Conditioned Pain Modulation Evoked by Different Intensities of Mechanical Stimuli Applied to the Craniofacial Region in Healthy Men and Women

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Aims: *To investigate systematically whether conditioned pain modulation (CPM) evoked by tonic mechanical stimuli applied to the craniofacial region is intensity-, assessment site–, and gender-dependent.* ***Methods:*** *Twenty healthy men and 20 women participated in four sessions. Tonic painful mechanical stimulation was applied to pericranial muscles by a mechanical headband pressure device. The pressures applied to four probes were adjusted via pain feedback from a 0 to 10 electronic visual analog scale (VAS) to generate different pain levels (VAS0, VAS1, VAS3, or VAS5) for 10 minutes. Pressure pain thresholds (PPTs) and pressure pain tolerance thresholds (PPTols) were assessed from right masseter muscle and left forearm by pressure algometry before, during, immediately after, 10 minutes after, and 20 minutes after the conditioning stimulus (CS). Data were analyzed with multilevel ANOVAs.* ***Results:*** *PPT values normalized to baseline recordings were not dependent on gender or assessment site, but dependent on intensity (*$P < .001$*) and time (*$P < .001$*). The most painful CS (VAS5) was associated with the highest PPT increases (32.6% ± 3.3%, mean value for the two assessment sites and two genders) during CS compared to all other intensities of CS (*$P < .001$*). PPTol values normalized to baseline recordings were also not dependent on gender or assessment site, but dependent on intensity (*$P < .001$*) and time (*$P < .001$*). The most painful CS (VAS5) was associated with higher PPTol increases (11.2% ± 2.8%, mean value for the two assessment sites and two genders) during CS (*$P < .001$*).* ***Conclusion:*** *CPM evoked by mechanical stimulation of the craniofacial region is intensity-dependent but not assessment site– or gender-dependent.* J OROFAC PAIN 2011;25:364–375

Key words: conditioned pain modulation (CPM), diffuse noxious inhibitory control (DNIC), experimental craniofacial pain, gender differences, trigeminal system

The prevalence of musculoskeletal pain conditions such as temporomandibular disorders (TMD) is around 5% to 10% and more prevalent in women than in men.[1] One intriguing concept related to TMD and other chronic pain conditions is they may reflect a dysfunctional state of endogenous pain-modulatory systems,[2] which might relate to pathological changes such as a decrease in volume of gray matter brain structures as shown in chronic tension-type headache (CTTH) patients.[3] One such pain-modulatory process is "diffuse noxious inhibitory controls" (DNIC). DNIC is a phenomenon whereby the activities of nociceptive neurons in the spinal dorsal horn[4] and trigeminal spinal tract nucleus (eg, trigeminal subnucleus caudalis)[5,6] are selectively inhibited by the application of noxious stimuli outside the excitatory receptive fields.[7] Le Bars et al[4,8] reported the DNIC phenomenon for the first time in rats. Subsequently, this inhibitory phenomenon was described in the

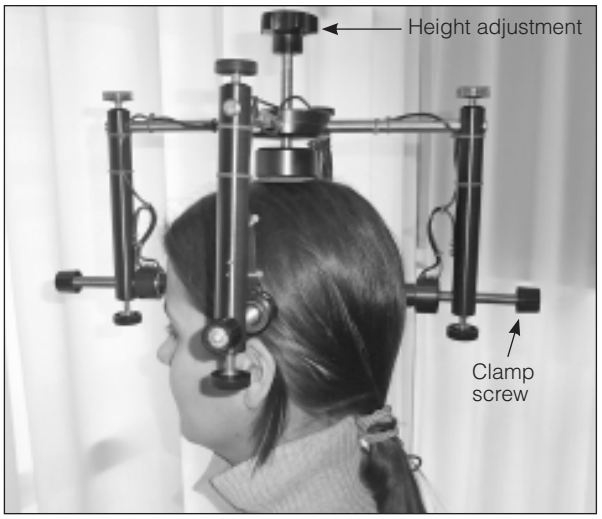

Fig 1 The compressive device for experimental craniofacial pain. The device was set on the vertex. It was height adjustable by a downwardly directed screw. Compression of the craniofacial region was achieved by tightening four horizontally opposed clamp screws with a force transducer.

spinal region (eg, nociceptive flexion reflex)[9–12] and the craniofacial region (eg, masseter silent period)[13] in humans. It has recently been suggested that the DNIC-like effects in humans should be termed "conditioned pain modulation" (CPM).[14]

Dysfunction of endogenous pain-modulatory systems may be assessed by CPM paradigms and could play an important role in the development and maintenance of craniofacial muscle pain conditions[15,16] such as TMD[17,18] and CTTH,[19,20] many of which display a female predominance.[21] Some of the recent studies have also shown there may be a significant gender difference in CPM responses,[22,23] although other studies have failed to show this,[24,25] and so the gender differences in CPM effects are still controversial.[26]

A study from this laboratory has shown that the craniofacial pain evoked by mechanical headband stimuli can induce widespread CPM responses in healthy humans without gender differences.[27] Moreover, an improved mechanical craniofacial compressive device has been developed and it has been reported very recently that tonic conditioning craniofacial pain causes segmental and extrasegmental CPM effects.[28] However, the results for the extrasegmental effect differed between assessment sites,[28] and the interrelation between the CPM effects and assessment site of the test stimulus has not yet been characterized.[24,29] Application of the developed mechanical headband enables testing of the CPM effect systematically. Furthermore, the compressive device produces pain that may mimic CTTH and may be a useful method to further explore CPM in other craniofacial pain conditions.

