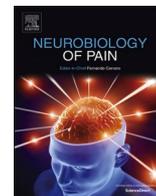




Contents lists available at ScienceDirect

Neurobiology of Pain

journal homepage: www.sciencedirect.com/journal/neurobiology-of-pain

The autonomic and nociceptive response to acute exercise is impaired in people with knee osteoarthritis

Neil R. Bossenger^a, Gwyn N. Lewis^{a,*}, David A. Rice^{a,b}, Daniel Shepherd^c

^a Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand

^b Waitematā Pain Services, Department of Anaesthesiology and Perioperative Medicine, Te Whatu Ora Waitematā, Auckland, New Zealand

^c Department of Psychology, Faculty of Health and Environmental Sciences, Auckland University of Technology, Auckland, New Zealand

ARTICLE INFO

Keywords:

Knee osteoarthritis
Fibromyalgia
Autonomic nervous system
Exercise-induced hypoalgesia
Pressure pain threshold
Isometric exercise

ABSTRACT

Objectives: An acute bout of exercise typically leads to short term exercise induced hypoalgesia (EIH), but this response is more variable in many chronic pain populations, including knee osteoarthritis (OA) and fibromyalgia (FM). There is evidence of autonomic nervous system (ANS) dysfunction in some chronic pain populations that may contribute to impaired EIH, but this has not been investigated in people with knee OA. The aim of this study was to assess the acute effects of isometric exercise on the nociceptive and autonomic nervous systems in people with knee OA and FM, compared to pain-free controls.

Methods: A cross-sectional study was undertaken with 14 people with knee OA, 13 people with FM, and 15 pain free controls. Across two experimental sessions, baseline recordings and the response of the nociceptive and autonomic nervous systems to a 5-min submaximal isometric contraction of the quadriceps muscle was assessed. The nociceptive system was assessed using pressure pain thresholds at the knee and forearm. The ANS was assessed using high frequency heart rate variability, cardiac pre-ejection period, and electrodermal activity. Outcome measures were obtained before and during (ANS) or immediately after (nociceptive) the acute bout of exercise.

Results: Submaximal isometric exercise led to EIH in the control group. EIH was absent in both chronic pain groups. Both chronic pain groups showed lower vagal activity at rest. Furthermore, people with knee OA demonstrated reduced vagal withdrawal in response to acute isometric exercise compared to controls. Sympathetic reactivity was similar across groups.

Discussion: The findings of reduced tonic vagal activity and reduced autonomic modulation in response to isometric exercise raise the potential of a blunted ability to adapt to acute exercise stress and modulate nociception in people with knee OA. The impairment of EIH in knee OA may, in part, be due to ANS dysfunction.

Introduction

The lifetime risk of developing symptomatic knee osteoarthritis (OA) is estimated to be approximately 14%, with higher risk for females and those with obesity (Losina et al., 2013). Chronic knee pain, reduced joint motion, and diminished quadriceps strength associated with knee OA reduce mobility and impair the ability to perform activities of daily living, leading to ongoing functional disability (Hunter et al., 2014). Pain associated with OA was once viewed as arising primarily through peripherally mediated joint nociception (Mandl, 2011). However, it is now known to have complex underlying central nervous system mechanisms that modulate peripheral nociception and strongly contribute to

OA symptomatology (King et al., 2013). OA also may be partly a systemic phenomenon, with the autonomic nervous system (ANS) hypothesised to play a multifactorial role in its pathogenesis (Yun et al., 2006; Berenbaum and Meng, 2016).

Dysfunction of the ANS has been demonstrated in several chronic pain conditions, including fibromyalgia (FM)/chronic widespread pain (Cohen, 2001; Reyes del Paso et al., 2011; Martínez-Lavin, 2007), irritable bowel syndrome (Adeyemi et al., 1999; Karling, 1998; Chalaye et al., 2012), complex regional pain syndrome (Terkelsen et al., 2012), and rheumatoid arthritis (Adlan et al., 2014). Typically, people with chronic pain conditions display reduced vagal activity and higher sympathetic activity at rest (Pollatos et al., 2011; Tracy et al., 2016),

* Corresponding author at: Health and Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand.
E-mail address: gwyn.lewis@aut.ac.nz (G.N. Lewis).

<https://doi.org/10.1016/j.ynpai.2023.100118>

Received 11 December 2022; Received in revised form 12 January 2023; Accepted 17 January 2023

Available online 19 January 2023

2452-073X/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

which creates a floor effect of diminished autonomic capacity to adapt and modulate in response to stress, including noxious stimuli (Laborde et al., 2018). This itself is likely to impair the capacity of the ANS to modulate nociception (Hohenschurz-Schmidt et al., 2020). For example, in healthy populations, acute mental stress results in both vagal withdrawal and sympathetic activation (Xie et al., 2017; Terkelsen et al., 2004), and is associated with inhibition of nociception (Terkelsen et al., 2004). The ANS response to stress has been shown to be more varied in people with chronic pain and is associated with impaired nociceptive inhibition, or even facilitation (Drummond et al., 2001; Drummond and Willox, 2013; Reyes del Paso et al., 2010; Thieme et al., 2006). To date, there have been no studies providing an in-depth examination of ANS function in people with OA.

Acute exercise can also impact the nociceptive system. In healthy people, there is a short-term inhibition of nociception following acute isometric exercise, termed exercise-induced hypoalgesia (EIH) (Koltyn, 2000). EIH effectiveness is dependent on the type of exercise, its intensity and duration, and the body part that is exercised (Hoeger Bement et al., 2008; Koltyn, 2002). EIH is elicited most consistently after high intensity aerobic exercise (~70 % maximal oxygen uptake) for durations longer than 10 mins or following short duration (5 mins) but fatiguing submaximal isometric exercise (Naugle et al., 2012).

The hypoalgesic response to isometric exercise in people with chronic pain is more variable with different studies showing hypoalgesia, hyperalgesia, or no change in pain sensitivity (Nijs et al., 2012). Indeed, previous studies have demonstrated EIH to be intact (Kosek et al., 2013; Neelapala, 2018; Fingleton et al., 2017) or impaired (Fingleton et al., 2017; Burrows et al., 2014) in people with knee OA depending on the type of exercise and characteristics of the population. The varied impact of exercise on nociception in people with knee OA may be due, in part, to functional deficits in descending nociceptive inhibitory pathways, including aberrant ANS and cardiovascular responses that may contribute to their activation (Chalaye et al., 2014). However, the ANS response to acute exercise has not been examined in people with knee OA. Therefore, the aim of this study was to assess the effects of acute, submaximal isometric exercise on the nociceptive and autonomic nervous systems in people with knee OA and people with FM, a population with a known ANS dysfunction and a varied EIH response (Staud, 2005). It was hypothesised that, compared to controls, people with knee OA and FM would exhibit (1) reduced vagal tone and increased pain sensitivity at rest, and (2) reduced autonomic modulation and reduced EIH in response to acute isometric exercise.

Materials and Methods

Participants

Fifteen pain free people, 14 people with knee OA, and 13 people with FM volunteered to participate in the study (Table 1). A sample size for this study was powered based on a previous study (Hallman et al., 2015) examining the reliability of heart rate variability (HRV) indices to a repetitive, low-force task. Based on the effect sizes, the sample size for detecting a change of 20% of the mean of most HRV parameters between groups, using an alpha level of 0.05 and power of 0.8, corresponded to approximately 20 participants per group.

