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Sex differences in conditioned pain modulation effects and its associations with autonomic nervous system activities in healthy, younger individuals: a pilot study

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Abstract

Introduction: Sex differences in conditioned pain modulation (CPM) have not been sufficiently explored.

Objectives: This pilot study aimed to examine sex differences in CPM effects and associations between autonomic activities and CPM effects in healthy, younger individuals.

Methods: University students were recruited from February to March 2021 and divided by sex. They remained seated for 10 minutes as a rest period, then immersed their right hands in cold water for 2 minutes as a cold period. The pressure pain threshold (PPT) was measured after each period, presenting the CPM index (%) using the formula: (PPT_{cold}/PPT_{rest}) × 100. Autonomic nervous system variables were calculated using the formula—(autonomic $variable_{cold}$/autonomic $variable_{rest}$) × 100—and suffixed by "index" such as low-frequency/high-frequency (LF/HF) index. Some psychological questionnaires were self-recorded. Sex differences in the CPM index were statistically compared, and a simple linear regression analysis between the CPM and autonomic indices was conducted.

Results: Thirty-two participants were analyzed (14 women and 18 men; aged 21.1 ± 0.6 and 20.9 ± 0.3 years, respectively). Conditioned pain modulation effects were not different at 127.0 ± 19.1% in women and 124.0 ± 18.7% in men. The LF/HF index, LF normalized unit (nu) index (LFnu), and HFnu index had significant predictor variables for the CPM index across overall samples. The LF/HF index and LFnu index were significant predictor variables for the CPM index for women but not for men.

Conclusions: Conditioned pain modulation effects between groups seem to be similar. The LF/HF and LFnu indices in women were significant, indicating that descending pain modulations in women might be more associated with autonomic activities than those in men.

Keywords: Conditioned pain modulation, Sex differences, Autonomic nervous system

1. Introduction

Conditioned pain modulation (CPM) is a psychophysical measure of the net effect of descending pain modulation that facilitates or inhibits afferent noxious stimuli.[26] Many painful conditions have impaired CPM.[25] Impaired CPM indicates a dysfunction of descending pain modulation, which is associated with the chronification of pain.[1] As pain chronification negatively affects patients' quality of life and carries a heavy economic burden,[8] assessing descending pain modulation is crucial to alleviate patients' pain and reduce the associated burdens.

The mechanisms of CPM and descending pain modulation are explained by 3 systems: the central nervous system, opioidergic system, and autonomic nervous system, where the autonomic nervous system potentially associates with descending pain modulation.[27] An increase in systolic blood pressure was significantly associated with CPM.[7] Another study[20] examined

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whether CPM and sympathetic activity showed a significant positive correlation. A recent study conducted by Makovac et al.[21] examined heart rate variability (HRV) during CPM and found significant correlations between CPM and overall autonomic activities. Furthermore, patients with impaired CPM showed low parasympathetic activity compared with individuals with normal CPM.[29] These studies support a relationship between CPM and the autonomic nervous system.

However, sex differences in the effects of CPM and autonomic activity during CPM have not been elucidated. Women tend to exhibit more pronounced pain and related symptoms than men.[32] Pain intensity was associated with fear avoidance and kinesiophobia in women, whereas no such correlation was found in men.[16,36] Additionally, central sensitization, defined as increased responsiveness of nociceptive neurons in the central nervous system[17] caused by impaired descending pain modulation,[26] was approximately twice as prevalent in Japanese women (4.9%) than in men (2.7%).[14] Although these studies indicate sex differences in descending pain modulation, some conflicts exist in their findings. One study[28] reported that the CPM effect was lower in women than in men. However, another study showed no difference in the CPM effect between women and men.[12] Furthermore, to the best of our knowledge, autonomic activities during CPM have only been investigated by a few studies,[20,21] and these studies did not examine sex differences related to the autonomic nervous system.