Although the relationship between the magnitude of the CPM effect and the intensity of the conditioning stimulus (CS) has not been studied in the craniofacial region in healthy humans, there is some indication that the magnitude of the CPM effect is related to the intensity of the CS in the spinal region of humans and craniofacial region of animals.[7,10,30] These considerations have led us to propose the general hypothesis that more intense CS evoked from the craniofacial region by the compressive device would result in larger CPM effects. Thus, the aim of the present study was to investigate systematically if the CPM evoked by the tonic mechanical stimuli applied to the craniofacial region is intensity-, assessment site (segmental [craniofacial region]; extrasegmental [spinal region])–, and gender-dependent.

Materials and Methods

Subjects

Twenty healthy men (mean ± SEM age: 24.1 ± 0.8 years, age range: 18 to 33 years) and 20 healthy women (mean ± SEM age: 23.7 ± 0.7 years, age range: 19 to 30 years) participated in the study. Nineteen men and 19 women described themselves as right-handed, while one man and one woman were left-handed. None of the subjects had any pain complaints or previous injuries that interfered with normal somatosensory functioning. Informed consent was obtained from all subjects before inclusion. The study followed the Helsinki Declaration and was approved by the local ethics committee (VN2008036).

Experimental Protocol

Subjects rested in a chair with an armrest. Tonic painful mechanical stimulation (the CS) was applied by a mechanical headband[28] which could be fastened on four probes around the skull (Fig 1).

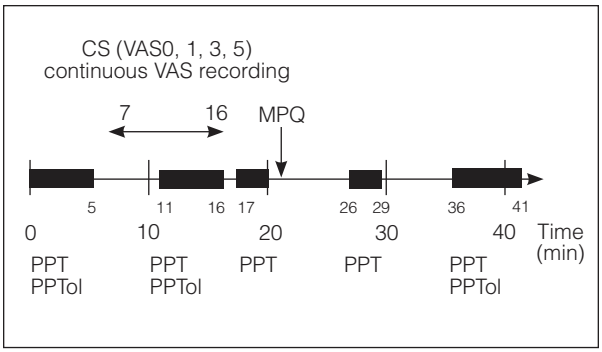

Fig 2 Overview of the study design. PPTs from right masseter and left forearm were measured at five time points in each session. PPTols were measured at three time points (before, during CS, and 20 minutes after the CS). The mechanical compression to the craniofacial region (conditioning stimulus: CS) was applied at four intensities for about 10 minutes from 7 to 16 minutes after the start of the study. The black square shows the period of PPT and PPTol recording. Subjects rated the pain intensity of the headband on a 0- to 10-cm electronic VAS. Subjects were also asked to fill in the MPQ after the mechanical compressive device was removed from the craniofacial region.

The pressure of these probes could be adjusted over time. The subjects were asked to rate the pain intensity continuously on a 0- to 10-cm electronic visual analog scale (VAS) by moving the indicator of the electronic VAS recorder with their right or left hand. The mechanical compression was applied at four target intensities (VAS0, VAS1, VAS3, VAS5) for about 10 minutes in four sessions; one intensity per one session. The four sessions were randomized and separated by at least 1 week. Pressure pain thresholds (PPTs) and pressure pain tolerance thresholds (PPTols) were used as test stimuli and were determined on the right masseter muscles (MAR) and left flexor carpi radialis muscle (forearm) with a pressure algometer (Somedic). The subjects kept the button of the pressure algometer in their right hand. The PPT was determined in triplicate and was recorded before (baseline), during CS, immediately after (within 60 seconds after the end of the PPT and PPTol recording during CS), 10 minutes after, and 20 minutes after the end of the CS (five time points). PPTol was recorded before (baseline), during CS, and 20 minutes after the end of the CS (three time points), and only once at each time point and site to avoid excessive stimulation and sensitization phenomena. The mechanical craniofacial compressive device was removed immediately after the PPT and PPTol recordings (Fig 2).

CS. The developed headband pressure model to induce experimental craniofacial pain with a specially designed compressive device (Fig 1) was used as the CS.[28] Briefly, the model is based on a mechanical craniofacial compressive device that can be fastened onto the four probes (left, occiput, right, forehead, 10-mm radius) around the skull with two centrally joined c-clamps offset from each other by 90 degrees. A strain gauge force transducer is attached on the four probes, and the VAS feedback from the subject can be used so that the pressure can be adjusted over time to maintain the pain intensity at a given level (target level). In this study, the device was gradually and continuously tightened until the participants scored their instantaneous pain at 1, 3, or 5 on the 0 to 10 electronic VAS (VAS1, 3, 5). In the control session (VAS0), the compressive device was just placed on the head of the subjects for about 10 minutes without tightening the clamp screws. The applied forces on the four probes were recorded in newtons (N).

Pain Ratings. Subjects continuously rated the pain intensity on a 0 to 10 electronic VAS (0 = no pain, 10 = worst imaginable pain) by moving the indicator of the electronic VAS recorder with their right or the left hand. The ratings were sampled and stored on a computer every 5 seconds from the start of the CS until the pain ratings returned to zero. The continuous VAS ratings and VAS peak pain values were used for further analysis.

Pain is not a simple, pure sensation varying only in intensity. The McGill Pain Questionnaire (MPQ)[31] is based on the concept that pain has many qualities including both evaluative and affective components. Subjects were asked to complete the English[31] or Danish[32] MPQ after the removal of the mechanical compressive device to obtain a qualitative description of the mechanically induced pain. The pain rating indices (PRI) for the different dimensions of pain (sensory, affective, evaluative, miscellaneous, and total) were calculated and used for further analysis.

Test Stimulus. PPT and PPTol were recorded on the MAR and subsequently left forearm by a pressure algometer as the test stimuli. The PPT measurement was followed by the PPTol measurement.

