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ORIGINAL RESEARCH

Factors Associated with Low Inter-Session Reliability of Conditioned Pain Modulation in Older People with or Without Chronic Musculoskeletal Pain

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Purpose: Conditioned pain modulation (CPM) is a measurement of the descending pain pathways that inhibit or facilitate afferent noxious stimuli. The reliability of CPM in older individuals with or without chronic musculoskeletal pain has not been sufficiently reported. This study aimed to examine the inter-session reliability of CPM in these cohorts and the factors in CPM reliability.

Patients and Methods: Individuals aged 65 or older were recruited in Narita, Japan. The measurements were performed on separate days 2 weeks apart (sessions 1 and 2). Each participant's hand was immersed in cold water, and we measured pressure pain threshold (PPT) before and after the immersion. The ratio before and after PPT measurements was presented as CPM index. The autonomic activities (heart rate variability, heart rate, and blood pressure) were simultaneously measured. An absolute reliability of CPM index was analyzed by the adjusted two-way analysis of variance (ANOVA) and the Bland Altman plot, and relative reliability was analyzed by intraclass correlation coefficient (ICC). Spearman's rho correlation and the adjusted multivariate regression analysis were utilized for examining the CPM reliability factors.

Results: Thirty-two participants were divided into two groups: chronic pain (n=19) and non-chronic pain (n=13) groups. The mean difference between session 1 and 2 in CPM index showed a systematic error in the chronic pain group at 17.3 (confidence interval, CI: 15.0 to 19.7), but none in the non-chronic pain group at 3.7 (CI: −0.02 to 7.4). The adjusted two-way ANOVA for CPM index did not identify any differences. ICC was not significant at p=−0.247 in the non-chronic and 0.167 in chronic pain. Multivariate regression analysis revealed total power and low/high frequencies as significant factors for CPM index.

Conclusion: This study identified low inter-session reliability in older adults with chronic musculoskeletal pain and autonomic nervous system activities as factors in CPM reliability.

Keywords: inter-session reliability, conditioned pain modulation, older people, autonomic nervous system, chronic musculoskeletal pain

Plain Language Summary

One cause for chronic musculoskeletal pain is a dysfunction in the central pain modulatory system, which can weaken painful stimuli. Conditioned pain modulation (CPM) is a measurement for this system and is important when identifying the cause of chronic pain for physicians or therapists. However, in some people, especially older individuals or patients with chronic musculoskeletal pain, the CPM shows different results when measured twice on different days. As this low reliability of CPM leads to a misunderstanding of the cause of chronic pain, and subsequently, inappropriate treatment, this study investigated the reliability of CPM in older individuals with or without chronic musculoskeletal pain and the factors in its reliability or lack thereof. We hypothesized that this cohort showed low

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reliability of CPM due to specific activities of the autonomic nervous system. In this study, we measured CPM twice 2 weeks apart, and the results indicated that this hypothesis was correct. We identified low reliability of CPM and greater activities of the autonomic nervous system, especially those of the sympathetic nervous system, were a possible factor in low reliability of CPM. As several neurons of the central pain modulatory system located in medulla oblongata have another role in controlling autonomic organs such as the heart or lungs, this study could obtain these results. Our results are useful for physicians and therapists when they interpret the consequences of CPM in older individuals with or without chronic musculoskeletal pain, leading them to decide on a more appropriate treatment.

Introduction

Conditioned pain modulation (CPM) is a psychophysical test that evaluates the descending pain pathways that inhibit or facilitate the degree of afferent noxious stimuli.[1] It reflects a model of "pain inhibits pain" and utilizes a noxious conditioning stimulus to affect another painful test stimulus, normally resulting in a decrease in pain sensitivity following conditioning stimulus.[2] Some patients with chronic pain, such as fibromyalgia or chronic fatigue syndrome, show increased pain sensitivity after applying the conditioning stimulus due to a dysfunction of the descending pain pathways.[3] Increased pain sensitivity may coexist with other cohorts, such as osteoarthritis,[4] chronic low back pain,[5] and patients with postoperative pain.[6] As dysfunction of the descending pain pathways and the subsequent abnormal pain sensitivity may cause pain chronification,[7] CPM is a necessary tool to discriminate the origin of pain and alleviate pain.

The reliability of CPM has been well researched and is reported to have good test–retest reliability. A recent systematic review and meta-analysis[8] revealed that intra-session reliability, indicating that the first and second tests were performed on the same day, was good at intraclass correlation coefficient (ICC)=0.64 (95% confidence interval, CI:0.45–0.77) in healthy individuals. In contrast, another systematic review[9] reported that inter-session reliability, which refers to tests repeated on separate days, showed inconsistent results due to several specific factors, such as age, hormones, and disease conditions. Although the inter-session reliability of CPM ranged from fair to excellent,[9] poor ICC was found in older individuals with chronic pancreatitis[10] and young females across menstrual cycles.[11] ICC for CPM in individuals with breast cancer had weak reliability.[12] Similarly, CPM in older individuals showed low inter-session reliability with no significant ICC at −0.19 (−1.31 to 0.39).[13] Thus, several specific factors reduce the inter-session reliability of CPM efficiency.

Prior studies have investigated the specific factors influencing CPM efficiency, such as age,[13] sex and hormone cycles,[14,15] and psychological aspects such as depression,[16] catastrophization[17] and anxiety.[18] The autonomic nervous system is a possible factor that affects CPM efficiency, although this factor has not been sufficiently researched and clarified.[1,19] The autonomic nervous system potentially controls the descending pain modulatory systems.[20] These systems are regulated by several neurons, such as the periaqueductal grey, rostral ventromedial medulla, hypothalamus, and amygdala, which secrete aminergic neurotransmitters to ascending pain pathways and modulate pain perception.[20,21] Functional magnetic resonance imaging showed that the periaqueductal grey and rostral ventromedial medulla were activated in CPM measurements.[22] These neurons have other functions such as acting as autonomous centers to control cardiovascular, respiratory, and gastrointestinal systems.[23] Therefore, patients with chronic pain and dysfunctional descending pain pathways tend to have autonomic disorders,[20] that is, CPM is potentially affected by the autonomic nervous system.