Participants were included in the study if they were aged over 18 years, diagnosed by a clinician with knee OA or FM and fulfilled the American College of Rheumatology criteria (Altman et al., 1986; Wolfe et al., 2016), and had experienced pain for at least 3 months on most days with a minimum level of 3 out of 10 in the previous 7 days. Participants were excluded from the study if they had a cardiac condition, hypertension (i.e., systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), or were taking medications that may alter cardiovascular and/or autonomic activity. Participants were asked to refrain from taking analgesic medication, e.g. opioidergic or anti-inflammatory, for 24 hr prior to data collection, and from taking

Table 1

Participant characteristics. Data are mean (standard deviation) unless otherwise stated.

Characteristic	Control n = 15	Knee OA n = 14	FM n = 13	p value
Age (years)	53 (10)	60 (9)	47 (14)	0.17
Gender female (n, %)	11 (73)	10 (71)	13 (100)	0.11
BMI (kg/m ²)	25 (3)	31 (7)*	31 (5)*	0.003 [#]
BPI severity	2 (3)	18 (10)*	20 (7)*	<0.001 [#]
BPI interference	1 (1)	30 (19)*	36 (19)*	<0.001 [#]
DASS-21 Depression	1 (1)	4 (3)*	6 (4)*	<0.001 [#]
DASS-21 Anxiety	1 (1)	3 (5)	6 (4)*	<0.001 [#]
DASS-21 Stress	2 (2)	5 (4)*	9 (5)*	<0.001 [#]
PCS	6 (7)	17 (13)*	22 (11)*	<0.001 [#]
WOMAC				
MVC (Nm)	200 (63)	135 (62)*	145 (32)*	0.01 [#]
Borg RPE (6 – 20)				
During ANS session	16 (3)	15 (2)	16 (2)	0.22
During QST session	16 (3)	14 (2)	16 (2)	0.052

BMI = Body mass index; BPI = Brief Pain Inventory; DASS-21 = Depression, Anxiety and Stress Scales; FM = fibromyalgia; OA = osteoarthritis; PCS = Pain Catastrophising Scale; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; RPE = ratings of perceived exertion; ANS = autonomic nervous system; MVC = maximal voluntary contraction; QST = quantitative sensory testing; * = significant difference from control; [#] = significant difference between groups.

caffeine and tobacco products 6 hr prior to data collection. Ethical approval was obtained from the institutional ethics committee and participants provided informed, written consent prior to participation.

Procedure

The study was a cross-sectional, experimental design undertaken in a laboratory setting within a public hospital. Data collection was conducted over three sessions separated by 7 days. The maximal voluntary contraction (MVC) was determined in the first session to avoid fatigue effects and any confounding effects on measures of the nociceptive and autonomic systems. Participants also completed the Brief Pain Inventory (BPI), Pain Catastrophising Scale (PCS), Depression, Anxiety, and Stress Scale (DASS-21), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; OA group only) at this session. To avoid the nociceptive outcome measures influencing ANS recordings, nociceptive and ANS outcomes in response to submaximal isometric contraction were recorded separately in the two remaining sessions. These two sessions were completed in a randomised order.

The testing protocol is outlined in Fig. 1. In both test sessions, outcome measures were first assessed while the participant was resting (baseline). The participant was then instructed to hold an isometric knee extension at 20% of the predetermined MVC for 5 mins. During the isometric exercise, the participant rated their perceived level of exertion every 60 s using the Borg scale (Borg, 1970), ranging from 6 (no exertion at all) to 20 (maximal exertion). The nociceptive outcome measures were assessed immediately following the isometric exercise. The ANS outcome measures were recorded continuously from 5 mins prior to baseline through to completion of the isometric exercise.

Isometric exercise

MVC of the quadriceps femoris was determined in all participants using a Biodex dynamometer (Biodex, USA). The most affected limb was used to perform the exercise in the knee OA group, while the other participants used their left leg. Participants were asked to recline in the supine position with the torso elevated at 30° and the knees flexed at 90°. Straps crisscrossed over the chest and the index thigh to prevent excess body movement. A warm-up procedure was performed for familiarisation with the task involving four repetitions of graded effort (25%, 50%, 50%, 75% of estimated maximum), and then four maximal

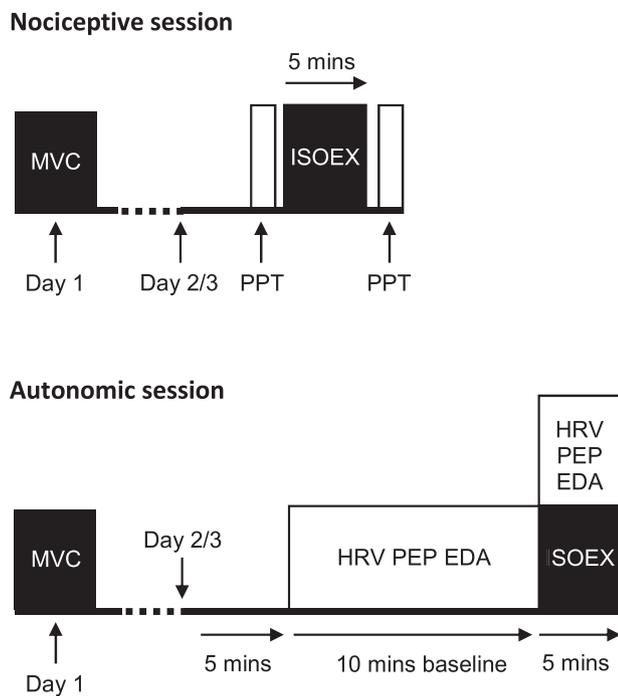


Fig. 1. Schematic diagram showing the protocol for the two testing sessions. Knee extension maximum voluntary contraction (MVC) was established in a separate session, and the order of the remaining two sessions was randomized. ISOEX = isometric exercise; PPT = pressure pain threshold; HRV = heart rate variability; PEP = pre-ejection period; EDA = electrodermal activity.

voluntary contractions of 5 s were performed with a 60 s rest between contractions. The peak torque (Nm) value in any of the four maximal contractions was recorded as MVC.

The intervention during the testing sessions involved sustaining 20% MVC in the same body position as described above for 5 mins. The target level of torque was displayed on a screen along with continuous visual feedback from the dynamometer of the knee extension torque being produced by the participant. If the participant was not able to maintain the required contraction level, they were permitted ~10 s rest breaks, as required, to achieve 5 mins. This was to ensure that all participants completed a similar volume of acute exercise and to match the duration of autonomic measurement recording at baseline and during exercise.

Nociceptive outcome measures

The nociceptive system was assessed using pressure pain threshold (PPT). PPT was assessed 2 cm distal to the inferior edge of the medial patella on the test knee (Arendt-Nielsen et al., 2010) and at the volar forearm on the ipsilateral limb, 5 cm distal to the elbow along the radial border. A handheld algometer (AlgoMed, Medoc, Israel) was applied to the test site and the pressure increased at 30 kPa/s until the participant pressed a button indicating the pressure had changed from uncomfortable to painful. The procedure was performed three times at each location with a 30 s interval between stimuli, and the average used for further analyses.