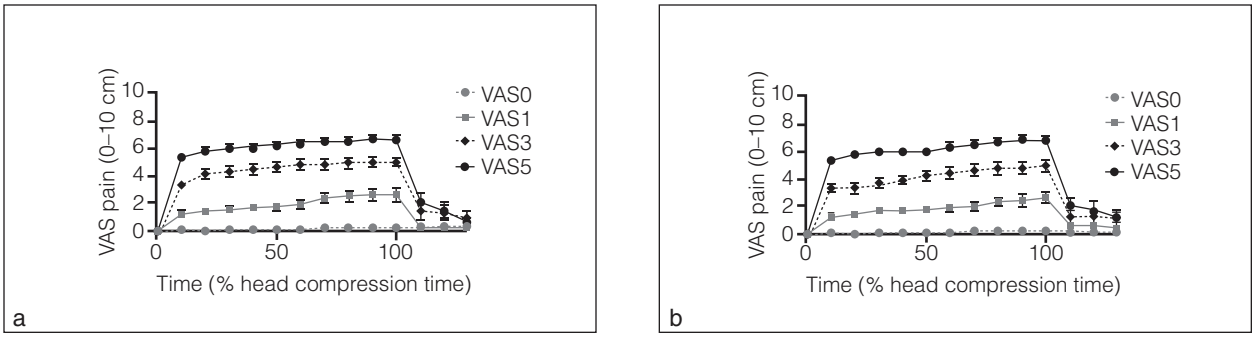

Fig 3 Continuous VAS ratings of pain intensity (mean ± SEM) during head compression in the different sessions (VAS0, 1, 3, 5) for *(a)* men (n = 20) and *(b)* women (n = 20). The positioning of the compressive device on the head did not elicit pain in any of the subjects and sessions before the application of the compression. The device was gradually and continuously tightened until the subject rated the target pain intensity on the VAS (1, 3, 5). Although the tightening of the compression was stopped as soon as the pain intensity reached the target level on the VAS (1, 3, 5), the pain intensity continued to increase gradually for the duration of the compression.

Measurements always followed this sequence: first, PPT MAR; second, PPT forearm; third, PPTol MAR; fourth, PPTol forearm. The PPT was defined as the amount of pressure (kPa) that the subjects first perceived to be painful, and the PPTol was defined as the most painful pressure (kPa) the subject could tolerate. The algometer probe (1 cm^2 area) was applied with a constant application rate of 30 kPa/s.[23] The subjects had the algometer stop button in their right hand and pushed the button to stop the pressure stimulation when the threshold was reached. The PPT measurements at each location were repeated three times with about 1 minute in between (for the MAR or forearm, respectively), and the average value was used for further analysis. PPTol was measured only once at each time point. PPT was recorded at five time points and PPTol was measured at three time points.

Statistical Analysis

The VAS peak pain values, the forces applied by the compressive device (mean values of the four probes), and the PRI for the different dimension of pain (sensory, affective, evaluative, miscellaneous, and total) were analyzed with mixed two-way ANOVA models with gender as between-group factor and target levels of CS (VAS0, 1, 3, 5) as the repeated factor. Absolute PPT values and PPTol values at baseline were analyzed by three-way ANOVA models: gender as between-group factor and assessment site (masseter/forearm) and intensity of CS (VAS0, 1, 3, 5) as repeated factors. In order to account for baseline differences between the four repeated sessions, assessment site and gender, the PPT values and PPTol values were normalized to the baseline value and were analyzed in a four-way ANOVA model with gender as the between-group factor and assessment site, intensity of CS and time (baseline, during CS, immediately after, 10 minutes after, and 20 minutes after the CS) as the repeated measures. The ANOVAs were followed by post-hoc Tukey-Kramer tests to compensate for multiple comparisons. The subjects who showed more than 10% relative increases in PPT values (ie, inhibitory CPM) were defined as responders and the number of responders was analyzed with the chi-square (χ^2) test. The correlations between the relative changes of PPT during CS and the VAS peak pain values from all sessions (correlation coefficient; R) were calculated by means of a least-squares regression analysis at each assessment site. Data from all subjects were incorporated into the analysis. All data are presented as mean values and standard errors of the mean (SEM). The level of significance was set at $P < .05$.

Results

Pain Ratings

Continuous VAS ratings of pain intensity (mean ± SEM) during head compression in the different sessions (VAS0, 1, 3, 5) for the men (n = 20) and women (n = 20) are shown in Fig 3. The positioning of the compressive device on the head did not elicit pain in any of the subjects and sessions before the application of the compression. The device was then gradually and continuously tightened until the subject rated the target pain intensity on the VAS (1, 3, or 5). The compressive device triggered craniofacial pain in all subjects. The tonic moderately severe craniofacial pain was reported as dull, bilateral, and similar to a strong headache consistent with the quality of

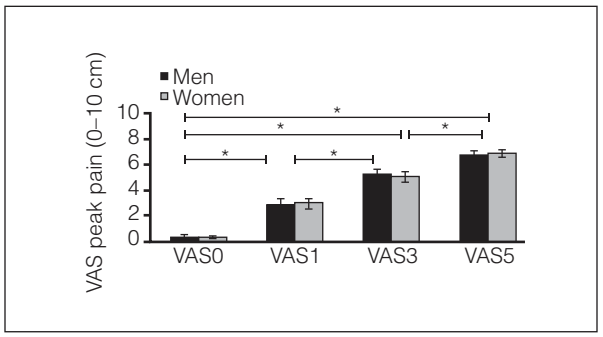

Fig 4a The VAS peak pain values (mean ± SEM) in the different sessions (VAS0, 1, 3, 5) reported by men (n = 20) and women (n = 20). There were no significant gender differences. *P < .001 versus other intensity of CS. There were significant differences between all sessions (VAS5 > VAS3 > VAS1 > VAS0).