This study aimed to reveal 1) the inter-session reliability of CPM in a cohort of older individuals with or without chronic musculoskeletal pain and 2) factors in the inter-session reliability. This cohort was selected for two reasons. First, to the best of our knowledge, the inter-session reliability of CPM in older individuals with chronic musculoskeletal pain has not been examined. Second, this population tends to have autonomic dysfunction due to age[24] and painful conditions.[25] Although the reliability of CPM is affected by age and/or pain, the autonomic nervous system may be a more essential and mediating factor. This study hypothesized that low inter-session reliability of CPM in older adults with chronic musculoskeletal pain was explained by a factor of the autonomic nervous system.

Materials and Methods

Participants

The participants were community-dwelling older adults residing in Narita, Chiba, Japan. Thirty-six participants were recruited via advertisements at a job placement and community support center in Narita between August 2021 and February 2022. Individuals satisfying the following criteria were included (1) age ≥65 years and (2) consented to participate in the study. The exclusion criteria were as follows: 1) cancer, facial and visceral pain, and headache; 2) autonomic nervous, endocrine, immune, and cognitive system issues; 3) severe sleep disorder; and 4) alcohol and tobacco overdose. Furthermore, the participants refrained from excessive exercise, drinking alcohol and caffeinated beverages, and smoking a day before and on the test day to reduce the influence on the autonomic nervous system measurements. Breakfast before 7 a.m. on the test day was allowed.

G*power 3.1.9.7 was utilized for power analysis with alpha at 0.05 and power set at 0.8. It indicated a sample size of 40 for detection of between session differences (effect size f = 0.4, large) and 16 for within/between interaction (f = 0.4, large) in a mixed-model analysis of variance (ANOVA).[26] Spearman's rho correlations required a sample size of 26 with f = 0.5 (large),[26] and the reliability study required at least a sample size of 30.[27] Finally, a multivariate regression analysis required a sample size of 31 with f = 0.35 (large).[26] In this study, a sample size of 30 participants was deemed appropriate as the estimated sample size varied because smaller sample size may lead to false negatives, inversely, a larger sample size may lead to false positives.[28,29]

The participants were divided into two groups: individuals with chronic musculoskeletal pain (chronic pain group) and those without (non-chronic pain group). Chronic musculoskeletal pain was defined as pain persisting for 3 months in the following body parts: neck, back, shoulder, elbow, wrist, hand, hip, knee, ankle, and foot.[30]

Protocols

This study was approved by the institutional review board of the International University of Health and Welfare (21-Im -025-2), and this study complies with the Declaration of Helsinki. The protocol was registered with the University Hospital Medical Information Network (UMIN000044507). During the orientation session, participants were screened according to the eligibility criteria and provided instructions regarding this research. A consent form was signed if the participants agreed to participate. Participants were invited to the university to measure CPM and any other measures on different days of the orientation session. All participants were screened for COVID-19 symptoms and signs, and no cases were confirmed. Measurements of CPM were obtained twice, 13–15 days apart (measurement sessions 1 and 2). In both measurement sessions, autonomic nervous system activity [heart rate variability (HRV), heart rate (HR), and blood pressure (BP)] was measured during CPM. To minimize the influence of circadian rhythms on these measurements, the experiment was conducted from 9 a.m. to noon. The room was kept at 22–24° C and was as silent as possible.

Conditioned Pain Modulation

CPM indicates the central process of descending pain pathways, which have inhibitory and facilitatory effects.[1] Although many protocols for assessing CPM exist, two stimuli were basically utilized: conditioning and test stimuli.[2,31] Painful conditioning stimulus is typically cold or hot water immersion or thermal contact-heat to activate the descending pain pathways and affect the following test stimulus such as pressure or thermal stimuli.[32] In healthy individuals, the pressure pain threshold (PPT) after cold water immersion is higher than the threshold before immersion as they have a normal descending pain inhibition system.[33] Conversely, in individuals with a dysfunctional system, the pressure pain threshold decreases after cold water immersion, increasing the pain sensitivity.[34]

The CPM procedure used in this study was based on the procedure used in prior research.[13] The participants were seated in a relaxed position, and their left arm was placed on a table. They remained seated for 10 min as a rest period to establish a baseline. Subsequently, PPT on the ventral side of the forearm was measured using Wagner FPX-25 (Wagner Instruments, Greenwich, CT).[35] The conditioning stimulus consisted of three 45-s cold water immersion sessions on the right hand with three 15-s interval periods.[13] The cold water was maintained at an average of 10°C. The CPM result was present as the CPM index (%) calculated by the following formula: (post-PPT/pre-PPT)×100.[14] CPM index >100%

indicates normal descending pain pathways and <100 indicates abnormal pain pathways.[13] All CPM procedures were performed by two assessors, and the same participant was assessed by the same assessor in both sessions.

CPM was conducted by well-trained assessors. Pre-examination was performed to calculate the inter-session reliability of CPM at a two-week interval in 12 healthy young individuals (20.3±1.07 years old, six females). The ICCs of the two assessors were 0.92 and 0.82, classified as excellent.[14]

Autonomic Nervous System

HRV is a non-invasive measurement that assesses the autonomic modulation of the cardiac sinus node, describing the fluctuations between continuous electrocardiogram R-R intervals.[36] Electrocardiogram was recorded by wearable WHS-1 (Union Tool Co. Ltd., Tokyo, Japan) attached on the left side of the participants' chest while measuring CPM. The data of the R-R intervals were analyzed by RRI Analyzer2 (Union Tool Co. Ltd., Tokyo, Japan) using frequency- and time-domain indices.[37] The frequency-domain indices estimate the absolute or relative power distributed into low and high frequencies (LF and HF, respectively), and the time-domain indices estimate the amount of variability in the measurements of the beat-to-beat interval, which is the time span between successive heartbeats.[37] HF was calculated as normalized units using the following formula: $HF/(HF+LF)$ and present as HFnu.[31] The indices of HRV are summarized in Supplementary Table 1.