Autonomic outcome measures

Heart rate variability

High frequency heart rate variability (HF HRV) was used as a measure of parasympathetic activity. Heart rate was obtained from continuous electrocardiogram (ECG) recordings (Cardio Vascular Lab, Medis, Germany). Pregelled 46 × 88 mm Ag/AgCl ICG/ECG electrodes were placed at each side of the participant's neck and on each side of the

thorax along the midaxillary line. The ECG signal was sampled at 200 Hz and time locked to the R wave. The variability of RR intervals was examined using Kubios HRV Premium v3.5.0 (Kubios Oy, Finland). Following fast-fourier transform, HF HRV (0.15–0.4 Hz) was extracted from the data obtained over 5-minute recording periods (baseline, during isometric exercise).

Cardiac pre-ejection period

Pre-ejection period (PEP) was used as a measure of central sympathetic activity. PEP data were extracted from the same impedance cardiography and ECG recording used for HRV. PEP was defined as the interval between the onset of electrical stimulation of the ventricles (Q wave on the ECG) and aortic valve opening (B point on impedance cardiography signal) (Burgess et al., 2004). The mean PEP of the last 30 s of each minute of the 5 min recordings was determined at baseline and during exercise.

Electrodermal activity

Electrodermal activity (EDA) was used as a measure of peripheral sympathetic activity. EDA was recorded by placing a pair of 6 cm diameter pregelled Ag/AgCl electrodes (Red Dot, 3 M) on the palmar tips of the index and middle fingers of the hand, after being pre-treated with ethanol wipes, at least 10 cm away from any region on the forearm receiving thermal stimulation. Data were sampled at 32 Hz using a NeXus-10 MKII analogue-to-digital convertor and BioTrace software (MindMedia, Netherlands). Tonic EDA (skin conductance level; SCL) was assessed by determining the mean amplitude of the EDA signal during the last 10 s of each minute during the 5 min recordings at baseline and during isometric exercise (Treister et al., 2012). Phasic EDA (skin conductance response; SCR) was calculated by determining the number of spontaneous EDA spikes per minute (>0.03 μS) during the 5 min recording periods at baseline and during isometric exercise (Braithwaite, 2013).

Statistical analyses

Demographic and clinical characteristics of the three groups were compared using one-way analysis of variance (ANOVA), Kruskal-Wallis tests, and the chi-square test, as appropriate. Significant main effects were followed up to compare the knee OA and FM groups to the control group.

To compare the outcome measures at rest (i.e., baseline) among the three groups, one-way ANOVA was used. Significant main effects were followed up with one-sided Dunnett's test to compare the knee OA and FM groups to the control group. To determine the effect of isometric exercise, two-way repeated measures ANOVAs were used to compare the outcome measures across the two time periods (baseline, during/following isometric exercise) and three groups (control, knee OA, FM). The Huynh-Feldt correction factor was used when Epsilon < 1. Significant main effects of time were investigated with paired *t*-tests to compare baseline to during/following exercise in the three groups. Significant interaction effects were investigated by comparing the change in outcome measure from baseline to during/following exercise between the three groups using a one-way ANOVA with follow-up one-sided Dunnett's test.

The alpha level for all statistical procedures was set to 0.05, and all statistical analyses were performed using SPSS v.28 (Armonk, NY: IBM Corp).

Results

Participant characteristics

During the period of recruitment, the worldwide COVID-19 pandemic led to several lockdown periods in the Auckland region, and a general hesitancy of participants to attend hospital-based

appointments for research involving face-to-face data collection. As such, only 42 of the planned 63 participants were able to be recruited. In addition, two participants exhibited previously undiagnosed cardiovascular anomalies; thus, these data were omitted from the analyses.

Table 1 shows demographic and clinical information of the three groups. There were no significant differences in age or gender in the two pain groups compared to controls. As expected, BPI severity, BPI interference, DASS-21, and PCS values were all significantly higher in the knee OA and FM groups compared to control (all $p < 0.001$). There were also significant differences between groups in MVC. Follow-up one-sided Dunnett’s test showed that, as expected, MVC was significantly lower in both the knee OA ($p = 0.003$) and FM ($p = 0.01$) groups compared to the control group. There were no significant differences between groups in Borg RPE during isometric exercise in the ANS ($p = 0.22$) or nociceptive ($p = 0.052$) testing sessions.

Autonomic outcome measures

Heart rate variability

Group results for HF HRV are shown in Fig. 2A and Table 2. There were significant differences among groups in HF HRV at baseline (rest) ($F_{2,37} = 6.90, p = 0.003$). Follow-up one-sided Dunnett’s test showed both the knee OA ($p < 0.001$) and FM ($p = 0.03$) groups to have significantly lower HF HRV at rest compared to the control group.

In examining the response to exercise, the main effect of time ($F_{1,37} = 72.2, p = 0.001$) and the time \times group interaction were significant ($F_{2,37} = 7.5, p = 0.002$). Compared to baseline, HF HRV was significantly lower in the control ($p < 0.001$), knee OA ($p = 0.02$), and FM ($p < 0.001$) groups during isometric exercise. To explore the interaction effect, change values in HF HRV from rest to during isometric exercise were

Table 2

Group averages (standard deviation) for the autonomic and nociceptive outcome measures at baseline and during/after isometric exercise.

	Control	Knee OA	FM	<i>p</i> value
HF HRV (nu)				
Baseline	61.0 (11.6)	38.0 (18.5) [#]	46.8 (17.4) [#]	0.003
During exercise	26.8 (14.5) [*]	27.7 (12.1) [*]	24.4 (15.3) [*]	
PEP (ms)				
Baseline	118 (18)	127 (23)	119 (11)	0.43
During exercise	109 (16) [*]	120 (22) [*]	114 (12) [*]	
SCL (μs)				
Baseline	5.3 (2.5)	7.6 (4.2)	10.4 (5.3) [#]	0.01
During exercise	10.6 (4.9) [*]	11.5 (6.3) [*]	13.4 (5.8) [*]	
SCR (spikes/min)				
Baseline	0.16 (0.51)	0.76 (1.01)	1.05 (1.45)	0.08
During exercise	4.77 (2.06) [*]	4.20 (1.88) [*]	4.85 (2.25) [*]	
Knee PPT (kPa)				
Baseline	330 (117)	253 (134)	217 (83) [#]	0.04
Following exercise	376 (143) [*]	272 (124)	248 (113)	
Arm PPT (kPa)				
Baseline	264 (118)	243 (95)	240 (209)	0.83
Following exercise	273 (141)	223 (88)	209 (103)	

HF HRV = high frequency heart rate variability; PEP = pre-ejection period; SCL = skin conductance level; SCR = skin conductance response; PPT = pressure pain threshold; OA = osteoarthritis; FM = fibromyalgia; * = significant difference from baseline; # = significant difference from control group.