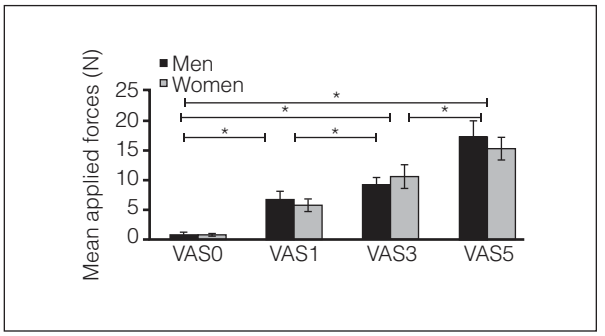

Fig 4b The applied forces of compressive device (mean values from four points; mean ± SEM) in the different sessions (VAS0, 1, 3, 5) to men (n = 20) and women (n = 20). There were no significant gender differences. *P < .05 versus other intensity of CS. There were significant differences between all sessions (VAS5 > VAS3 > VAS1 > VAS0).

Table 1 Applied Forces of Compressive Device (Newtons [N])

Gender/session	Left	Occiput	Right	Forehead	Mean
Men (n = 20)					
VAS0	0.3 ± 0.1	0.4 ± 0.1	2.0 ± 0.3	0.4 ± 0.2	0.8 ± 0.1
VAS1	3.5 ± 1.6	6.5 ± 1.2	11.8 ± 2.6	4.9 ± 0.9	6.6 ± 1.4
VAS3	5.6 ± 1.3	8.1 ± 1.5	14.7 ± 1.7	8.9 ± 1.3	9.3 ± 1.0
VAS5	12.0 ± 3.0	16.4 ± 2.8	22.1 ± 2.9	19.9 ± 2.9	17.6 ± 2.2
Women (n = 20)					
VAS0	0.2 ± 0.1	0.7 ± 0.2	1.7 ± 0.3	0.3 ± 0.1	0.7 ± 0.1
VAS1	3.8 ± 1.0	5.6 ± 1.5	8.0 ± 1.0	5.0 ± 1.5	5.6 ± 1.0
VAS3	6.1 ± 1.3	10.4 ± 2.2	15.1 ± 3.3	10.4 ± 2.8	10.5 ± 1.9
VAS5	12.4 ± 2.2	14.7 ± 2.9	21.2 ± 2.7	13.1 ± 2.0	15.3 ± 1.9

CTTH.[33] Although the tightening of the compression was stopped as soon as the pain intensity reached the target level on the VAS (1, 3, or 5), the pain intensity continued to increase gradually for the duration of the compression.

The ANOVA showed that the VAS peak pain values were significantly dependent on the intensity of the CS (F = 255.000, degrees of freedom: df = 3, P < .001) but not gender (F = .001, df = 1, P = .970). As expected, the VAS peak pain values were significantly highest in the session which targeted VAS5 compared to all other targeted VAS levels (P < .001). There were significant differences between all sessions (VAS5 > VAS3 > VAS1 > VAS0, P < .001) (Fig 4a).

The forces applied by the compressive device in order to obtain the different target VAS levels are shown in Table 1. The ANOVA showed that the mean forces of the four probes were significantly dependent on the intensity of the CS (F = 57.717, df = 3, P < .001) but not gender (F = .164, df = 1, P = .687). As expected, the mean values of applied forces were significantly highest in the session that targeted VAS5 compared to all other targeted VAS levels (P < .001). There were significant differences between all sessions (VAS5 > VAS3 > VAS1 > VAS0, P < .05) (Fig 4b).

The pain rating indices of the sensory [PRI(S)], affective [PRI(A)], evaluative [PRI(E)], miscellaneous [PRI(M)], and total [PRI(T)] dimension of pain after mechanical compression are shown in Table 2. The ANOVA showed that the [PRI(T)] induced by mechanical compression was significantly dependent on the intensity of the CS (F = 72.576, df = 3, P < .001) but not on gender (F = 2.363, df = 1, P = .133). As expected, the [PRI(T)] was significantly highest in the session that targeted VAS5 compared to all

Table 2 Mean PRI Values for the Different Dimensions of Pain According to MPQ

Gender/session	Sensory	Affective	Evaluative	Miscellaneous	Total
Men (n = 20)					
VAS0	3.15 ± 1.13	0.20 ± 0.16	0.40 ± 0.17	0.65 ± 0.42	4.40 ± 1.61
VAS1	11.55 ± 1.21	1.80 ± 0.43	1.35 ± 0.23	3.50 ± 0.71	18.20 ± 2.18
VAS3	14.35 ± 1.38	2.80 ± 0.53	2.25 ± 0.37	5.20 ± 0.80	24.60 ± 2.34
VAS5	18.05 ± 1.69**	4.65 ± 0.81**	2.20 ± 0.37**	6.30 ± 0.84**	31.20 ± 3.11*
Women (n = 20)					
VAS0	2.25 ± 0.98	0.25 ± 0.20	0.20 ± 0.09	0.85 ± 0.59	3.55 ± 1.63
VAS1	9.65 ± 1.30	1.70 ± 0.50	1.25 ± 0.20	2.20 ± 0.61	14.80 ± 2.19
VAS3	12.00 ± 1.54	3.20 ± 0.68	1.80 ± 0.29	3.55 ± 0.78	20.55 ± 2.59
VAS5	13.40 ± 1.32**	3.05 ± 0.72**	2.35 ± 0.32**	4.65 ± 0.91**	23.45 ± 2.74*

*Indicates significant difference between VAS5 and VAS0, 1, 3 ($P < .05$).
**Indicates significant difference between VAS5 and VAS0, 1 ($P < .001$).