Descending pain modulation and CPM are controlled by several neurons, including those in the periaqueductal gray, rostral ventromedial medulla, and subnucleus reticularis dorsalis.[2,25,33] As those neurons have other functions acting as autonomous centers to regulate cardiovascular and respiratory systems, descending pain modulation and CPM are associated with autonomic nervous system activities.[2,3] Additionally, it is reported that there are sex disparities in autonomic nervous system activities.[19] For example, baroreceptors, a component of the autonomic nervous system, exert stronger control over blood pressure in women than in men.[18] Conversely, the central nervous system in female rats showed weaker connectivity with neurons involved in descending pain modulation, such as those in the periaqueductal gray, compared with male rats.

The aims of this pilot study were to explore sex differences in (1) the effects of CPM and (2) the relationships between autonomic activities and CPM in healthy, younger individuals. Our first hypothesis was that women would exhibit a reduced CPM effect compared with men because women tend to exhibit higher pain intensities and pain sensitization.[14,32] The second hypothesis was that autonomic activities in women are more strongly associated with descending pain modulation (ie, CPM). If women exhibit elevated autonomic nervous system activity and weaker connections between the central nervous system and periaqueductal gray than men, our hypothesis posits that autonomic activities in women may be more strongly associated with CPM.

2. Methods

2.1. Study design and ethical considerations

This cross-sectional study was conducted at the International University of Health and Welfare. The study was approved by the institutional review board of the International University of Health and Welfare (19-Io-213-2) and complies with the Declaration of the World Medical Association. Written informed consent was obtained from all participants.

2.2. Participants

Participants included university students from the International University of Health and Welfare at Narita, Chiba, Japan. Thirty-three individuals voluntarily participated in response to announcements regarding this study from February to March 2021. The average age was 21.0 ± 0.5 years in total, 21.1 ± 0.6 years in women, and 20.9 ± 0.3 years in men. The inclusion criterion for this study was an agreement to participate. The following participants were excluded: (1) those with severe issues relating to the autonomic nervous system, endocrine system, immune system, or cognitive function; (2) those with facial, visceral, or cancer pain; (3) those with excessive intake of tobacco or alcohol; and (4) those with severe sleep disorders. Additionally, drinking caffeinated beverages and alcohol, excessive exercise, and smoking a day before and on the test day were prohibited to reduce the influence on the autonomic nervous system. Breakfast was not restricted on the test day. The participants were divided into 2 groups based on sex.

G*power 3.1.9.7 was used for power analysis with alpha set to 0.05 and power set to 0.8. It indicated that a sample size of 25 was sufficient for simple linear regression analysis with an effect size (f) of 0.35 (considered large). Furthermore, a post hoc analysis was performed for a *t* test with alpha set to 0.05, n = 32, and a large effect size of 0.8. It indicated a power of 0.7.

2.3. Protocols and outcomes

On the first day of the study, orientation and screening for eligibility were conducted at the university. The experiment was conducted on a different day from the orientation from 9 AM to noon. The room was maintained at 22 to 24°C and was as silent as possible to minimize any influence on the autonomic nervous system.

Conditioned pain modulation was measured on the day of experimentation as previously described.[31] First, the participants were seated in a relaxed position for 10 minutes for the "rest" period. After the rest period, cold-water immersion was conducted for the "cold" period. The conditioning stimulus was cold-water immersion at an average of 10°C ranging from 8°C to 12°C. The participants immersed their right hand in the cold water for 2 minutes. Test stimuli were performed after rest and cold periods using a pressure algometer (Wagner FPX-25; Wagner Instruments, Greenwich, CT) to measure the pressure pain threshold (PPT) in the upper fibers of the left trapezius.[37] Conditioned pain modulation was presented as a ratio between the PPT after the cold period and the PPT after the rest period; a CPM index (%) was computed using the following formula[23]: $\frac{\text{PPT after cold period}}{\text{PPT after rest period}} \times 100$.

A CPM index above 100% indicates normal descending pain modulation, and that under 100% infers abnormal descending pain modulation.[27] All measurements were performed by the first author with expertise in measuring the CPM.