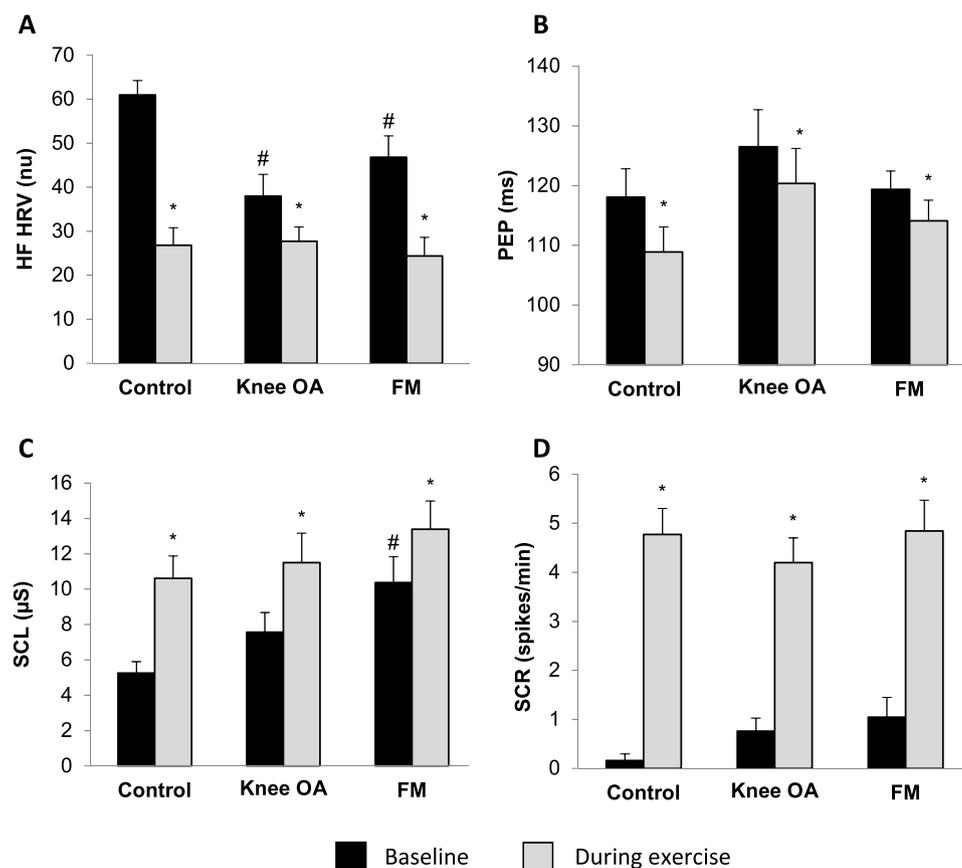


Fig. 2. Group results showing data from the autonomic nervous system session. HF HRV = high frequency heart rate variability; PEP = pre-ejection period; SCL = skin conductance level; SCR = skin conductance response; OA = osteoarthritis; FM = fibromyalgia. * = significant difference from baseline; # = significant difference from control group. Error bars are 1 standard error of the mean.

compared between the control group and the two chronic pain groups. One-sided Dunnett's test showed the reduction in HF HRV during isometric exercise was significantly smaller in the knee OA group compared to the control group ($p < 0.001$). While the reduction in HF HRV values was lower in the FM group compared to the control group, this difference did not reach statistical significance ($p = 0.063$).

Cardiac PEP

Group results for PEP are shown in Fig. 2B and Table 2. There were no significant differences among groups in PEP at baseline (rest) ($F_{2,39} = 0.87, p = 0.43$). The main effect of time was significant for PEP ($F_{1,39} = 21.1, p < 0.001$) but the interaction effect was not ($F_{2,39} = 0.64, p = 0.53$). Compared to rest, PEP was significantly shorter in the control ($p = 0.009$), knee OA ($p = 0.02$), and FM ($p = 0.03$) groups during isometric exercise.

Electrodermal activity

Group results for SCL are shown in Fig. 2C and Table 2. There were significant differences among groups in SCL at baseline (rest) ($F_{2,39} = 5.5, p = 0.01$). Follow-up one-sided Dunnett's test showed that SCL at rest was significantly higher in the FM group compared to the control group ($p = 0.002$), while the knee OA group were not significantly different from the control group ($p = 0.12$). The main effect of time was significant for SCL ($F_{1,39} = 64.4, p < 0.001$) but the interaction effect was not ($F_{2,39} = 1.9, p = 0.16$). Compared to rest, SCL was significantly higher in the control ($p < 0.001$), knee OA ($p < 0.001$), and FM ($p = 0.002$) groups during isometric exercise.

Group results for SCR are shown in Fig. 2D and Table 2. There were no significant differences among groups in SCR at baseline (rest) ($F_{2,39} = 2.7, p = 0.08$). The main effect of time was significant for SCR ($F_{1,39} = 210.4, p < 0.001$) but the interaction effect was not ($F_{2,39} = 1.7, p = 0.20$). Compared to rest, SCR was significantly higher in the control ($p < 0.001$), knee OA ($p < 0.001$), and FM ($p < 0.001$) groups during isometric exercise.

Nociceptive outcome measures

Knee PPT

Group results for knee PPT are shown in Fig. 3A and Table 2. There were significant differences among groups in knee PPT at baseline ($F_{2,39} = 3.58, p = 0.04$). Follow-up one-sided Dunnett's test showed the FM group to have significantly lower knee PPT at baseline compared to the control group ($p = 0.01$). While knee PPT values were lower in the knee OA group compared to the control group, this difference did not reach statistical significance ($p = 0.07$).

The main effect of time was significant for knee PPT ($F_{1,39} = 8.1, p = 0.007$) but the interaction effect was not ($F_{2,39} = 0.5, p = 0.61$). Compared to baseline, knee PPT was significantly lower immediately following exercise in the control group ($p = 0.01$), but not in the knee OA ($p = 0.20$) and FM ($p = 0.06$) groups.

Arm PPT

Group results for arm PPT are shown in Fig. 3B and Table 2. There were no significant differences among groups in arm PPT at baseline ($F_{2,39} = 0.2, p = 0.83$). Neither the main effect of time ($F_{1,39} = 2.5, p = 0.13$) or the interaction effect ($F_{2,39} = 1.8, p = 0.18$) were significant for arm PPT.

Relationship between autonomic and nociceptive function

To investigate the relationship between EIH and autonomic function, the change in knee PPT following exercise was correlated with the change in HF HRV during exercise in each group, as HF HRV was the only ANS outcome measure that showed a significant interaction between time and group. Pearson's r was not significant in the control ($r = 0.24, p = 0.43$), knee OA ($r = 0.12, p = 0.69$), or FM groups ($r = -0.20, p = 0.52$).

Discussion

This is the first study to examine the effects of acute isometric exercise on the ANS in people with knee OA. Participants with knee OA and FM both exhibited signs of ANS dysfunction at rest and, for the knee OA group, in response to isometric exercise. Furthermore, both the knee OA and FM groups demonstrated impaired EIH in response to acute isometric exercise.

Autonomic function

The study demonstrated reduced resting vagal tone in both the knee OA and FM groups. While this is a novel finding for people with knee OA, it is in line with previous meta-analytic evidence that chronic pain populations exhibit reduced vagal tone (Tracy et al., 2016), as well as specific studies involving people with FM (Cohen, 2001; Reyes del Paso et al., 2011; Furlan, 2005; Cohen et al., 2000). Higher resting vagal tone is associated with better executive function, reactivity to environmental demands, and emotional regulation (Laborde et al., 2018; Tonhajzerova et al., 2016; Appelhans and Luecken, 2006). Therefore, low resting vagal tone may be a measure for increased risk to external stressors (Thayer and Brosschot, 2005). Importantly, a loss of normal vagal tone may