other targeted VAS levels ($P < .05$). The ANOVA also showed that the [PRI(S)], [PRI(A)], [PRI(E)], and [PRI(M)] were significantly dependent on the intensity of the CS (F = 66.169, df = 3, $P < .001$; F = 28.004, df = 3, $P < .001$; F = 26.210, df = 3, $P < .001$; F = 29.978, df = 3, $P < .001$; [PRI(S)], [PRI(A)], [PRI(E)], and [PRI(M)], respectively) but not on gender (F = 2.831, df = 1, $P = .101$; F = .288, df = 1, $P = .595$; F = .386, df = 1, $P = .538$; F = 1.960, df = 1, $P = .170$; [PRI(S)], [PRI(A)], [PRI(E)], and [PRI(M)], respectively). Again as expected, the [PRI(S)], [PRI(A)], [PRI(E)], and [PRI(M)] were significantly highest in the session that targeted VAS5 compared to the sessions that targeted VAS levels of 0 and 1 ($P < .001$) (see Table 2).

Test Stimulus

Baseline Values. The ANOVA analysis revealed an effect of gender (F = 5.327, df = 1, $P = .027$) on PPT values with significantly higher PPT in men (372.1 ± 20.5 kPa) than women (302.2 ± 12.7 kPa) ($P = .027$). There were significant differences between assessment sites (F = 360.605, df = 1, $P < .001$), with significantly higher PPT at the forearm (477.3 ± 17.4 kPa) compared to MAR (197.0 ± 6.9 kPa) ($P = .001$). Finally, there were significant differences between sessions (F = 4.577, df = 3, $P = .005$), with significantly higher PPT at the VAS1 session (392.2 ± 30.8 kPa) compared to the VAS5 session (297.1 ± 19.5 kPa) ($P = .004$) (VAS0 session: 317.9 ± 20.9 kPa and VAS3 session: 341.4 ± 24.1 kPa). A normalization of the PPT values to baseline recordings was performed for direct comparison of the effects of intensity, assessment site, and gender on CPM-induced threshold changes.

Also for PPTol values, the ANOVAs indicated significant differences between gender (F = 6.716, df = 1, $P = .013$) with significantly higher PPTol in men (710.1 ± 35.8 kPa) than women (542.9 ± 23.6 kPa) ($P = .014$). There were significant differences between assessment sites (F = 291.225, df = 1, $P < .001$), with significantly higher PPTol at the forearm (900.6 ± 29.1 kPa) compared to MAR (352.3 ± 11.6 kPa) ($P = .001$). Again for the PPTol values, there were significant differences between sessions (F = 4.536, df = 3, $P = .005$), with significantly higher PPTol at the VAS1 session (683.8 ± 47.4 kPa) compared to the VAS5 session (579.7 ± 39.7 kPa) ($P = .002$) (VAS0 session: 622.9 ± 43.9 kPa and VAS3 session: 619.6 ± 43.9 kPa). Thus, the PPTol values were also normalized to directly compare the effects of CPM.

Normalized Values. ANOVAs on normalized PPT values indicated no main effects of gender (F = .517, df = 1, $P = .476$) or assessment site (F = 4.092, df = 1, $P = .0502$), but a significant intensity (F = 6.279, df = 3, $P < .001$) and time (F = 44.139, df = 4, $P < .001$) effect with a significant session and time interaction (F = 11.586, df = 12, $P < .001$). Although the ANOVAs showed that the effect of assessment site was close to the significant level ($P = .0502$), none of the interaction with assessment site indicated a significant difference. Post-hoc tests revealed that the normalized PPT values at VAS5 were significantly larger than VAS0 ($P = .009$) and VAS1 ($P < .001$). Post-hoc tests also showed that the normalized PPT significantly increased during the CS ($P < .001$) and immediately after the CS ($P < .001$) than baseline values. In the following, the increases are the mean values for the two assessment sites and two genders. The session and time interaction showed that the