The autonomic nervous system was assessed using HRV, heart rate (HR), and blood pressure. A wearable electrocardiogram (ACTIVETRACER AC-301A; GMS Co Ltd, Tokyo, Japan) was attached to the participants' chests to continuously measure beat-to-beat intervals during the rest and cold periods. The beat-to-beat interval data were calculated using analysis software (MemCalc; GMS Co Ltd). The maximum entropy method was used with a 5-second time frame to present power in high-frequency (HF; 0.15–0.40 Hz) and low-frequency (LF; 0.04–0.15 Hz) bands, reflecting respiratory sinus arrhythmia and baroreceptor activities, respectively.[30] High-frequency band, which

indicates parasympathetic activity, was normalized as HFnu (nu: normalized unit) using the following formula: HF/(HF + LF).

As LF bands represent both sympathetic and parasympathetic activities, sympathetic activity was presented as the LF/HF.[30] LFnu was also estimated to explore a more generalized value of baroreceptor activities.[30] Heart rate was measured by the wearable electrocardiogram. Blood pressure was measured using a digital sphygmomanometer (Kenzmedico Co Ltd, Saitama, Japan) for systolic and diastolic blood pressure (SBP and DBP, respectively). Heart rate, systolic blood pressure, and diastolic blood pressure values were averaged at each rest and cold period. In this study, all autonomic variables were estimated using the following formula: $\frac{\text{an autonomic variable after cold period}}{\text{an autonomic variable after rest period}} \times 100$.

This formula exhibits a ratio of autonomic variables between the after-rest and cold periods, and the resultant value was called the autonomic "index," ie, the LF/HF index.

Participants' characteristics and several questionnaires were self-reported on the same day as the experiments. Participant characteristics included age, sex, body mass index, and experience of orthopedic surgery. The Pain Catastrophizing Scale was used to evaluate pain catastrophizing, defined as an exaggerated negative feeling caused by an actual or anticipated painful experience.[34] The Hospital Anxiety and Depression Scale was used to assess anxiety and depression, with 7 questions on each test.[39] The Pittsburgh Sleep Quality Index was used as a subjective measurement of sleep quality and sleep disorders.[6] A Checklist for Individual Strength was used to assess fatigue severity and fatigue-related symptoms.[38] On all questionnaires, higher scores indicated more severe symptoms. The International Physical Activity Questionnaire was used to assess the amount of physical activity: a higher score indicates a higher amount of physical activity.[9]

2.4. Statistical analyses

Statistical analysis was performed using SPSS 27.0 for Windows (SPSS Inc, Chicago, IL). Mean values and SDs were calculated for all outcome measures in both groups. All variables were examined for normality using the Shapiro–Wilk test, and a threshold of $P > 0.05$ was deemed to be significant. Participant characteristics and questionnaire results were compared between the groups to assess baseline comparability using the following 3 statistical methods. The independent samples *t* test was used for the body mass index, Pain Catastrophizing Scale, Pittsburgh Sleep Quality Index, and Checklist for Individual Strength. The Mann–Whitney *U* test was used to compare age, International Physical Activity Questionnaire scores, and Hospital Anxiety and Depression Scale for anxiety and depression scores. The χ^2 analyses were performed for a number of participants with experience in orthopedic surgery.

The CPM, LF/HF, LFnu, Hfnu, SBP, DBP, and HR indices were compared using the independent samples *t* test for assessing group differences.

Simple linear regression analysis across whole samples and both groups was performed, with the CPM index as the dependent variable. The independent variables were the autonomic indices (LF/HF index, LFnu index, Hfnu index, SBP index, DBP index, and HR index) and other possible factors (body mass index, Pain Catastrophizing Scale scores, International Physical Activity Questionnaire scores, Hospital Anxiety and Depression Scale for anxiety and depression scores, Pittsburgh Sleep Quality Index, and Checklist for Individual Strength). Statistical significance was set at a threshold of $P < 0.05$ for all tests except for simple linear regression analysis. We performed the regression analysis 3 times for each independent variable (women, men, and overall samples). Therefore, statistical significance was set at $P < 0.0167$ (0.05/3).[5]

3. Results

One participant was excluded because of a diagnosis of an autonomic disorder, and 32 participants completed the experiment and were finally analyzed. The average age of the participants was 21.0 ± 0.5 years. Fourteen women and 18 men with mean ages of 21.1 ± 0.6 and 20.9 ± 0.3 years, respectively, were included. The participants' characteristics and the results of the questionnaires are presented in **Table 1**. No group differences were observed in those outcomes.