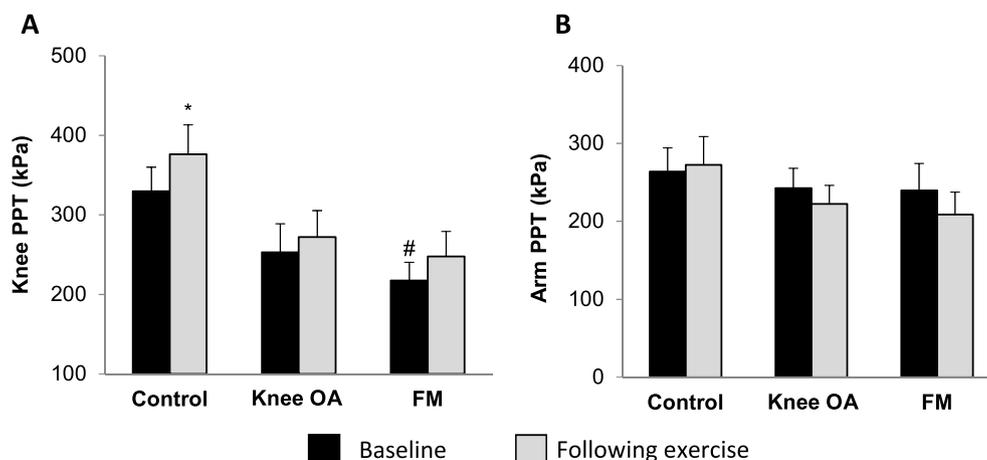


Fig. 3. Group results showing data from the nociceptive system session. PPT = pressure pain threshold; OA = osteoarthritis; FM = fibromyalgia. * = significant difference from baseline; # = significant difference from control group. Error bars are 1 standard error of the mean.

impair a person's ability to adapt to nociceptive stimuli and reduce tonic descending inhibition of nociceptive pathways (Hohenschurz-Schmidt et al., 2020). In addition, it has been hypothesised that a loss of vagal tone may increase both systemic and local joint inflammation, potentially enhancing disease progression and sensitisation of nociceptive pathways in people with OA (Yeater et al., 2022; Courties et al., 2017).

Vagal withdrawal is one of the first autonomic responses to stress (Martin et al., 1974) and HF HRV has long been known to decrease in healthy people immediately following isometric exercise (Taylor et al., 1995; Boutcher and Stocker, 1999). If vagal tone is already reduced at rest, further withdrawal may not be able to occur in response to such stimuli (Laborde et al., 2018). Following this, participants with knee OA in the current study demonstrated a reduced vagal withdrawal in response to acute isometric exercise compared to controls. A smaller reduction in HF HRV was also evident in the FM group but this did not reach statistical significance. A similar impaired vagal withdrawal in response to isometric exercise has been reported in healthy older adults (~67 years old) who also had lower baseline HF HRV (Taylor et al., 1995). These findings align with the concept that reduced tonic vagal activity impairs the capacity to modulate vagal drive appropriately in response to stressors, including exercise.

Only one previous study (Hallman et al., 2011) has examined HF HRV in response to isometric exercise in a chronic pain condition. In their study involving people with chronic neck-shoulder pain, (Hallman et al., 2011) reported a trend to reduced HF HRV at baseline but found no significant difference to controls in the response to isometric exercise (hand grip test), potentially due to the involvement of a smaller muscle group. Autonomic reactivity to stress, including vagal withdrawal, may be involved in triggering descending nociceptive modulation (Hohenschurz-Schmidt et al., 2020; Makovac et al., 2021). Therefore, vagal dysfunction may contribute to impaired nociceptive processing in people with knee OA and FM due to the blunted ability to respond to stimuli and initiate appropriate endogenous nociceptive inhibitory responses (Barakat, 2012).

There are limited studies on the sympathetic nervous system (SNS) in people with OA (Courties et al., 2017). Indeed, this is the first study to investigate EDA and PEP in people with OA. There were no significant differences from control evident at baseline in either of the EDA measures or PEP, suggesting intact resting SNS function in people with knee OA. PEP shortened and EDA increased significantly in all three groups during isometric exercise, reflecting an increase in SNS activity. Many previous studies have shown PEP to decrease in healthy people in response to isometric exercise (Boutcher and Stocker, 1999; Kino et al., 1975; Chirife, 1988; Nishiyasu et al., 1994), reflecting an increase in metabolic demand that enhances sympathetic drive to the heart to increase its rate and force of contraction. Previous studies, primarily utilising microneurography, have also shown that isometric muscle contraction increases sympathetic outflow to the skin in healthy people (Saito et al., 1990; Vissing et al., 1991; Seals, 1993; Schestatsky et al., 2009) and people with FM (Elam et al., 1992), although this does not always result in a change in EDA (Crandall et al., 1995; Ray and Wilson, 2004). Given the lack of difference from controls in both the knee OA and FM groups in the response to exercise, it is assumed this sympathetic response is intact in these populations but further, higher powered studies are needed to confirm this.

Nociceptive function

The chronic pain groups were expected to have reduced PPTs at rest, based on previous research that has revealed nociceptive sensitisation in people with knee OA (Suokas et al., 2012; Fingleton et al., 2015) and FM (Blumenstiel et al., 2011; Hilgenberg-Sydney et al., 2016). While knee PPT was significantly lower in the knee OA group compared to controls, it was not significantly different in the knee OA group. The effect size between the knee OA and control group is comparable to a previous study (Arendt-Nielsen et al., 2010) that found significantly reduced

mechanical thresholds, although is smaller than that seen in other studies (Fingleton et al., 2017). This suggests that while sample size may have been a factor in the lack of significant findings for PPT in the knee OA group, there may also be other differences between the studies leading to discrepancies in the findings, such as testing sites, resting pain levels, or participant characteristics.

The results for arm PPT showed no differences between groups. Again, previous studies testing PPT at remote anatomical sites have consistently found lowered thresholds in people with knee OA (Suokas et al., 2012; Fingleton et al., 2015), suggestive of widespread sensitisation in central nociceptive pathways and/or impaired descending inhibition of spinal nociceptive pathways.

Immediately following acute isometric exercise, a significant increase in knee PPT was evident in the control group. This result is congruent with previous research showing the presence of EIH in healthy, pain free populations by way of increased PPT following isometric exercise (Hoeger Bement et al., 2008; Koltyn and Umeda, 2007; Kosek and Lundberg, 2003; Naugle et al., 2014; Umeda et al., 2010; Vaegter et al., 2014). In contrast, people with knee OA and FM showed a more variable response in our study, with an absence of EIH via lack of significant increase in knee PPT immediately following acute isometric exercise. The hypoalgesic effect of exercise occurs at peripheral, spinal, and supraspinal levels of the nociceptive system (Koltyn, 2000; Rice et al., 2019) and can be the net result of increased activity in descending pain modulating pathways facilitated by the baroreflex system, endogenous opioids, cannabinoids, serotonin, and/or noradrenaline (Koltyn, 2000; Umeda et al., 2010; Rice et al., 2019; Tour et al., 2017).

Impairment of EIH has previously been shown in people with chronic pain (Wewege and Jones, 2021; Nijs et al., 2012), including knee OA (Fingleton et al., 2017; Burrows et al., 2014) and FM (Staud, 2005; Kosek et al., 1996; Lannersten and Kosek, 2010), but this is not always consistent (Kosek et al., 2013; Neelapala, 2018; Fingleton et al., 2017). Impaired EIH has also previously been shown at sites distal to the contracted muscle in people with chronic pain (Staud, 2005; Lannersten and Kosek, 2010; Kadetoff and Kosek, 2007). However, no statistically significant differences in arm PPT were found among the groups in the current study. This suggests that only a local EIH effect was observed, which is supported by previous research reporting remote EIH to be either absent, or smaller in magnitude, compared to local EIH in healthy people (Gajsar, 2016; Vaegter et al., 2019) and people with knee OA (Hansen et al., 2020). Correlations between the extent of EIH at the knee and vagal withdrawal during exercise revealed a lack of relationship between these variables in any of the groups. While we were therefore not able to provide evidence of a direct association between ANS dysfunction and reduced EIH, it is possible that an indirect or non-linear relationship exists or that more participants with varied EIH are required to reveal a relationship.