The heart rate (HR) and systolic and diastolic blood pressures (SBP and DBP, respectively) were measured after the rest and cold-water immersion periods using a digital sphygmomanometer (Kenzmedico Co. Ltd., Saitama, Japan).

Possible Factors Influencing the CPM Index

In session 1, the participant characteristics and all questionnaires were self-reported. The following participant characteristics were recorded: age, gender, marital and educational status, experience of orthopedic surgery, and medications. The level of care needed was assessed in accordance with a Japanese eight-point classification system rated as independent, level one and two support required, and level one to five care required.[38] A history of the following diseases was assessed: neurological and cardiovascular diseases, hypertension, diabetes, depression, and dementia. Several questionnaires were administered to assess the possible clinical, psychological, behavioral, and cognitive factors associated with the test–retest reliability of CPM.

The Central Sensitization Inventory is a questionnaire used to assess central sensitization, which refers to pain hypersensitivity due to an amplification of neural signaling in the central nervous system.[39] The PainDETECT questionnaire detects the neuropathic pain components, and higher scores indicate higher neuropathic pain.[40] The Pain Catastrophizing Scale evaluates pain catastrophizing defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience", and higher scores indicate greater catastrophizing.[41] The Geriatric Depression Scale is a screening tool for depressive symptoms with 15 items, and higher scores indicate a greater likelihood of depression.[42] The International Physical Activity Questionnaire assesses the physical activity. The subjects recall the duration of physical activity in the last 7 days, and the Japanese version was validated.[43] Vigorous and moderate physical activity and walking are calculated as time × days × each metabolic equivalents level (METs, vigorous, 8.0 METs; moderate, 4.0 METs; walking, 3.3 METs).[44] The Mini-Mental State Examination consists of 11 questions to assess five cognitive aspects: orientation, registration, attention, calculation, and recall and language.[45] The total score is 30, and a score of 23 or less indicates cognitive problems.[45]

Blood samples from each subject were drawn to measure the interleukin 6 (IL-6) levels, which indicates inflammation.[46] Body compositions were measured through a validated bioelectrical impedance analyzer using InBody 570 (InBody Japan Inc., Tokyo, Japan).[47] The participants were instructed to stand with bear feet and grip the handles of the analyzer. The outcome measures were the total fat percentage and total muscle percentage.

Statistical Analyses

Descriptive Statistics

Analyses were conducted using SPSS, 27.0 for Windows (SPSS INC, Chicago, IL, USA) and GraphPad Prism9 software (GraphPad Software Inc., San Diego, CA, USA). Means and standard deviations were estimated for all outcome

measures. The Shapiro–Wilk's test for normality was performed for all outcome variables and deemed to be significant at a threshold of $p > 0.05$. Independent samples *t*-test, Mann–Whitney *U*-test, and Chi-square analyses were used to compare the anthropometric and pain characteristics, comorbidity, medications, and the results of questionnaires between the non-chronic and chronic pain groups, depending on normality and scale (categorical data or not). The Mann–Whitney *U*-test was performed for age, pain intensity, IL-6, Pain Catastrophizing Scale, Geriatric Depression Scale, Mini-Mental State Examination, and International Physical Activity Questionnaire. Chi-square analyses were conducted for sex, experience of orthopedic surgery, level of support needed, comorbidities, and medications. Other variables were analyzed using an independent samples *t*-test. The CPM index, PPT, and autonomic variables (HR, BP, and HRV) were analyzed using a two (pain group: non-chronic and chronic) × two (session: 1 and 2) analysis of variance (ANOVA) and post-hoc analysis (Tukey's test) to examine the main effect on group, session, and group×session interaction. The two-way ANOVA was adjusted by sex because of a group imbalance in the number of participants' sex.

Test-Retest Reliability of CPM and Associated Factors

The test–retest reliability for CPM was evaluated as two dimensions of reliability: absolute and relative reliabilities, similar to prior studies.[13,14,48] First, a two-way ANOVA (group × session) to assess the difference in the CPM index was performed to examine the absolute reliability. This analysis was also adjusted for sex due to the same reason as previously stated. In this study, absolute reliability referred to the mean change in the CPM index between the sessions.[14] Additionally, the Bland–Altman analysis was performed to evaluate the absolute reliability.[12] The average and difference between the two measurement sessions in the CPM index were plotted in y and x axes, respectively, namely the Bland–Altman plots.[49,50] If the two sessions were in perfect agreement, the plots would be equal to the x-axis.[50] However, some degree of error occurs, and the Bland–Altman plots can visually describe whether systematic errors have occurred.[49,50] Means and standard deviations in the difference between the two sessions were calculated. Confidence intervals were also computed; if a value did not include zero, systematic error had occurred.[51] Statistical calculation was also performed to determine the limits of agreement (LoA) using the following formula: $HF/(HF + LF)$, where $HF/(HF + LF)$ denotes the means of the difference and s denotes the standard deviation.[50] The 95% CI of LoA, defined as the estimate of the size of the possible sampling error, was calculated using the following formula: $HF/(HF + LF)$ for lower limits and $HF/(HF + LF)$ for upper limits, where n denotes the participants' number.[50]

Second, we examined the relative reliability of CPM, which refers to the reliability of the CPM index of individuals relative to others.[52] In this study, Spearman's rho correlations and ICC were calculated in accordance with prior research.[13,14,48] Values of 0.00–0.40, 0.41–060, 0.61–0.80, and 0.81–1.00 were interpreted as poor, moderate, good, and excellent, respectively.[14] Additionally, the intra-individual reliability coefficients for CPM (ISC-CPM) were calculated.[13,14] CPM for both sessions was standardized across all subjects. ISC-CPM was calculated using the formula $HF/(HF + LF)$, where Z_1 and Z_2 represent standardized CPM scores across the subjects for sessions 1 and 2, respectively. A lower ISC-CPM indicates lower inter-session reliability, that is, a greater CPM change between the sessions.