Results of the independent samples *t* test for the CPM index and autonomic indices are described in **Table 2**. Conditioned pain modulation indices were 127.0 ± 19.1% in women and 124.0 ± 18.7% in men, with no statistical difference between the groups ($P = 0.661$). No group differences were identified in the LF/HF, LFnu, HFnu, SBP, DBP, and HR indices.

After simple linear regression analysis, the LF/HF, LFnu, and HFnu indices across overall samples ($P = 0.001$, 0.004, and 0.014, respectively) and the LF/HF and LFnu indices in women ($P = 0.004$ and 0.008, respectively) were found to be significant factors. No other variables were significant across whole samples and both groups. **Table 3** describes the results of the simple linear regression analysis, and scatter plots with regression lines describing associations between the LF/HF and CPM indices and between the HFnu and CPM indices are shown in **Figure 1**.

Table 1

Participant characteristics and results of questionnaires.

Variables	Women (n = 14)	Men (n = 18)	*P*
Age (years)	21.1 ± 0.6	20.9 ± 0.3	0.464
Body mass index (kg/m^2)	20.0 ± 1.5	21.3 ± 2.3	0.081
Experience of orthopedic surgery, *n* (%)	4 (28.6)	2 (11.1)	0.212
Pain Catastrophizing Scale	15.1 ± 9.3	13.1 ± 8.3	0.524
Hospital Anxiety and Depression Scale (Anxiety)	5.1 ± 2.7	4.9 ± 4.0	0.398
Hospital Anxiety and Depression Scale (Depression)	5.2 ± 2.8	5.7 ± 3.5	0.808
Pittsburgh Sleep Quality Index	5.8 ± 2.7	5.2 ± 2.2	0.480
International Physical Activity Questionnaire	24.4 ± 25.0	25.0 ± 22.2	0.866
Checklist for Individual Strength	77.0 ± 8.3	80.0 ± 9.3	0.352

Table 2

Group differences in conditioned pain modulation and autonomic indices.

Variables	Women (n = 14)	Men (n = 18)	P
CPM index (%)	127.0 ± 19.1	124.0 ± 18.7	0.661
LF/HF index (%)	128.8 ± 56.8	119.2 ± 35.2	0.558
LFnu index (%)	111.7 ± 17.4	104.6 ± 9.2	0.189
HFnu index (%)	91.5 ± 21.5	92.4 ± 20.6	0.908
SBP index (%)	110.6 ± 8.6	107.9 ± 9.7	0.414
DBP index (%)	116.5 ± 17.9	116.7 ± 27.6	0.973
HR index (%)	99.7 ± 7.0	99.7 ± 7.8	0.992

CPM, conditioned pain modulation; DBP, diastolic blood pressure; HF, high frequency; HR, heart rate; LF, low frequency; SBP, systolic blood pressure.

4. Discussion

The aims of this pilot study were to explore sex differences in (1) CPM effects and (2) the associations between autonomic activities and CPM in healthy, younger individuals. Our results indicated that women and men showed a similar inhibitory effect after cold-water immersion. This result did not correspond with our first hypothesis, which was that women would show a lower CPM effect. In contrast, the results of simple linear regression analysis indicated that sympathetic and parasympathetic activities across whole samples were significant for CPM. Furthermore, the sympathetic nervous system activities in women were also significant for the CPM index, whereas men did not show any significant variables. This finding seems to be consistent with our second hypothesis that autonomic activities in women may have a stronger association with CPM effects than those in men.

Our results indicated a similar tendency of CPM effects between younger women and men at 127.0 ± 19.1% and 124.0 ± 18.7%, respectively ($P = 0.661$). As women tend to exhibit greater pain and pain-related psychological symptoms than men,[32,36] we hypothesized that the CPM effect in women would be lower than that in men. A study comparing CPM effects in younger women and men showed a lower CPM effect (−0.35 ± 0.54%) in women than in men (−0.71 ± 0.69%), where a smaller value indicates a larger CPM effect.[28] Whereas, Firouzian et al.[12] found no sex differences in CPM effects at −8.8 ± 35.6% in women and −7.7 ± 34.6% in men ($P = 0.87$). Another study[25] also found no sex difference in CPM effects. The discrepancies among these studies could be attributed to variations in the participants' ages because those aged 40 years or older are known to experience alterations in CPM.[15] Although the abovementioned study[28] included individuals from 19 to 49 years of age, another study included individuals aged 26.8 ± 5.3 years, with exclusion criteria of 40 years of age or over,[12] and yet another study included individuals aged 23.7 ± 0.7 years ranging from 18 to 33 years.[25] In this study, female participants were aged 21.1 ± 0.6 years, and male participants were aged 20.9 ± 0.3 years. Consequently, the younger age of the participants possibly led to a tendency of similar CPM effects between the 2 groups.

