, the findings of the present study suggest that isometric exercise may be more effective than aerobic exercise in inducing EIH in individuals with mild to moderate WAD symptoms, but also that 30 minutes of submaximal aerobic exercise does not increase pain sensitivity.

Exercise activates opiate and noradrenergic systems [42] proportional to parameters such as the intensity and duration of exercise [2, 43], resulting in EIH [1]. Despite both groups in our study exercising for an adequate duration of time to produce EIH [43], 30 minutes of sub-maximal aerobic bicycle exercise at 75% predicted HR_{max} did not induce EIH. Results from previous research regarding optimal exercise intensity are equivocal. Some research has shown that exercise performed by healthy participants at the same intensity of exercise as the present study (75% age-predicted maximum heart rate or VO_{2max}) [9, 12] demonstrated EIH, while others suggest that higher intensities (85% of HR_{max} [44]) are required to induce EIH. Note must be made of the considerable variance demonstrated in the data, indicating significant heterogeneity of response to exercise. Thus, further research is needed to explore the effect of exercise intensity on EIH and larger sample sizes are likely required to address these heterogeneous responses.

Although endogenous analgesia may result from both CPM and exercise paradigms we found no significant correlation between the two, possibly suggesting that different mechanisms underlie these phenomena. Our results support recent research in healthy participants showing no correlation between the change in PPTs induced by CPM or EIH [14], but contrasts with another study that showed CPM efficacy predicts EIH [15]. The study participants (healthy males only) and methodology employed in the study by Lemley et al. (2015), differed from those used in our study. For example, the different isometric exercise parameters (biceps vs wall squat), different conditioning (feet vs hand cold water immersion) and test stimuli (pressure pain perception performed at finger vs PPT performed over cervical spine and tibialis anterior) utilized, all may have influenced the difference in results. Thus, there continues to be uncertainty as to whether different mechanisms are involved. Recent research has demonstrated that EIH following isometric exercise may be influenced by non-opioidergic mechanisms, and in particular have an endocannabinoid underpinning [45]. Conversely, it has been suggested that CPM appears to be sensitive to opioids [46-48] and N-methyl-D-aspartate (NMDA) receptor antagonism [49]. Thus, although CPM may predict EIH in healthy adults, our results, although speculative, would suggest that, in the absence of dysfunctional CPM, other mechanisms may also be involved. Further exploration is warranted.

EIH measured at either the cervical spine or lower limb, was not associated with psychological measures. This was a surprising result, given previous research in WAD. Although not specifically

measuring EIH, relationships between post-traumatic stress symptoms and PPTs [50], and pain catastrophizing and cold pain thresholds [51] have been demonstrated. Patients in our study reported lower levels of pain catastrophizing and posttraumatic stress symptoms, pain and disability suggesting that relationships between these factors and pain threshold measures may be stronger in participants with higher symptomatology. The influence of psychological measures on EIH has not been as well studied, apart from one study in a young, healthy male cohort [11]. Although the study demonstrated that pain catastrophizing was predictive of EIH, it appeared to be test specific and associated with reduction of temporal summation, not PPTs after exercise [11]. Further investigation is warranted to explore the relationship of psychological manifestations and EIH.

There are several limitations to the present study. Firstly, a possible ceiling effect for PPTs was noted at the cervical spine for the healthy participants, which may explain differences to previous research in healthy control participants. However, this ceiling effect of PPTs did not apply to the WAD group. Hence, future research involving healthy participants should consider utilization of physical measures that do not result in a ceiling effect. Secondly, the participants with WAD reported mild to moderate levels of pain and disability. Whilst isometric and aerobic exercise did not induce pain in individuals with mild symptoms, it is possible that dysfunctional EIH may occur in individuals with higher levels of pain and disability. Thirdly, this study utilised EIH and CPM as measures associated with central pain modulatory processes. Another such measure is temporal summation [52]. Temporal summation has been associated with enhanced pain facilitation in a number of clinical disorders [53-56]. Therefore, it may better reflect the pain modulation profile demonstrated by the WAD group and could be considered in future studies. Finally, this research focussed on outcomes associated with one bout of acute exercise. It is not known whether or not the same results would occur following repeated bouts of exercise. Future research should also consider the effect of repeated bouts of exercise on pain sensitivity, to determine if similar results are obtained as demonstrated in this study.