Factors Associated to the Reliability of CPM

At first, Spearman's rho correlations were conducted for screening what variables should be included in the multivariate regression analysis. We performed this correlation analysis between ISC-CPM and the potential influencing factors in each of the following groups, non-chronic pain, chronic pain, and overall samples. The potential factors were age, pain intensity, IL-6, Central Sensitization Inventory, PainDETECT, Pain Catastrophizing Scale, International Physical Activity Questionnaire, Depression Scale, and total fat and muscle percentages. Autonomic variables (HR, SBP, DBP, LF/HF, HFnu, TP, RMSSD, SDNN, and pNN50) were also analyzed by Spearman's rho correlations in terms of the following five variables: rest period in session 1, cold period in session 1, rest period in session 2, cold period in session 2, and the difference from cold to rest periods between session 1 and 2.

After calculating Spearman's rho correlations, we used the forced entry selection method of multivariate regression analysis, with ISC-CPM as the dependent variable and the variables that were found to be significantly correlated as the independent variables. First, each of the significantly correlated variable was analyzed and described as the model

number and "A" (eg, Model 1A). If the model "A" was significant, sex was added to the model "A", describing the model number and "B" (eg, Model 1B) for adjusting sex differences between groups. All statistical tests were considered statistically significant at a threshold of $p < 0.05$.

Results

Descriptive Statistics

Thirty-six individuals participated in the two measurement sessions. Four participants were excluded from the analysis. One had been diagnosed with dysautonomia, one had consumed alcohol a day before the experiment, and HRV of the remaining two participants could not be recorded because of a malfunction of the laptop. Thirty-two participants were analyzed, ranging in age from 66 to 88 years in both groups (Figure 1). The IL-6 level of one participant in the chronic pain group was not calculated because of the difficulty in blood sampling, whereas all other variables were measured and analyzed. Although HRV of 10 participants was measured three times because of an electrocardiogram malfunction on the first day of the measurement, their HRVs were measured normally on different days. The anthropometric and pain characteristics, comorbidities, medications, and questionnaire results are presented in Table 1. Although most variables showed no group differences at baseline, several were statistically different between the groups; the non-chronic pain group consisted of four females and nine males, and the chronic pain group consisted of 13 females and six males (p=0.036). The total fat percentage in the chronic pain group was higher (34.1±7.5%) than that in the non-chronic pain group (28.1±5.8%, p=0.020). The total muscle percentage was lower in the chronic pain group (62.0±7.0%) than that in the non-chronic pain group (67.8±5.3%, p=0.018). Pain intensity and Pain Catastrophizing Scale scores were higher in the chronic pain group (3.9±1.2 and 24.2±9.9, respectively) than that in the non-chronic pain group (1.2±1.4 and 15.5±8.7; $p \leq 0.001$ and 0.005, respectively).

The results of the adjusted two-way ANOVA (group×session) and Tukey's test for the CPM index, PPT, and all autonomic variables are presented in Table 2. Significant main effects on group were identified at HR cold ($F_{1,60}$=4.67; p=0.035), HFnu rest ($F_{1,60}$=11.20; p<0.001), RMSSD rest ($F_{1,60}$=6.79; p=0.012), RMSSD cold ($F_{1,60}$=11.26; p<0.001), SDNN rest ($F_{1,60}$=6.24; p=0.015), SDNN cold ($F_{1,60}$=15.16; p<0.001), pNN50 rest ($F_{1,60}$=4.94; p=0.030), and pNN50 cold ($F_{1,60}$=6.77; p=0.012). Tukey's test revealed that significant group differences in session 1 at HFnu rest (p=0.009), RMSSD rest (p=0.031) and cold (p=0.018), SDNN rest (p=0.034) and cold (p=0.010) and pNN50 cold (p=0.021) and in session 2 for RMSSD cold (p=0.017) and SDNN cold (p=0.004). No main effect on session were identified. Group×session interaction was found on HFnu cold ($F_{1,60}$=5.91; p=0.018).

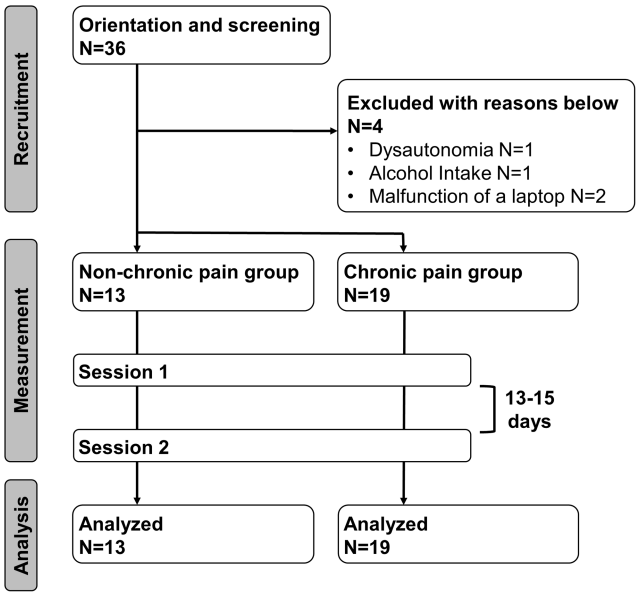

Figure 1 Flow chart of the study.