Strengths and limitations

The strengths of this study include the range of validated outcome measures collected in a controlled laboratory environment; however, there were also some limitations. While MVC values were different between groups, the relative intensity of exercise was standardised and Borg ratings of perceived exertion were no different between groups during both testing sessions. This suggests the chosen intensity and duration of exercise provided a comparable level of controlled, tolerable muscle activation for all groups. Related to this, exercise-associated pain in the knee OA and FM groups may have additionally impacted the ANS response to isometric contraction but was not measured in the current study. COVID-19 restrictions led to the sample size being smaller than intended, with the study potentially being underpowered to detect some differences between groups and/or over time, as well as associations between ANS measures and EIH.

Conclusions

The findings indicated impaired resting vagal function and reduced vagal reactivity to exercise stress in people with knee OA. Due to the many interconnections of the autonomic and nociceptive systems, this dysfunction may contribute to impaired descending inhibition of the nociceptive system and ongoing pain in this population. Mechanisms to support parasympathetic function should be investigated in people with knee OA to determine the effect on the nociceptive system (Van Den Houte et al., 2018).

CRedit authorship contribution statement

Neil R. Bossenger: Conceptualization, Methodology, Investigation. **Gwyn N. Lewis:** Conceptualization, Methodology, Supervision. **David A. Rice:** Conceptualization, Methodology, Resources, Supervision. **Daniel Shepherd:** Conceptualization, Methodology, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Adeyemi, E.O.A., Desai, K.D., Towsey, M., Ghista, D., 1999. Characterization of autonomic dysfunction in patients with irritable bowel syndrome by means of heart rate variability studies. *Am. J. Gastroenterol.* 94 (3), 816–823.

Adlan, A.M., Lip, G.Y.H., Paton, J.F.R., Kitas, G.D., Fisher, J.P., 2014. Autonomic function and rheumatoid arthritis – A systematic review. *Semin. Arthritis Rheum.* 44 (3), 283–304.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., Christy, W., Cooke, T. D., Greenwald, R., Hochberg, M., Howell, D., Kaplan, D., Koopman, W., Longley, S., Mankin, H., McShane, D.J., Medsger, T., Meenan, R., Mikkelsen, W., Moskowitz, R., Murphy, W., Rothschild, B., Segal, M., Sokoloff, L., Wolfe, F., 1986. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American rheumatism association. *Arthritis Rheum.* 29 (8), 1039–1049.

Appelhans, B.M., Luecken, L.J., 2006. Heart rate variability as an index of regulated emotional responding. *Rev. Gen. Psych.* 10 (3), 229–240. <https://doi.org/10.1037/1089-2680.10.3.229>.

Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., Graven-Nielsen, T., 2010. Sensitization in patients with painful knee osteoarthritis. *Pain.* 149 (3), 573–581.

Barakat, A., et al., 2012. Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain. *Arthritis Care Res.* 64 (8), 1209–1216. <https://doi.org/10.1002/acr.21669>.

Berenbaum, F., Meng, Q.J., 2016. The brain-joint axis in osteoarthritis: nerves, circadian clocks and beyond. *Nat. Rev. Rheumatol.* 12 (9), 508–516. <https://doi.org/10.1038/nrrheum.2016.93>.

Blumenstiel, K., Gerhardt, A., Rolke, R., Bieber, C., Tesarz, J., Friederich, H.-C., Eich, W., Treede, R.-D., 2011. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clin. J. Pain.* 27 (8), 682–690.

Borg, G., 1970. Perceived exertion as an indicator of somatic stress. *Scand. J. Rehabil. Med.* 2 (2), 92–98.

Boutcher, S.H., Stocker, D., 1999. Cardiovascular responses to light isometric and aerobic exercise in 21- and 59-year-old males. *Eur. J. Appl. Physiol.* 80 (3), 220–226. <https://doi.org/10.1007/s004210050585>.

Braithwaite, J.J., et al., 2013. A guide for Analysing Electrodermal Activity (EDA) & Skin Conductance Responses (SCRs) for Psychological Experiments. University of Birmingham.

Burgess, H.J., Penev, P.D., Schneider, R., Van Cauter, E., 2004. Estimating cardiac autonomic activity during sleep: impedance cardiography, spectral analysis, and Poincaré plots. *Clin. Neurophysiol.* 115 (1), 19–28.

Burrows, N.J., Booth, J., Sturmiels, D.L., Barry, B.K., 2014. Acute resistance exercise and pressure pain sensitivity in knee osteoarthritis: a randomised crossover trial. *Osteoarthritis Cartilage.* 22 (3), 407–414.

Chalaye, P., Goffaux, P., Bourgault, P., Lafrenaye, S., Devroede, G., Watier, A., Marchand, S., 2012. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. *Clin. J. Pain.* 28 (6), 519–526.

Chalaye, P., Lafrenaye, S., Goffaux, P., Marchand, S., 2014. The role of cardiovascular activity in fibromyalgia and conditioned pain modulation. *Pain* 155 (6), 1064–1069.

Chirife, R., 1988. Physiological principles of a new method for rate responsive pacing using the pre-ejection interval. *Pacing Clin. Electrophysiol.* 11 (11 Pt 1), 1545–1554. <https://doi.org/10.1111/j.1540-8159.1988.tb06272.x>.

Cohen, H., et al., 2001. Autonomic nervous system derangement in fibromyalgia syndrome and related disorders. *Isr. Med. Assoc. J.* 3 (10), 755–760.

Cohen, H., Neumann, L., Shore, M., Amir, M., Cassuto, Y., Buskila, D., 2000. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Semin. Arthritis Rheum.* 29 (4), 217–227.

Courties, A., Sellam, J., Berenbaum, F., 2017. Role of the autonomic nervous system in osteoarthritis. *Best Pract. Res. Clin. Rheumatol.* 31 (5), 661–675.

Crandall, C.G., Musick, J., Hatch, J.P., Kellogg, D.L., Johnson, J.M., 1995. Cutaneous vascular and sudomotor responses to isometric exercise in humans. *J. Appl. Physiol.* 79 (6), 1946–1950.

Drummond, P.D., Finch, P.M., Skipworth, S., Blockey, P., 2001. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. *Neurology* 57 (7), 1296–1303.

Drummond, P.D., Willox, M., 2013. Painful effects of auditory startle, forehead cooling and psychosocial stress in patients with fibromyalgia or rheumatoid arthritis. *J. Psychosom. Res.* 74 (5), 378–383. <https://doi.org/10.1016/j.jpsychores.2013.01.011>.

Elam, M., Johansson, G., Wallin, G.B., 1992. Do patients with primary fibromyalgia have an altered muscle sympathetic nerve activity? *Pain* 48 (3), 371–375.

Fingleton, C., Smart, K., Moloney, N., Fullen, B.M., Doody, C., 2015. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 23 (7), 1043–1056.