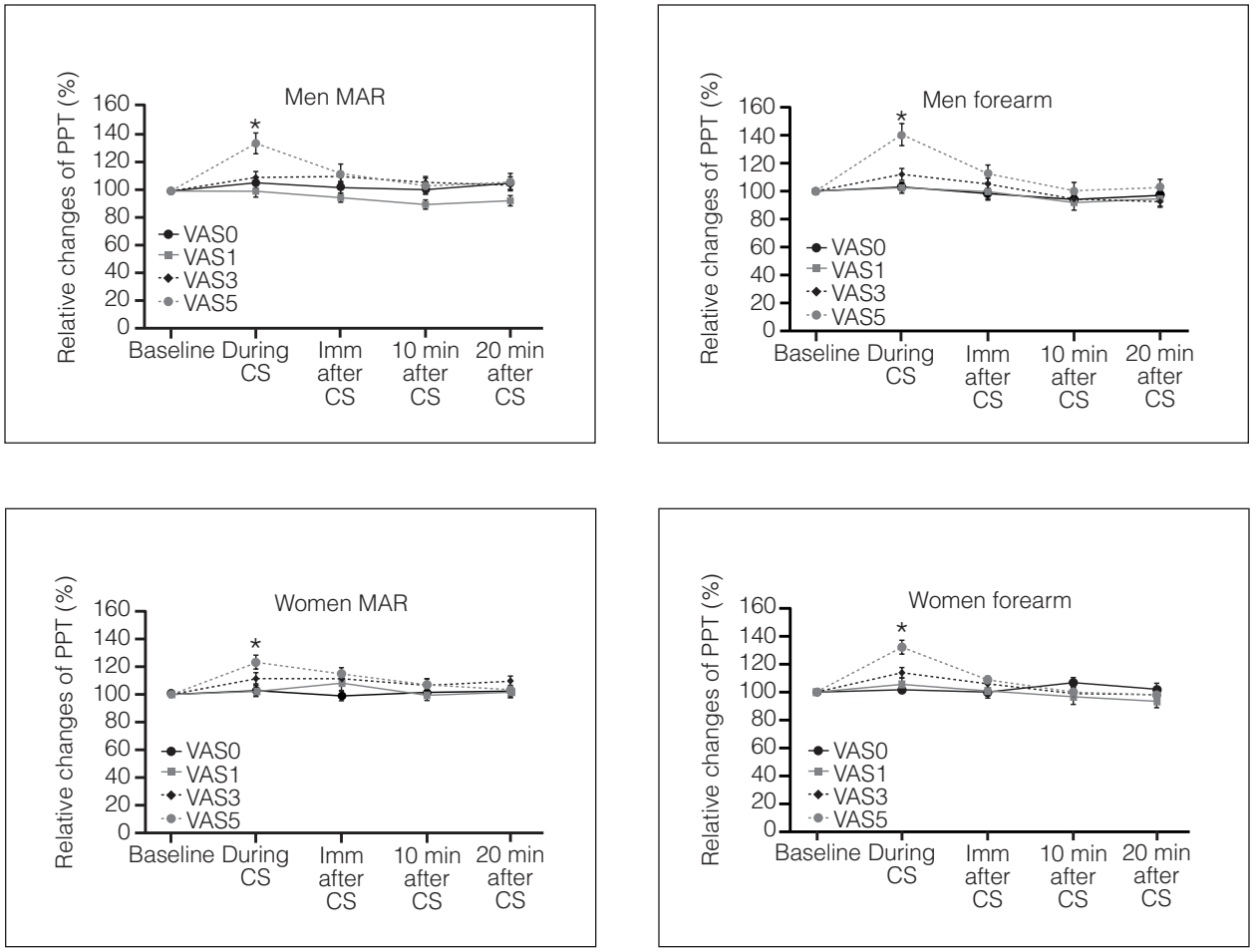

Fig 5 Relative changes of the PPT values (%, mean ± SEM) assessed at MAR and forearm at five time points in response to the CS at different intensities (VAS0, 1, 3, 5) in men (n = 20) and women (n = 20). *Indicates significant increase ($P < .001$) of normalized PPT values in VAS5 compared to all other intensities of the CS during the application of the CS (overall effect from four-way ANOVA and post-hoc tests).

session with the most painful CS (VAS5) was associated with the significantly highest PPT increases (32.6% ± 3.3%) compared to all other levels of the CS (VAS0: 3.3% ± 1.6%, VAS1: 2.5% ± 2.1%, VAS3: 11.8% ± 2.0%) during CS ($P < .001$) (Fig 5). There were significantly higher PPT increases for VAS5 (12.2% ± 2.6%) as compared to VAS0 (–0.1% ± 1.7%) and VAS1 (0.9% ± 2.5%) immediately after the CS ($P < .001$). The second-most painful CS (VAS3) had significantly higher normalized PPT values than VAS1 during CS ($P = .016$).

The ANOVAs of the normalized PPTol values indicated no main effects of gender (F = 1.899, df = 1, $P = .176$) or assessment site (F = 2.190, df = 1, $P = .147$), but a significant intensity (F = 6.106, df = 3, $P < .001$) and time (F = 8.656, df = 2, $P < .001$) effect with a significant session and time interaction (F = 4.699, df = 6, $P < .001$). Post-hoc tests revealed that the normalized PPTol values were significantly higher during CS at VAS5 (11.2% ± 2.8%) compared to VAS0 (–2.2% ± 2.5%) and VAS1 (–4.8% ± 2.2%) ($P < .001$), but not significantly higher compared to VAS3 (4.3% ± 2.4%) ($P = .331$) (Fig 6).

CPM Responders. The number and frequency of responders are shown in Table 3. There were significant differences in the number of responders between the sessions for both genders and both assessment sites (χ^2 test; $\chi^2 = 17.050$, df = 3, $P < .001$; $\chi^2 = 13.200$, df = 3, $P = .004$; $\chi^2 = 11.700$, df = 3, $P = .008$; $\chi^2 = 19.550$, df = 3, $P < .001$; men, women, MAR, and forearm, respectively).

Correlation Between Relative Changes of PPT and Intensity of the CS. The VAS peak pain values versus relative PPT changes obtained from 40 subjects in all sessions at forearm and MAR are shown in Fig 7. A positive and significant correlation was detected between the relative PPT changes and the VAS peak pain values at the forearm ($R = 0.456$, $P < .001$) and at MAR ($R = 0.333$, $P < .001$).