Clinical Implications

This study showed that individuals with chronic WAD and mild to moderate levels of pain and disability and no evidence of dysfunctional CPM demonstrated reduced pain sensitivity, both in the cervical spine and over the tibialis anterior following an isometric, timed wall squat exercise. Whereas, there was no EIH induced in either group with aerobic bicycle exercise. Isometric exercise of non-painful muscles may be indicated to reduce pain sensitivity in patients with chronic WAD. Thirty minutes of sub-maximal aerobic exercise may be undertaken without increasing pain sensitivity.

Ethical Issues:

All participants provided informed consent in each testing session, prior to completing baseline questionnaires and resting physical measures. Ethical clearance for this study was granted by the University of Queensland Medical Research Ethics Committee (Ref: 2014 – 000553).

Conflicts of Interest:

The authors do not have any conflicts of interest to declare. Michele Sterling is supported by a fellowship through the National Health and Medical Research Council of Australia. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References:

1. Koltyn, K.F., Analgesia following exercise: a review. *Sports Med* 2000;29:85-98.
2. Koltyn, K.F., Exercise-induced hypoalgesia and intensity of exercise. *Sports Med* 2002;32:477-87.
3. Schwarz, L. and W. Kindermann, Changes in beta-endorphin levels in response to aerobic and anaerobic exercise. *Sports Med* 1992;13:25-36.
4. Koltyn, K., Exercise-Induced Hypoalgesia and Intensity of Exercise. *Sports Medicine* 2002;32:477-487.
5. Meeus, M., L. Hermans, K. Ickmans, F. Struyf, D. Van Cauwenbergh, L. Bronckaerts, L.S. De Clerck, G. Moorken, G. Hans, S. Grosemans, and J. Nijs, Endogenous Pain Modulation in Response to Exercise in Patients with Rheumatoid Arthritis, Patients with Chronic Fatigue Syndrome and Comorbid Fibromyalgia, and Healthy Controls: A Double-Blind Randomized Controlled Trial. *Pain Practice* 2014;n/a-n/a.
6. Nijs, J., E. Kosek, J. Van Oosterwijck, and M. Meeus, Dysfunctional endogenous analgesia during exercise in patients with chronic pain: to exercise or not to exercise? *Pain Physician* 2012;15:ES205-ES213.
7. Ng, T.S., A. Pedler, B. Vicenzino, and M. Sterling, Less Efficacious Conditioned Pain Modulation and Sensory Hypersensitivity in Chronic Whiplash-associated Disorders in Singapore. *Clin J Pain* 2013;30:436-42.
8. Daenen, L., J. Nijs, N. Roussel, K. Wouters, M. Van Loo, and P. Cras, Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: an experimental study. *Clin Rheumatol* 2013;32:23-31.
9. Van Oosterwijck, J., J. Nijs, M. Meeus, M. Van Loo, and L. Paul, Lack of endogenous pain inhibition during exercise in people with chronic whiplash associated disorders: an experimental study. *J Pain* 2012;13:242-54.
10. Sterling, M., Physiotherapy management of whiplash-associated disorders (WAD). *J Physiother* 2014;60:5-12.
11. Naugle, K.M., K.E. Naugle, R.B. Fillingim, and J.L. Riley, 3rd, Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Med* 2014;15:692-701.
12. Naugle, K.M., R.B. Fillingim, and J.L. Riley, 3rd, A meta-analytic review of the hypoalgesic effects of exercise. *J Pain* 2012;13:1139-50.
13. Lannersten, L. and E. Kosek, Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain* 2010;151:77-86.
14. Vaegter, H.B., G. Handberg, and T. Graven-Nielsen, Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain* 2014;155:158-67.
15. Lemley, K.J., S.K. Hunter, and M.K. Bement, Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. *Med Sci Sports Exerc* 2015;47:176-84.
16. Spitzer, W.O., M.L. Skovron, L.R. Salmi, J.D. Cassidy, J. Duranceau, S. Suissa, and E. Zeiss, Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine* 1995;20:1S-73S.
17. ACSM, Health/Fitness Standards and Guidelines. 1997, Indianapolis, In: American College of Sports Medicine.
18. Kosek, E. and G. Ordeberg, Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain* 2000;88:69-78.
19. France, C.R. and S. Suchowiecki, A comparison of diffuse noxious inhibitory controls in men and women. *Pain* 1999;81:77-84.
20. Telford, R., A. Minikin, L. Hahn, and A. Hooper, A simple method for the assessment of general fitness: the tri-level profile. *Australian Journal of Science and Medicine in Sports* 1989;21:6-9.