Fingleton, C., Smart, K.M., Doody, C.M., 2017. Exercise-induced hypoalgesia in people with knee osteoarthritis with normal and abnormal conditioned pain modulation. *Clin. J. Pain.* 33 (5), 395–404.

Furlan, R., et al., 2005. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *J. Rheumatol.* 32 (9), 1787–1793.

Gajjar, H., et al., 2016. Isometric back exercise has different effect on pressure pain thresholds in healthy men and women. *Pain Med.* 18 (5), 917–923. <https://doi.org/10.1093/pm/pnw176>.

Hallman, D.M., Lindberg, L.-G., Arnetz, B.B., Lyskov, E., 2011. Effects of static contraction and cold stimulation on cardiovascular autonomic indices, trapezius blood flow and muscle activity in chronic neck-shoulder pain. *Eur. J. Appl. Physiol.* 111 (8), 1725–1735.

Hallman, D.M., Srinivasan, D., Mathiassen, S.E., 2015. Short- and long-term reliability of heart rate variability indices during repetitive low-force work. *Eur. J. Appl. Physiol.* 115 (4), 803–812.

Hansen, S., Vaegter, H.B., Petersen, K.K., 2020. Pretreatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis. *Clin. J. Pain.* 36 (1), 16–24.

Hilgenberg-Sydney, P.B., Kowacs, P.A., Conti, P.C.R., 2016. Somatosensory evaluation in dysfunctional syndrome patients. *J. Oral Rehabil.* 43 (2), 89–95.

Hoeger Bement, M.K., Dicapo, J., Rasiarmos, R., Hunter, S.K., 2008. Dose response of isometric contractions on pain perception in healthy adults. *Med. Sci. Sports Exerc.* 40 (11), 1880–1889.

Hohenschurz-Schmidt, D.J., Calcagnini, G., Dipasquale, O., Jackson, J.B., Medina, S., O'Daly, O., O'Muircheartaigh, J., de Lara Rubio, A., Williams, S.C.R., McMahon, S. B., Makovac, E., Howard, M.A., 2020. Linking pain sensation to the autonomic nervous system: the role of the anterior cingulate and periaqueductal gray resting-state networks. *Front. Neurosci.* 14 <https://doi.org/10.3389/fnins.2020.00147>.

Hunter, D.J., Schofield, D., Callander, E., 2014. The individual and socioeconomic impact of osteoarthritis. *Nat. Rev. Rheumatol.* 10 (7), 437–441.

Kadottoff, D., Kosek, E., 2007. The effects of static muscular contraction on blood pressure, heart rate, pain ratings and pressure pain thresholds in healthy individuals and patients with fibromyalgia. *Eur. J. Pain.* 11 (1), 39–47. <https://doi.org/10.1016/j.ejpain.2005.12.013>.

Karling, P., et al., 1998. Spectral analysis of heart rate variability in patients with irritable bowel syndrome. *Scand. J. Gastroenterol.* 33 (6), 572–576. <https://doi.org/10.1080/00365529850171800>.

King, C.D., Sibille, K.T., Goodin, B.R., Cruz-Almeida, Y., Glover, T.L., Bartley, E., Riley, J. L., Herbert, M.S., Sotolongo, A., Schmidt, J., Fessler, B.J., Redden, D.T., Staud, R., Bradley, L.A., Fillingim, R.B., 2013. Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. *Osteoarthritis Cartilage.* 21 (9), 1243–1252.

Kino, M., Lance, V.Q., Shahamatpour, A., Spodick, D.H., 1975. Effects of age on responses to isometric exercise. Isometric handgrip in noninvasive screening for cardiovascular disease. *Am. Heart J.* 90 (5), 575–581.

Koltyn, K.F., 2000. Analgesia following exercise: a review. *Sports Med.* 29 (2), 85–98. <https://doi.org/10.2165/00007256-200029020-00002>.

Koltyn, K.F., 2002. Exercise-induced hypoalgesia and intensity of exercise. *Sports Med.* 32 (8), 477–487. <https://doi.org/10.2165/00007256-200232080-00001>.

Koltyn, K.F., Umeda, M., 2007. Contralateral attenuation of pain after short-duration submaximal isometric exercise. *J. Pain* 8 (11), 887–892. <https://doi.org/10.1016/j.jpain.2007.06.003>.

Kosek, E., Lundberg, L., 2003. Segmental and plurisegmental modulation of pressure pain thresholds during static muscle contractions in healthy individuals. *Eur. J. Pain* 7 (3), 251–258. [https://doi.org/10.1016/s1090-3801\(02\)00124-6](https://doi.org/10.1016/s1090-3801(02)00124-6).

Kosek, E., Ekholm, J., Hansson, P., 1996. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain* 64 (3), 415–423.

Kosek, E., Roos, E.M., Ageberg, E., Nilsson, A., 2013. Increased pain sensitivity but normal function of exercise induced analgesia in hip and knee osteoarthritis—treatment effects of neuromuscular exercise and total joint replacement. *Osteoarthritis Cartilage.* 21 (9), 1299–1307.