Table 1 Participant Characteristics in the Non-Chronic and Chronic Pain Groups

Variable (unit)	Non-Chronic Pain (n=13)	Chronic Pain (n=19)	P value
Anthropometric characteristics			
Age (years)	74.6±6.2	74.5±5.6	0.970
Gender (female number, %)	4(30.8)	13(68.4)	0.036*
BMI (kg/m2)	23.5±2.8	24.8±3.1	0.235
Total fat (%)	28.1±5.8	34.1±7.5	0.020*
Total muscle (%)	67.8±5.3	62.0±7.0	0.018*
Experience of orthopedic surgery (number experienced, %)	0(0.0)	2(10.5)	0.345
Level of care needed (number support required, %)	0(0.0)	1(5.3)	0.594
Pain characteristics			
Pain intensity (NRS)	1.2±1.4	3.9±1.2	<0.001*
IL-6 (pg/mL)	0.40±0.37	0.87±1.07	0.068
Central Sensitization Inventory	17.2±7.9	22.5±10.4	0.135
PainDETECT	6.3±5.1	10.0±5.5	0.065
Pain Catastrophizing Scale	15.5±8.7	24.2±9.9	0.005*
Comorbidity			
Neurological (number diagnosed, %)	0(0.0)	1(5.3)	0.594
Cardiovascular (number diagnosed, %)	3(23.1)	2(10.5)	0.47
Hypertension (number diagnosed, %)	7(46.2)	13(68.4)	0.208
Diabetes (number diagnosed, %)	2(15.4)	2(10.5)	0.542
Depression (number diagnosed, %)	0(0.0)	0(0.0)	-
Dementia (number diagnosed, %)	0(0.0)	0(0.0)	-
Medications			
Anxiolytic (number intaken, %)	0(0.0	1(5.3)	0.594
Antidepressants (number intaken, %)	0((0.0)	0(0.0)	-
Anticonvulsant (number intaken, %)	0((0.0)	0(0.0)	-
ACE inhibitors (number intaken, %)	4((30.8)	8(42.1)	0.393
Alpha-blocker (number intaken, %)	1((7.7)	0(0.0)	0.406
Beta-blocker (number intaken, %)	1((7.7)	0(0.0)	0.406
Calcium channel blocker (number intaken, %)	6((46.2)	8(42.1)	0.821
Muscle relaxant (number intaken, %)	1((7.7)	0(0.0)	0.406
Opioid (number intaken, %)	0((0.0)	0(0.0)	-
Other questionnaires			
Geriatric Depression Scale	4.0±(3.1)	4.2±2.6	0.596
Mini-Mental State Examination	26.9±(2.0)	27.7±2.2	0.270
International Physical Activity Questionnaire (Mets)	44.3±(36.1)	32.1±30.3	0.270

Notes: *P<0.05.
Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; IL-6, interleukin 6; NRS, numerical rating scale.

Inter-Session Reliability for CPM and Its Factors

Absolute and Relative Reliability of CPM

The CPM indices in sessions 1 and 2 were 124.7±26.7% and 128.4±23.1% in the non-chronic pain group and 110.1±19.9% and 127.4±19.2% in the chronic pain group, respectively. However, the adjusted two-way ANOVA (group×session) revealed no significant main effects on the groups ($F_{1,60}$=2.17; p=0.146) and sessions ($F_{1,60}$=3.52; p=0.066) and group×session interaction ($F_{1,60}$=1.48; p=0.228). The mean ($HF/(HF+LF)$) and standard deviation(s) of the difference in CPM index of the two sessions were 3.7 ($HF/(HF+LF)$) and 37.7 (s) in the non-chronic pain group and 17.3 ($HF/(HF+LF)$) and 23.4 (s) in the chronic pain group. CIs were −0.02 to 7.4 in the non-chronic pain group and 15.0 to 19.7 in the chronic pain group, indicating that a systematic error occurred in the chronic pain group. The lower and upper LoA (95% CI) were −70.3 (−109.8 to −30.8) and 77.7 (38.2 to 117.2) in the non-chronic pain group and −28.6 (−48.1 to −9.01) and 63.2 (43.7 to 82.8) in the chronic pain group, respectively, as shown in the Bland–Altman plots (Figure 2a and b).

Table 2 Means and Standard Deviations for CPM Index and Autonomic Variables

Variables	Main Tests								Tukey's Test	
	Mean Difference (95% CI) Between Session 1 and 2		Group		Session		Group*Session		Session 1	Session 2
	Non-Chronic Pain	Chronic Pain	F value	P value	F value	P value	F value	P value	P adj	P adj
CPM index (%)	−3.7(−26.5 to 19.1)	−17.3(−28.6 to -6.0)	2.169	0.146	3.518	0.660	1.482	0.228	-	-
PPT rest (kgf)	−0.1(−0.4 to 0.2)	0.2(−0.1 to 0.5)	0.863	0.357	0.072	0.789	0.399	0.530	-	-
PPT cold (kgf)	−0.2(−0.8 to 0.3)	−0.2(−0.5 to 0.2)	3.009	0.880	0.492	0.486	0.011	0.915	-	-
HR rest (bpm)	−1.7(−6.7 to 3.3)	1.1(−2.0 to 4.2)	2.057	0.157	0.018	0.892	0.419	0.520	-	-
HR cold (bpm)	0.6(−2.8 to 4.0)	0.9(−1.7 to 3.6)	4.669	0.035*	0.145	0.704	0.007	0.936	0.372	0.438
SBP rest (mmHg)	9.3(−2.6 to 21.2)	−1.6(−8.6 to 5.3)	3.473	0.067	0.981	0.326	1.992	0.163	-	-
SBP cold (mmHg)	16.0(4.2 to 27.8)	0.1(−7.1 to 7.4)	1.957	0.167	3.595	0.063	3.502	0.066	-	-
DBP rest (mmHg)	4.5(−3.2 to 12.3)	1.8(−2.5 to 6.0)	3.796	0.056	1.885	0.175	0.335	0.553	-	-
DBP cold (mmHg)	3.3(−2.3 to 8.9)	1.8(−2.4 to 6.0)	0.007	0.933	1.301	0.259	0.105	0.747	-	-
LF/HF rest (%)	−2.0(−7.0 to 2.9)	−0.5(−4.6 to 3.6)	0.220	0.641	0.731	0.396	0.296	0.588	-	-
LF/HF cold (%)	−1.7(−4.5 to 1.2)	0.5(−0.2to1.2)	0.003	0.954	1.040	0.312	3.738	0.058	-	-
HFnu rest (%)	9.6(−6.0 to 25.2)	−1.4(−13.3 to 10.3)	11.198	<0.001*	0.643	0.426	1.199	0.278	0.009*	0.322
HFnu cold (%)	9.8(−10.0 to 29.6)	−12.0(−21.3 to -2.8)	1.490	0.227	0.061	0.805	5.917	0.018*	-	-
TP rest (ms^2)	−15,144.3(−50,909.4 to 20620.9)	1578.5(−2812.7 to 5969.8)	0.824	0.368	0.925	0.340	1.405	0.241	-	-
TP cold (ms^2)	−14,462.1(−44,188.8 to15264.6)	−365.3(−1354.3 to 623.7)	1.271	0.264	1.619	0.208	1.464	0.231	-	-
RMSSD rest (ms)	10.7(−7.3 to 28.6)	−3.0(−16.1 to 10.1)	6.790	0.012*	0.180	0.673	0.568	0.454	0.031*	0.299
RMSSD cold (ms)	−4.2(−20.3 to 12.0)	−4.0(−12.8 to 4.8)	11.261	0.001*	0.256	0.615	0.000	0.990	0.018*	0.017*
SDNN rest (ms)	7.4(−2.4 to17.2)	−2.6(−12.0 to 6.8)	6.238	0.015*	0.171	0.681	0.745	0.391	0.034*	0.401
SDNN cold (ms)	−4.6(−15.3 to 6.0)	−2.1(−8.0 to 3.7)	15.156	<0.001*	0.420	0.519	0.058	0.810	0.010*	0.004*
pNN50 rest (%)	4.1(−1.2 to 9.4)	−1.2(−7.4 to 5.0)	4.937	0.030*	0.147	0.703	0.484	0.489	0.072	0.440
pNN50 cold (%)	7.4(0.4 to 14.4)	−0.9(−6.8 to 4.9)	6.773	0.012*	0.146	0.704	0.737	0.394	0.021*	0.297