21. Borg, G., Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise* 1982;14:377-381.
22. Wallman, K.E., A.R. Morton, C. Goodman, and R. Grove, Physiological Responses during a Submaximal Cycle Test in Chronic Fatigue Syndrome. *Medicine & Science in Sports & Exercise* 2004;36:1682-1688.
23. Goldring, N., J.D. Wiles, and D. Coleman, The effects of isometric wall squat exercise on heart rate and blood pressure in a normotensive population. *Journal of Sports Sciences* 2013;32:129-136.
24. Pengel, L.H.M.M., K.M.P. Refshauge, and C.G.P. Maher, Responsiveness of Pain, Disability, and Physical Impairment Outcomes in Patients With Low Back Pain. *Spine* 2004;29:879-883.
25. Macdermid, J., D. Walton, S. Avery, A. Blanchard, E. Etruw, C. McAlpine, and e. al, Measurement Properties of the Neck Disability Index: A Systematic Review. *Journal of Orthopaedic & Sports Physical Therapy* 2009;39:400-C12.
26. Sullivan, M., S. Bishop, and J. Pivik, The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7:524-532.
27. Vlaeyen, J.W.S., A.M.J. Kole-Snijders, R.G.B. Boeren, and H. Van Eek, Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 1995;62:363-372.
28. Foa, E., *Posttraumatic Stress Diagnostic Scale: Manual*. 1995, Minneapolis: NCS Pearson.
29. Sterling, M., G. Jull, B. Vicenzino, and J. Kenardy, Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain* 2003;104:509 - 517.
30. Chien, A., E. Eliav, and M. Sterling, Hypoesthesia occurs in acute whiplash irrespective of pain and disability levels and the presence of sensory hypersensitivity. *Clin J Pain* 2008;24:759-66.
31. Chien, A., E. Eliav, and M. Sterling, Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash - Further evidence of a neuropathic condition. *Manual Therapy* 2009;14:138-146.
32. Sterling, M., G. Jull, B. Vicenzino, and J. Kenardy, Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain* 2003;104:509-17.
33. Hsieh, A.Y., D.A. Tripp, L.J. Ji, and M.J.L. Sullivan, Comparisons of catastrophizing, pain attitudes, and cold-pressor pain experience between chinese and european canadian young adults. *Journal of Pain* 2010;11:1187-1194.
34. Ng, T.S.P.-C., A.P. Pedler, B.P. Vicenzino, and M.P. Sterling, Less Efficacious Conditioned Pain Modulation and Sensory Hypersensitivity in Chronic Whiplash-associated Disorders in Singapore. *Clinical Journal of Pain* 2013.
35. Sterling, M., Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain* 2010;150:501-6.
36. Carroll, L.J., L.W. Holm, S. Hogg-Johnson, P. Cote, J.D. Cassidy, S. Haldeman, M. Nordin, E.L. Hurwitz, E.J. Carragee, G. van der Velde, P.M. Peloso, and J. Guzman, Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine* 2008;33:S83-92.
37. Stone, A.M., B. Vicenzino, E.C. Lim, and M. Sterling, Measures of central hyperexcitability in chronic whiplash associated disorder--a systematic review and meta-analysis. *Man Ther* 2013;18:111-7.
38. Van Oosterwijck, J., J. Nijs, M. Meeus, and L. Paul, Evidence for central sensitization in chronic whiplash: a systematic literature review. *Eur J Pain* 2013;17:299-312.
39. Vaegter, H.B., G. Handberg, and T. Graven-Nielsen, Hypoalgesia After Exercise and the Cold Pressor Test is Reduced in Chronic Musculoskeletal Pain Patients With High Pain Sensitivity. *Clin J Pain* 2016;32:58-69.