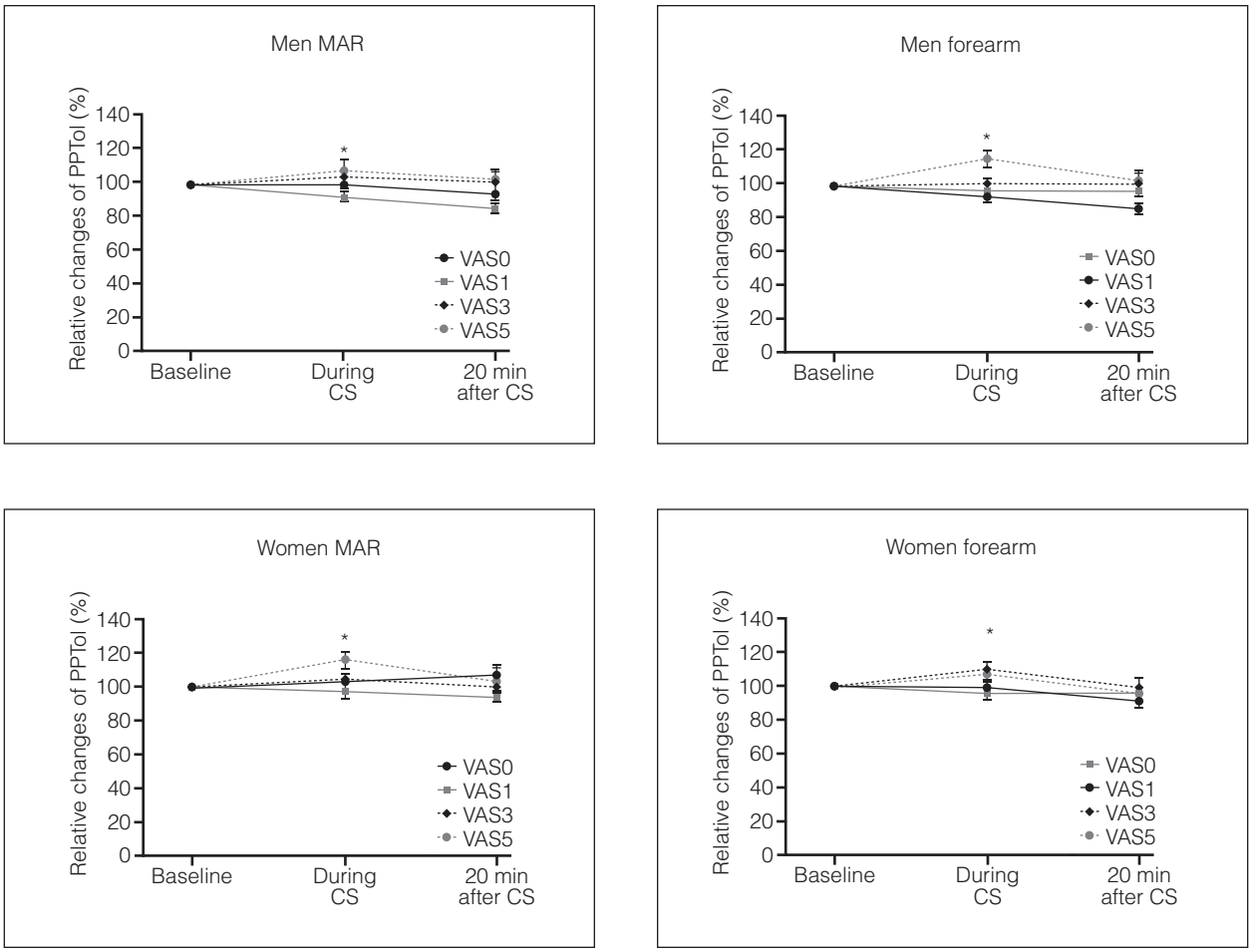

Fig 6 Relative changes of the PPTol values (%, mean ± SEM) assessed at MAR and forearm at three time points in response to the CS at different intensities (VAS0, 1, 3, 5) in men (n = 20) and women (n = 20). *Indicates significant increase ($P < .001$) of normalized PPTol values in VAS5 compared to VAS0 and VAS1 during the application of the CS (overall effect from four-way ANOVA and post-hoc tests).

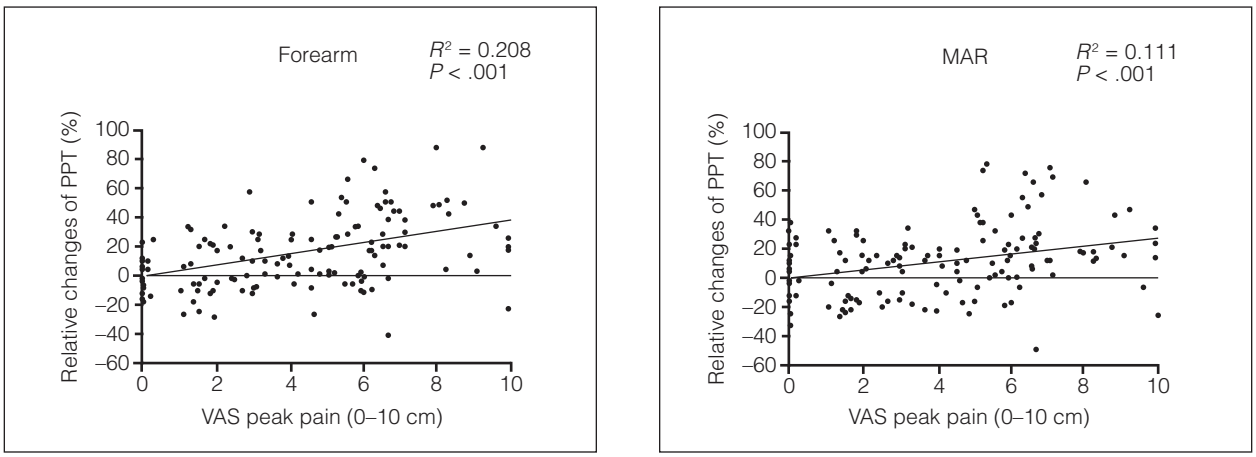

Fig 7 Correlation between the relative PPT changes and the VAS peak pain values at *(left)* the forearm and *(right)* MAR, combined data from all subjects in all sessions. Linear regression lines are fitted to the data. Pearson's correlation tests indicated significant associations between the two variables ($R = 0.456$, $P < .001$; $R = 0.333$, $P < .001$; at the forearm and MAR, respectively).

Discussion

This study showed that CPM evoked by mechanical painful stimulation of the craniofacial region is intensity-dependent but not assessment site– or gender-dependent. A systematic and standardized paradigm was applied to test CPM and, in accordance with the recent concept from this laboratory,[27,28] robust inhibitory effects were detected.