- Laborde, S., Mosley, E., Mertgen, A., 2018. Vagal tank theory: The three Rs of cardiac vagal control functioning – resting, reactivity, and recovery. *Neurosci* 12.
- Lannersten, L., Kosek, E., 2010. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain* 151 (1), 77–86. <https://doi.org/10.1016/j.pain.2010.06.021>.
- Losina, E., Weinstein, A.M., Reichmann, W.M., Burbine, S.A., Solomon, D.H., Daigle, M. E., Rome, B.N., Chen, S.P., Hunter, D.J., Suter, L.G., Jordan, J.M., Katz, J.N., 2013. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res.* 65 (5), 703–711.
- Makovac, E., Venezia, A., Hohenschurz-Schmidt, D., Dipasquale, O., Jackson, J.B., Medina, S., O'Daly, O., Williams, S.G.R., McMahon, S.B., Howard, M.A., 2021. The association between pain-induced autonomic reactivity and descending pain control is mediated by the periaqueductal grey. *J. Physiol.* 599 (23), 5243–5260.
- Mandl, L., 2011. Treating the pain of osteoarthritis - where do we go from here? *J. Rheumatol.* 38 (8), 1535–1537. <https://doi.org/10.3899/jrheum.110671>.
- Martin, C.E., Shaver, J.A., Leon, D.F., Thompson, M.E., Reddy, P.S., Leonard, J.J., 1974. Autonomic mechanisms in hemodynamic responses to isometric exercise. *J. Clin. Invest.* 54 (1), 104–115.
- Martinez-Lavin, M., 2007. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res. Ther.* 9 (4), 216. <https://doi.org/10.1186/ar2146>.
- Naugle, K.M., Fillingim, R.B., Riley, J.L., 2012. A meta-analytic review of the hypoalgesic effects of exercise. *J. Pain* 13 (12), 1139–1150.
- Naugle, K.M., Naugle, K.E., Fillingim, R.B., Riley, J.L., 2014. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Med.* 15 (4), 692–701.
- Neelapala, Y.V.R., et al., 2018. Influence of isometric exercise on pressure pain sensitivity in knee osteoarthritis. *J. Pain Manage.* 11 (4), 361–367.
- Nishiyasu, T., Tan, N., Morimoto, K., Nishiyasu, M., Yamaguchi, Y., Murakami, N., 1994. Enhancement of parasympathetic cardiac activity during activation of muscle metaboreflex in humans. *J. Appl. Physiol.* 77 (6), 2778–2783.
- Pollatos, O., Dietel, A., Herbert, B.M., Wankner, S., Wachsmuth, C., Henningsen, P., Sack, M., 2011. Blunted autonomic reactivity and increased pain tolerance in somatoform patients. *Pain* 152 (9), 2157–2164.
- Ray, C.A., Wilson, T.E., 2004. Comparison of skin sympathetic nerve responses to isometric arm and leg exercise. *J. Appl. Physiol.* 97 (1), 160–164. <https://doi.org/10.1152/jappphysiol.00699.2003>.
- Reyes del Paso, G.A., Garrido, S., Pulgar, Á., Martín-Vázquez, M., Duschek, S., 2010. Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosom. Med.* 72 (5), 462–470.
- Reyes del Paso, G.A., Garrido, S., Pulgar, Á., Duschek, S., 2011. Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *J. Psychosom. Res.* 70 (2), 125–134.
- Rice, D., Nijs, J., Kosek, E., Wideman, T., Hasenbring, M.L., Koltyn, K., Graven-Nielsen, T., Polli, A., 2019. Exercise-induced hypoalgesia in pain-free and chronic pain populations: State of the art and future directions. *J. Pain* 20 (11), 1249–1266.
- Saito, M., Naito, M., Mano, T., 1990. Different responses in skin and muscle sympathetic nerve activity to static muscle contraction. *J. Appl. Physiol.* 69 (6), 2085–2090.
- Schestsatsky, P., Valls-Solé, J., Felix-Torres, V., Guarany, F.C., Castellote, J.M., Pérez, D., Costa, J., 2009. Sympathetic skin responses evoked by muscle contraction. *Neurosci. Lett.* 463 (2), 140–144.
- Seals, D.R., 1993. Influence of force on muscle and skin sympathetic nerve activity during sustained isometric contractions in humans. *J. Physiol.* 462 (1), 147–159.
- Staud, R., et al., 2005. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain* 118 (1), 176–184. <https://doi.org/10.1016/j.pain.2005.08.007>.
- Suokas, A.K., Walsh, D.A., McWilliams, D.F., Condon, L., Moreton, B., Wylde, V., Arendt-Nielsen, L., Zhang, W., 2012. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 20 (10), 1075–1085.
- Taylor, J.A., Hayano, J., Seals, D.R., 1995. Lesser vagal withdrawal during isometric exercise with age. *J. Appl. Physiol.* 79 (3), 805–811.
- Terkelsen, A.J., Andersen, O.K., Molgaard, H., Hansen, J., Jensen, T.S., 2004. Mental stress inhibits pain perception and heart rate variability but not a nociceptive withdrawal reflex. *Acta Physiol. Scand.* 180 (4), 405–414.
- Terkelsen, A., Molgaard, H., Hansen, J., Finnerup, N., Krøner, K., Jensen, T., 2012. Heart rate variability in complex regional pain syndrome during rest and mental and orthostatic stress. *Anesthesiology* 116 (1), 133–146.
- Thayer, J.F., Brosschot, J.F., 2005. Psychosomatics and psychopathology: looking up and down from the brain. *Psychoneuroendocrinology* 30 (10), 1050–1058. <https://doi.org/10.1016/j.psyneuen.2005.04.014>.
- Thieme, K., Rose, U., Pinkpank, T., Spies, C., Turk, D.C., Flor, H., 2006. Psychophysiological responses in patients with fibromyalgia syndrome. *J. Psychosom. Res.* 61 (5), 671–679.
- Tonhajzerova, I., Mestanik, M., Mestanikova, A., Jurko, A., 2016. Respiratory sinus arrhythmia as a non-invasive index of 'brain-heart' interaction in stress. *Indian J. Med. Res.* 144 (6), 815.
- Tour, J., Löfgren, M., Mannerkorpi, K., Gerdle, B., Larsson, A., Palstam, A., Bileviciute-Ljungar, I., Bjersing, J., Martin, I., Ernberg, M., Schalling, M., Kosek, E., 2017. Gene-to-gene interactions regulate endogenous pain modulation in fibromyalgia patients and healthy controls-antagonistic effects between opioid and serotonin-related genes. *Pain* 158 (7), 1194–1203.
- Tracy, L.M., Ioannou, L., Baker, K.S., Gibson, S.J., Georgiou-Karistianis, N., Giummarra, M.J., 2016. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *Pain* 157 (1), 7–29.
- Treister, R., Kliger, M., Zuckerman, G., Aryeh, I.G., Eisenberg, E., 2012. Differentiating between heat pain intensities: the combined effect of multiple autonomic parameters. *Pain* 153 (9), 1807–1814.
- Umeda, M., Newcomb, L.W., Ellingson, L.D., Koltyn, K.F., 2010. Examination of the dose-response relationship between pain perception and blood pressure elevations induced by isometric exercise in men and women. *Biol. Psychol.* 85 (1), 90–96.
- Vaegter, H.B., Handberg, G., Graven-Nielsen, T., 2014. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain* 155 (1), 158–167.
- Vaegter, H.B., Lyng, K.D., Yttereng, F.W., Christensen, M.H., Sørensen, M.B., Graven-Nielsen, T., 2019. Exercise-induced hypoalgesia after isometric wall squat exercise: a test-retest reliability study. *Pain Med.* 20 (1), 129–137.
- Van Den Houte, M., Van Oudenhove, L., Bogaerts, K., Van Diest, I., Van den Bergh, O., 2018. Endogenous pain modulation: Association with resting heart rate variability and negative affectivity. *Pain Med.* 19 (8), 1587–1596.
- Vissing, S.F., Scherrer, U., Victor, R.G., 1991. Stimulation of skin sympathetic nerve discharge by central command. Differential control of sympathetic outflow to skin and skeletal muscle during static exercise. *Circ. Res.* 69 (1), 228–238.
- Wewege, M.A., Jones, M.D., 2021. Exercise-induced hypoalgesia in healthy individuals and people with chronic musculoskeletal pain: a systematic review and meta-analysis. *J. Pain* 22 (1), 21–31. <https://doi.org/10.1016/j.jpain.2020.04.003>.
- Wolfe, F., Clauw, D.J., Fitzcharles, M.-A., Goldenberg, D.L., Häuser, W., Katz, R.L., Mease, P.J., Russell, A.S., Russell, I.J., Walitt, B., 2016. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin. Arthritis Rheum.* 46 (3), 319–329.
- Xie, L., Liu, B., Wang, X., Mei, M., Li, M., Yu, X., Zhang, J., 2017. Effects of different stresses on cardiac autonomic control and cardiovascular coupling. *J. Appl. Physiol.* 122 (3), 435–445.
- Yeater, T.D., Cruz, C.J., Cruz-Almeida, Y., Allen, K.D., 2022. Autonomic nervous system dysregulation and osteoarthritis pain: Mechanisms, measurement, and future outlook. *Curr. Rheumatol. Rep.* 24 (6), 175–183.
- Yun, A.J., Lee, P.Y., Doux, J., 2006. Osteoarthritis: an example of phenoptosis through autonomic dysfunction? *Med. Hypotheses.* 67 (5), 1079–1085.
- Nijs, J., Kosek, E., Van Oosterwijk, J., Meus, M., 2012. Dysfunctional endogenous analgesia during exercise in patients with chronic pain: to exercise or not to exercise? *Pain Physician.* 35;15 (3S;7), ES205-ES213.