Notes: The participants were instructed to remain calm while sitting for 10 minutes as "rest" period and subsequently immerse their right hands into ice water as "cold" period. The adjusted two-way ANOVA was conducted to assess differences on group, session, and group*session interactions. Post hoc analysis was performed and demonstrated. *P<0.05.

Abbreviations: CPM, conditioned pain modulation; DBP, diastolic blood pressure; HF, high frequency; HR, heart rate; LF, low frequency; nu, normalized units; PPT, pressure pain threshold; pNN50, percentage of adjacent normal-to-normal intervals that differ from each other by more than 50 ms; RMSSD, root mean square of successive differences between normal heartbeats; SBP, systolic blood pressure; SDNN, standard deviation of normal-to-normal intervals; TP, total power.

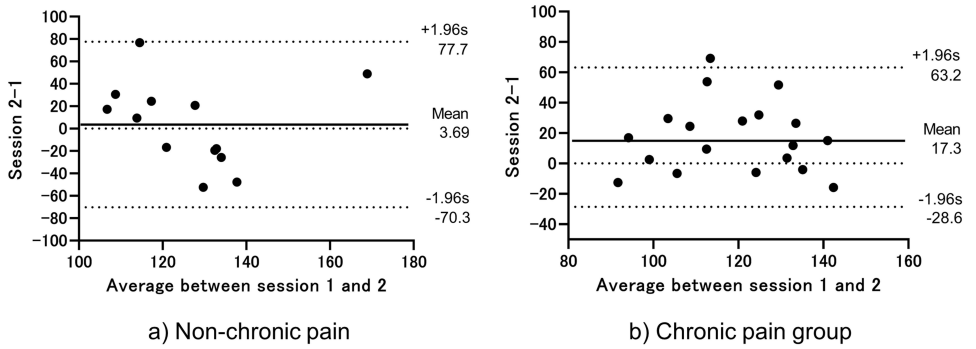

Figure 2 Bland–Altman Plot of the two CPM measurements.
Notes: (**a** and **b**) Indicate the non-chronic and chronic pain groups, respectively. The y-axis is the difference in the CPM index between sessions 1 and 2, and the x-axis is the average between the groups. The mean of the difference is presented as a black line, and it was higher than zero (x-axis), indicating graphically higher scores on the CPM index in session 2 than that in session 1. The dotted lines represent the limits of agreement.
Abbreviations: CPM, conditioned pain modulation; s, standard deviation.

Spearman's rho correlations for the CPM indices between the sessions showed no significant relationships at r=−0.418 in the non-chronic pain group (p=0.157) and 0.191 in the chronic pain group (p=0.433). The ICCs in the non-chronic and chronic pain groups were not significant at −0.247 (p=0.646) and 0.167 (p=0.348), respectively. ISC-CPM was −0.5±1.7 in the non-chronic pain group and 0.4±0.8 in the chronic pain group. An independent samples *t*-test revealed that the average ISC-CPM was not significantly different between the non-chronic and chronic pain groups (p=0.147).

Factors Potentially Influencing Low Inter-Session Reliability for CPM

Spearman's rho correlations were performed to assess the correlation coefficients between ISC-CPM and participant characteristics. No significant correlations were detected between the ISC-CPM and participant characteristics in the chronic pain group and overall samples. In the non-chronic pain group, ISC-CPM and pain intensity were statistically correlated (r=0.601, p=0.030). The correlations between ISC-CPM and autonomic variables were also performed. DBP rest in session 1 (r=−0.582, p=0.037), SBP rest in session 2 (r=0.602, p=0.029) and LF/HF rest in session 2 (r=−0.575, p=0.04) in the non-chronic pain group were statistically correlated with ISC-CPM. In the chronic pain group, TP rest in session 1 (r=−0.546, p=0.016) and SDNN rest in session 1 (r=−0.485, p=0.035) and LF/HF cold in session 1 (r=−0.464, p=0.046) were correlated. Furthermore, in overall samples, TP rest in session1 (r=−0.453, p=0.009), RMSSD rest in session 1 (r=−0.357, p=0.045), SDNN rest in session 1 (r=−0.445, p=0.011), pNN50 cold in session 1 (r=−0.385, p=0.029), SBP rest in session 2 (r=0.387, p=0.029) and SBP cold in session 2 (r=0.356, p=0.045). Other variables were not significantly correlated with ISC-CPM.