The results of our simple linear regression analysis indicated that sympathetic and parasympathetic nervous systems activities across the whole sample were significantly associated with CPM effects. Additionally, although no variables among men were identified as significant, the LF/HF and LFnu indices in women were significantly associated with the CPM index ($P = 0.004$ and 0.008, respectively). The R^2 of the LF/HF index was 0.52 in women and 0.33 across the overall sample. The R^2 of the LFnu was higher in women than in the overall sample, indicating that a higher coefficient was detected in the cohort of women.[40] In contrast, both women and men showed elevated LF/HF indices and decreased HFnu indices after cold-water immersion, and no group differences in the CPM index were identified after conditioning stimuli, indicating that both groups showed comparable levels of descending pain modulation and autonomic activities. The potential explanation for these findings is that there may be varying degrees of associations between descending pain modulation and autonomic activities in women and men. As mentioned previously, descending pain modulation can be explained by the activities of 3 systems (the autonomic nervous, central nervous, and opioidergic systems),[27] and each of these systems has sex differences. For example, the central nervous system in male rats showed stronger connectivity with the neurons related to descending pain modulation, such as those in the periaqueductal gray, prelimbic cortex, anterior cingulate

Table 3

Simple linear regression analysis between conditioned pain modulation index and other variables.

Variables	Overall			Women			Men		
	B [95% CI]	P	R^2	B [95% CI]	P	R^2	B [95% CI]	P	R^2
LF/HF index (%)	0.24 [0.11 to 0.36]	0.001*	0.33	0.24 [0.10 to 0.39]	0.004*	0.52	0.22 [−0.03 to 0.48]	0.085	0.17
LFnu index (%)	0.68 [0.24 to 1.12]	0.004*	0.25	0.74 [0.24 to 1.25]	0.008*	0.46	0.58 [−0.45 to 1.60]	0.253	0.08
HFnu index (%)	−0.39 [−0.69 to −0.09]	0.014*	0.19	−0.42 [−0.91 to 0.07]	0.088	0.22	−0.36 [−0.80 to 0.08]	0.103	0.16
SBP index (%)	0.23 [−0.53 to 0.98]	0.540	0.01	−0.25 [−1.65 to 1.14]	0.699	0.01	0.49 [−0.51 to 1.48]	0.313	0.06
DBP index (%)	−0.00 [−0.30 to 0.29]	0.994	0.00	0.32 [−0.33 to 0.96]	0.304	0.09	−0.10 [−0.46 to 0.25]	0.549	0.02
HR index (%)	−0.06 [−1.01 to 0.88]	0.893	0.00	−0.37 [−2.07 to 1.33]	0.648	0.02	0.13 [−1.15 to 1.40]	0.837	0.00
BMI (kg/m^2)	−2.26 [−5.47 to 0.96]	0.162	0.06	−3.86 [−11.32 to 3.59]	0.281	0.10	−1.72 [−5.89 to 2.45]	0.395	0.05
PCS	0.45 [−0.34 to 1.23]	0.254	0.04	0.46 [−0.80 to 1.71]	0.442	0.05	0.40 [−0.77 to 1.57]	0.475	0.03
IPAQ (Mets)	−0.19 [−0.48 to 0.11]	0.207	0.05	−0.38 [−0.80 to 0.03]	0.067	0.25	0.01 [−0.44 to 0.46]	0.96	0.00
HADS A	−0.08 [−2.12 to 1.95]	0.934	0.00	−1.04 [−5.49 to 3.41]	0.621	0.02	0.23 [−2.26 to 2.72]	0.846	0.00
HADS D	1.31 [−0.81 to 3.43]	0.216	0.05	0.70 [−3.52 to 4.92]	0.723	0.01	1.68 [−0.99 to 4.36]	0.201	0.10
PSQI	2.89 [0.22 to 5.56]	0.035	0.14	3.58 [−0.22 to 7.38]	0.063	0.26	2.00 [−2.43 to 6.42]	0.353	0.05
CIS	−0.41 [−1.18 to 0.35]	0.278	0.04	−0.52 [−1.92 to 0.88]	0.437	0.05	−0.32 [−1.37 to 0.73]	0.525	0.03