40. Meeus, M., N.A. Roussel, S. Truijen, and J. Nijs, Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med* 2010;42:884-90.
41. Hoffman, M.D., M.A. Shepanski, S.P. Mackenzie, and P.S. Clifford, Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. *J Rehabil Res Dev* 2005;42:183-90.
42. Angelopoulos, T.J., B.G. Denys, C. Weikart, S.G. Dasilva, T.J. Michael, and R.J. Robertson, Endogenous opioids may modulate catecholamine secretion during high intensity exercise. *Eur J Appl Physiol Occup Physiol* 1995;70:195-9.
43. Hoffman, M.D., M.A. Shepanski, S.B. Ruble, Z. Valic, J.B. Buckwalter, and P.S. Clifford, Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. *Arch Phys Med Rehabil* 2004;85:1183-7.
44. Sternberg, W.F., C. Bokar, L. Kass, A. Alboyadjian, and R.H. Gracely, Sex-dependent components of the analgesia produced by athletic competition. *J Pain* 2001;2:65-74.
45. Koltyn, K.F., A.G. Brellenthin, D.B. Cook, N. Sehgal, and C. Hillard, Mechanisms of exercise-induced hypoalgesia. *J Pain* 2014;15:1294-1304.
46. King, C.D., B. Goodin, L.L. Kindler, R.M. Caudle, R.R. Edwards, N. Gravenstein, J.L. Riley, 3rd, and R.B. Fillingim, Reduction of conditioned pain modulation in humans by naltrexone: an exploratory study of the effects of pain catastrophizing. *J Behav Med* 2013;36:315-27.
47. Pertovaara, A., P. Kemppainen, G. Johansson, and S.L. Karonen, 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.
48. Willer, J.C., D. Le Bars, and T. De Broucker, Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. *Eur J Pharmacol* 1990;182:347-55.
49. Niesters, M., A. Dahan, M. Swartjes, I. Noppers, R.B. Fillingim, L. Aarts, and E.Y. Sarton, Effect of ketamine on endogenous pain modulation in healthy volunteers. *Pain* 2011;152:656-63.
50. Pedler, A. and M. Sterling, Patients with chronic whiplash can be subgrouped on the basis of symptoms of sensory hypersensitivity and posttraumatic stress. *Pain* 2013;154:1640-8.
51. Sterling, M., E. Hodkinson, C. Pettiford, T. Souvlis, and M. Curatolo, Psychologic factors are related to some sensory pain thresholds but not nociceptive flexion reflex threshold in chronic whiplash. *Clin J Pain* 2008;24:124-30.
52. Yarnitsky, D., M. Granot, and Y. Granovsky, Pain modulation profile and pain therapy: between pro- and antinociception. *Pain* 2014;155:663-5.
53. Arendt-Nielsen, L., H. Nie, M.B. Laursen, B.S. Laursen, P. Madeleine, O.H. Simonsen, and T. Graven-Nielsen, Sensitization in patients with painful knee osteoarthritis. *Pain* 2010;149:573-81.
54. Price, D.D. and R. Staud, Neurobiology of fibromyalgia syndrome. *J Rheumatol Suppl* 2005;75:22-8.
55. Sarlani, E., E.G. Grace, M.A. Reynolds, and J.D. Greenspan, Evidence for up-regulated central nociceptive processing in patients with masticatory myofascial pain. *J Orofac Pain* 2004;18:41-55.
56. Weissman-Fogel, I., E. Sprecher, Y. Granovsky, and D. Yarnitsky, Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. *Pain* 2003;104:693-700.