Multivariate regression analysis included ISC-CPM as a dependent variable and the TP rest in session 1 (Model 1A) and LF/HF cold in session 1 (Model 2A) as independent variables. The variable of sex was added to Model 1A and 2A for adjusting the group imbalance of sex, named Model 1B and 2B. Chronic pain group showed a significant explanatory factor in Model 1A (p<0.001) and 2A (p<0.001). Although Model 2A and 2B revealed the same results for TP rest in session 1 (p<0.001) and LF/HF cold in session 1 (p=0.001), sex was not significant in both Model 2A and 2B (p=0.342 and 0.847, respectively). The results of the multivariate regression analysis are shown in Table 3.

Discussion

This study aimed to reveal 1) the inter-session reliability of CPM in a cohort of older individuals with or without chronic musculoskeletal pain and 2) the factors affecting the inter-session reliability of CPM. The results indicated that the chronic pain group showed low absolute and relative reliability, while the non-chronic pain group showed sufficient absolute reliability and low relative reliability. ISC-CPM correlated with several parameters of HRV and BP. Furthermore, TP and LF/HF in the chronic pain group were identified as significant factors in low inter-session reliability of CPM. These findings support our hypothesis.

Table 3 The Results of Multivariate Regression Analysis

Variables				
Model 1A	***B***	**Std.error**	**Beta**	**P value**
Non-chronic				
TP rest session 1	<0.001	0.000	0.002	0.995
Chronic				
TP rest session 1	<0.001	0.000	−0.77	<0.001*
Overall				
TP rest session 1	<0.001	0.000	−0.331	0.065
Model 1B	***B***	**Std.error**	**Beta**	**P value**
Non-chronic				
TP rest session 1	<0.001	0.000	−0.197	0.518
Sex	1.931	1.047	0.542	0.095
Chronic				
TP rest session 1	<0.001	0.000	−0.798	<0.001*
Sex	−0.253	0.259	−0.154	0.342
Overall				
TP rest session 1	<0.001	0.000	−0.328	0.071
Sex	0.188	0.454	0.072	0.682
Model 2A	***B***	**Std.error**	**Beta**	**P value**
Non-chronic				
LF/HF cold session 1	0.666	0.768	0.253	0.866
Chronic				
LF/HF cold session 1	−0.489	0.123	−0.694	<0.001*
Overall				
LF/HF cold session 1	0.019	0.222	0.015	0.085
Model 2B	***B***	**Std.error**	**Beta**	**P value**
Non-chronic				
LF/HF cold session 1	0.698	0.702	0.265	0.343
Sex	1.699	0.95	0.476	0.104
Chronic				
LF/HF cold session 1	−0.491	0.127	−0.697	0.001*
Sex	0.058	0.295	0.035	0.847
Overall				
LF/HF cold session 1	0.036	0.227	0.029	0.876
Sex	0.232	0.486	0.089	0.637

Notes: Significantly correlated factors in the non-chronic and chronic pain groups and whole samples were examined using multivariate regression analysis. Model "A" only analyzed statistically correlated variables in Spearman's rho correlation, and Model "B" included Model "A" with sex to adjust the imbalance in the groups' sex ratios. *P<0.05.
Abbreviations: HF, high frequency, LF, low frequency; Std. error, Standard error; TP, total power.

Although the CPM indices in the chronic pain group did not significantly differ between the sessions, the Bland–Altman analysis showed a significant systematic error, with a mean difference of 17.3% (CI: 15.0–19.7). This systematic error indicated low agreement between the measurement sessions.[53] A prior study[13] investigating CPM reliability in healthy older individuals reported no mean difference between the two sets of measurements. Although this result[13] corresponded with the non-chronic pain group in this study with a mean difference of 3.7 (CI: −0.02 to 7.4), the chronic pain group in this study was not comparable because our group consisted of older individuals with chronic musculoskeletal pain. A similar trend was observed in a cohort of patients with chronic musculoskeletal pain. A study including patients with chronic low back pain reported a significantly different CPM effect between the measurement sessions with

an interval of 7–28 days.[54] Another study also showed low intra-session reliability for CPM in patients, with shoulder pain awaiting orthopedic operation.[55] These results suggest that chronic musculoskeletal pain affects low CPM reliability.

In contrast, both groups exhibited low correlation coefficients at −0.418 (p=0.157) and 0.191 (p=0.433) and low ICCs at −0.247 (p=0.646) and 0.167 (p=0.348), respectively. These results indicated relatively low correlations between the sessions.[50] Low ICCs with no significance for CPM were found in a previous study,[13] which included healthy older participants. Another study, which did not include chronic musculoskeletal pain but painful chronic pancreatitis, showed a low ICC of 0.10.[10] Thus, similar to prior studies, our study also identified low inter-session reliability in older individuals, especially those with chronic musculoskeletal pain.