*$P < 0.0167$.

BMI, body mass index; CI, confidence interval; CIS, checklist for individual strength; CPM, conditioned pain modulation; DBP, diastolic blood pressure; HADS, hospital anxiety and depression scale; HF, high frequency; HR, heart rate; IPAQ, International Physical Activity Questionnaire; LF, low frequency; nu, normalized unit; PCS, pain catastrophizing scale; PSQI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure.

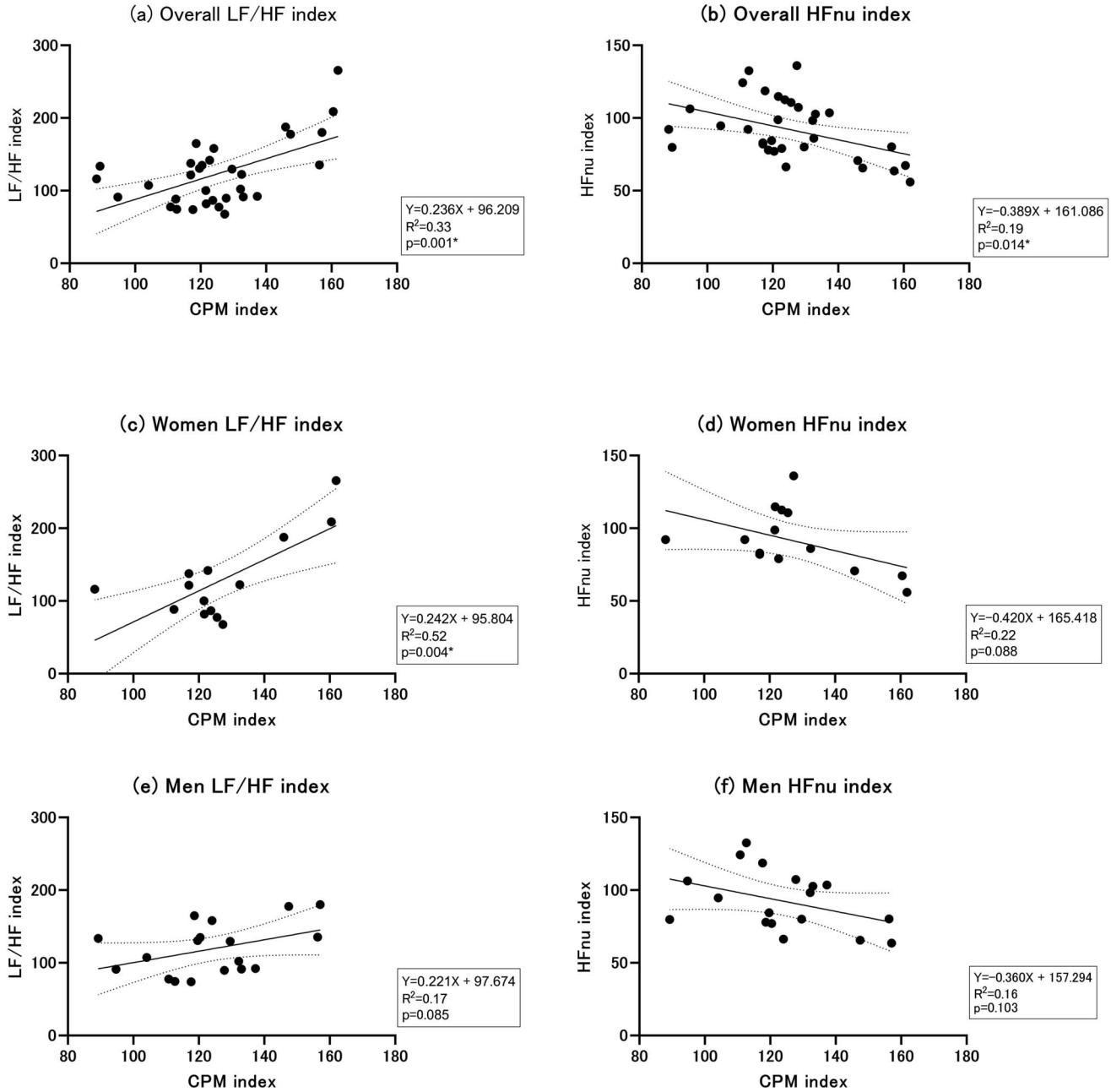

Figure 1. Scatter plots depicting the associations between the CPM index and autonomic activity. Results of simple linear regression analysis for the LF/HF and HFnu indices are shown. Solid and dotted lines indicate the line of regression and 95% confidence bands, respectively. The regression equation, R^2, and P values are also present ($P < 0.0167$). (A, C, and E) show the associations between the LF/HF index and the CPM index; (B, D, and F) show the associations between the HFnu index and the CPM index. CPM, conditioned pain modulation; HF, high frequency; LF, low frequency.

cortex, and insula compared with female rats.[11] Additionally, a human study identified a sex disparity in carotid baroreceptor activity, which are a component of the autonomic nervous system, with carotid baroreceptors in women demonstrating a more pronounced elevation in blood pressure than in men.[18]

In our study, only the LFnu and LF/HF indices in women were significantly associated with the CPM index. Sex differences in CPM effects and autonomic activities could be caused by varying degrees of associations between descending pain modulation and the autonomic nervous system (ie, carotid baroreceptor) because the LFnu and LF/HF indices reflect the activity of the carotid baroreceptor.[30] Therefore, CPM effects and descending pain modulation in women might be controlled to a greater extent by the autonomic nervous system than the other 2 systems (the central nervous and opioidergic systems).[27]

This study has 4 limitations. First, it used simple linear regression analysis. Although this analysis indicates statistical predictor variables for a dependent variable, it examines only one predictor variable in contrast to multiple regression,[40] which may affect this study's results. Second, the power calculation indicated that the sample size for the t test was insufficient to detect significance. This implies that there might be false negatives. However, if this study included a greater number of participants, such as 42 individuals, with a power set to 0.8, the sample size for the regression analysis would be excessive. It was established that 25 participants were adequate, and an excessive

number could lead to an increased likelihood of false positives. Therefore, the sample size in our study may have been optimal. Third, different CPM procedures exist in academic studies.[10,24] One type of CPM procedure is characterized by heterotopic stimulations which make use of areas such as the left hand and right foot.[4] Alternatively, similarly to our study, CPM procedures can make use of both the right and left upper limbs (or lower limb).[13,22,35] More specifically, we used the left upper trapezius as the test stimulus and the right hand as the conditioning stimulus. One limitation of our study is that our CPM procedure may have been affected by the segmental effect, thereby influencing our results. Therefore, a study that evaluates another type of CPM (eg, heterotopic stimulation) would be useful for the exploration of sex differences and the relationship between autonomic activities and CPM. Fourth, although we believe that the autonomic nervous system may influence CPM procedures, we could not examine this causal relationship because our study had a cross-sectional design; we were therefore unable to exclude the possibility that CPM influences the autonomic nervous system activities. Further consideration to explore the causal relationship between autonomic activities and CPM would be required.

5. Conclusion

This pilot study indicated a tendency for similar CPM effects between young, healthy female and male participants. Autonomic nervous system activities were associated with CPM effects, specifically, the process of descending pain modulation. Furthermore, sympathetic nervous system activities in women showed significant associations with CPM effects in simple linear regression analysis. This result indicated that descending pain modulation in women might be more strongly associated with the autonomic nervous system, potentially implying that women and men exhibit varying degrees of association between descending pain modulation and autonomic nervous system activity.

Disclosures

The authors have no conflict of interest to declare.

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