ISC-CPM was significantly correlated with autonomic variables such as LF/HF, RMSSD, and SDNN in the chronic pain group; SBP, DBP, and LF/HF in the non-chronic pain group; and SBP, TP, RMSSD, SDNN, and pNN50 in overall samples. All other variables, such as age, pain intensity, and the results of the questionnaires, were not significant. Furthermore, multivariate regression analysis showed that TP rest session 1 and LF/HF cold session 1 were significant factors in ISC-CPM in the chronic pain group, despite the variable of sex being adjusted as a covariate. Multivariate regression analysis for the non-chronic pain group and all samples did not detect any significant factors. Previous studies have reported that the autonomic nervous system is a potential factor in descending pain modulation.[20] Neural pathways of descending pain modulation and autonomic nervous system intersect at several neurons, such as the rostral ventromedial medulla and periaqueductal grey, and these neurons modulate pain sensitivity and control the cardiovascular and respiratory organs through the autonomic nervous system.[20–23,56,57] In this study, TP at rest in session 1 was negatively affected by ISC-CPM, indicating that greater TP during the rest period tended to show lower ISC-CPM, that is, a greater difference between the sessions. TP is calculated by frequency analysis of HRV, which represents the entire activity of the autonomic nervous system.[31,58] The calculation of TP is Higher TP values reflect higher activity in the autonomic nervous system. In this case, some participants showed high autonomic nervous activity, while they remained seated for 10 min in a relaxed position. This may indicate abnormal and excessive autonomic activities, and may possibly lead to greater changes between the sessions. Additionally, the LF/HF ratio during the cold period in session 1 was also negatively affected by ISC-CPM. As LF/HF reflects the sympathetic nervous system, this result indicates that greater sympathetic activity corresponded with a greater change in CPM between the sessions. Individuals with chronic musculoskeletal pain tended to have high sympathetic nervous system activity.[59] The chronic pain group had higher LF/HF during the cold period in session 1 than the non-chronic pain group, despite no significant group differences. We determined that an abnormal level of sympathetic nervous system activity, as indicated by a higher LF/HF ratio, may lead to decreased inter-session reliability in CPM. Only the factors on the first day of measurement influenced low inter-session reliability of CPM. One reason might be that the participants were unfamiliar with the CPM protocol. It could cause fear and/or stress and possibly lead to a greater change in HRV.

Other potential factors contributing to low inter-session reliability were investigated. Spearman's rho correlations revealed no correlations between participant characteristics, such as pain catastrophizing, depression, body composition, neuropathic pain, central sensitization, IL-6, physical activity, and age, in the chronic and non-chronic pain groups, and all samples. Psychological conditions have been known as factors in CPM reliability,[17,18,60] which is in contrast with the results of this study. However, recent articles[16] have revealed that psychological factors, such as depression, anxiety, and pain catastrophizing, do not influence inter-individual reliability in healthy young adults. Furthermore, the article[17] reporting a significant relationship between pain catastrophizing and CPM reliability included patients with pain at a numerical rating scale (NRS) score of 6, which may have caused the discrepancy from this study including 3.9±1.2 in the chronic pain group. Different results in terms of depression might have been caused by different cohorts as our participants were not diagnosed with depression and had a cut-off score of five on the Geriatric Depression Scale at 4.0±3.1 in the non-chronic and 4.21±2.6 in the chronic pain group. A prior study reported that body composition did not correlate with CPM reliability in healthy young adults.[61] Similarly, older individuals with or without chronic pain did not correlate with CPM reliability. As the relationship between body composition (total fat and muscle) and CPM reliability has not been sufficiently researched,[62] our result is novel. To our knowledge, the relationship between neuropathic pain, central sensitization, and CPM reliability has not been investigated. In this study, no relationships were found between the abovementioned factors, and our participants were

under the cutoff scores of the PainDETECT and Central Sensitization Inventory. These two factors should be studied further as neuropathic pain and central sensitization normally influence the descending pain modulation system.[63,64] IL-6 was also a novel parameter of interest in this study. Although our result indicated no correlations between IL-6 and CPM reliability in elderly individuals, further studies are required as our samples had low values (0.4±0.4 in the non-chronic and 0.9±1.1 in the chronic pain groups). The amount of physical activity and CPM reliability was not correlated in this study; physical activity influenced descending pain modulation pathways, possibly affecting low amounts of physical activity in our samples.[65] Age was not correlated with CPM reliability. Although this was a different result from that of a previous study,[13] this study compared older individuals with younger adults, indicating a different study design from our study. Only pain intensity in the non-chronic pain group was correlated with ISC-CPM at r=0.601, indicating that greater pain showed higher inter-session reliability, eg, the low variance between the measurements. However, as the non-chronic pain group showed a low NRS score of 1.2±1.4, this result should be interpreted with caution.

This study has several limitations. First, this study followed the CPM protocols by Naugle et al[13] as their study had a similar interest as this one, CPM reliability in healthy older individuals. However, other studies used a different length and repetition of the conditioning stimulus when assessing CPM. For example, Naugle et al[13] utilized a 45-s cold-water immersion and repeated it three times. On the other hand, the conditioning stimulus in Skovbjerg et al[66] was a single 2-min cold-water immersion. Second, although some stimuli such as pressure, thermal, or electrical stimuli are utilized as conditioning and test stimulus,[32] this study only examined ice-water immersion as a conditioning stimulus and pressure pain threshold as test stimulus. Third, this study investigated two measurement sessions at an interval of 13–15 days. Long intervals (eg, two or four month) decreased the test–retest reliability for CPM.[67] As such diversity of protocols leads to differences in the reliability for CPM,[68–70] further investigation is necessary for other protocols of CPM.

Conclusion

This study examined the low inter-session reliability in older individuals with chronic musculoskeletal pain and identified specific variables of the autonomic nervous system as possible factors of low inter-session reliability. As autonomic nervous system and descending pain modulation have a common neural pathway, abnormal autonomic activities following chronic musculoskeletal pain may lead to low inter-session reliability. These findings could benefit clinicians assessing CPM in a cohort of patients with chronic musculoskeletal pain and could help with the interpretation of the results. Further research is required to investigate other measuring protocols for CPM.

Abbreviations

CPM, conditioned pain modulation; DBP, diastolic blood pressure; HF, high frequency; HR, heart rate; IL-6, interleukin 6; ISC, intra-individual stability coefficient; LF, low frequency; NRS, numerical rating scale; nu, normalized units; PPT, pressure pain threshold; pNN50, percentage of adjacent normal-to-normal intervals that differ from each other by more than 50 ms; RMSSD, root mean square of successive differences between normal heartbeats; SBP, systolic blood pressure; SDNN, standard deviation of normal-to-normal intervals; TP, total power.

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Author Contributions

All authors made significant contributions to the study, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in any combination of these; took part in drafting, revising, or critically reviewing the article; have given final approval of the version to be published; have agreed on the journal of submission; and have agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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