Methodological Concerns

Various methodologies have been developed and described to evoke and characterize CPM.[34] In this study, about 25% of the subjects had CPM effects in the control session (VAS0) with the compressive device. Previously, an animal study has shown that non-noxious mechanical or electrical stimuli applied to the craniofacial region as well as the spinal region could reduce the responses of trigeminal subnucleus caudalis nociceptive neurons to craniofacial noxious stimuli.[35] The nonpainful mechanical (tactile) stimulation simply due to the weight and placement of the device may have triggered this phenomenon.[29] Alternatively, placebo effects or anticipation could have played a role in the modest CPM effects of the control session. PPT and PPTol tend to give large and robust CPM responses,[21,23,27] and hence they were used in the present study. To compare the different sessions, the data were normalized. Both the CS and test stimulus were adequately standardized to support the suggested conclusions.

Intensity Effects of CPM

Mechanical CS with intensities of four target levels (VAS0 as control, VAS1 and VAS3 as mild pain, and VAS5 as moderate pain) were applied to investigate systematically the intensity effects of CPM in the craniofacial region. Although the pain intensity of the compression increased gradually and the VAS peak pain values of the compression were higher than the initial target level, the compressive device enabled the investigators to apply significantly different pain levels between all sessions, reflecting the applied forces of the compressive device. It should be noted that there were no gender differences in the amount of applied forces required to reach the different target levels on the VAS and in the PRI indices derived from the MPQ for the quality of the mechanically evoked craniofacial pain (see below). This is the first human study to the authors' knowledge that applied different CS intensities to the craniofacial region to trigger CPM.

Table 3 Number and Frequency (%) of Responders

	Men (n = 20)		Women (n = 20)	
Session	MAR	Forearm	MAR	Forearm
VAS0	5 (25)	5 (25)	8 (40)	2 (10)
VAS1	7 (35)	7 (35)	8 (40)	8 (40)
VAS3	12 (60)	11 (55)	12 (60)	10 (50)
VAS5	17 (85)	17 (85)	15 (75)	17 (85)

The subjects who showed more than 10% relative increases in PPT values (ie, inhibitory CPM) were defined as responders.

The effects of CPM are known to differ, depending on the magnitude and nature of the CS and stimulated nerve fibers.[12,30,34] Various experimental pain modalities (thermal,[20,36–39] electrical,[40] and chemical[41–43]) have been applied to many body regions to estimate CPM effects in healthy subjects. According to a recent review, the approximated median magnitude of the CPM effect was 29%.[34] In the present study, the craniofacial compressive device increased the pain threshold by 33% (overall effects from all subjects).

The current study showed that the largest CPM effect was induced by the most painful conditioning craniofacial pain at VAS5, followed by VAS3, VAS1, and VAS0, with significant differences in the magnitude of CPM effects. These findings indicate that the CPM effect is intensity-dependent in the craniofacial region in humans, consistent with previous findings in the spinal and craniofacial regions of animals[7,12,30,44] and in the spinal region of humans.[7,10,12,45,46] The significant differences in the number of responders between the sessions could also imply that the CPM effect was intensity-dependent.

This study has demonstrated significant differences in the magnitude of CPM effects between CS at VAS5 and VAS3 in PPT but not in PPTol. One possible reason why robust CPM effects could not be found in an intensity-dependent manner with PPTol is reduced sampling of PPTol compared to PPT, ie, PPTol was measured only once at each time point. Another considerable factor is that there might be bigger individual differences in PPTol compared to PPT.

Overall, the present findings are in accordance with previous reports[7,10,12,30,44–46] and furthermore clearly demonstrate that CPM evoked by mechanical stimulation of the craniofacial region is intensity-dependent in humans.

Assessment Site Effects in CPM

Hand dominancy is a factor considered for characterizing individual variations in sensitivity to pain.[47] However, laterality differences in experimental pain sensitivity have yielded inconsistent results.[48] Even so, the fact that two left-handed subjects participated in this study might have affected the experimental outcomes.

No significant differences in the CPM effects were found between segmental (craniofacial region) or extrasegmental (spinal region) application of the test stimulus, and so robust and widespread effects were apparent.

Initially, DNIC was defined as the inhibitory effects triggered by noxious CS applied to an area remote from the excitatory receptive field.[4,8] So far, the CPM effect evoked by the heterotopic CS applied to the spinal region has been examined and revealed in a large number of studies with human volunteers.[23,42,43,49] Subsequently, the CPM effect induced by homotopic CS has been reported. Graven-Nielsen et al[50] noted that there was no change in the pain intensity following homotopic noxious pressure stimulation, whereas heterotopic application caused CPM. Contrary to that report, Pud et al[24] showed that there were similar effects of CPM between heterotopic and homotopic sites. The discrepancies in the results among these reports suggest that, in addition to heterotopic CPM, homotopic CPM may also be explained by the differences in stimulus modalities used, testing regions, assessment methods, and sample sizes.

The CPM effect in the craniofacial region[13,38,39] has not received a lot of attention, especially for the effect of homotopic CS. Svensson et al[51] demonstrated that tonic painful stimulation of the ipsilateral MAR has a significant suppressive effect on a jaw inhibitory reflex. The latest report from this laboratory has also shown that pain applied to the craniofacial region evokes CPM at segmental (up to 23% increase) as well as extrasegmental (up to 39% increase) sites.[28] The result from the present study is consistent with these previous reports.

The MAR is innervated by the mandibular branch of the trigeminal nerve (V3), and the flexor carpi radialis muscle is innervated by the median nerve (C5-Th1). The CS was applied to the craniofacial region, including the temporalis muscle, which is innervated by the mandibular branch of the trigeminal nerve (V3); the ventral part (forehead), which is innervated by the ophthalmic branch of the trigeminal nerve (V1); and the dorsal part (occiput), which is innervated by the second cervical nerve (C2). The convergence of afferent inputs from skin, viscera, and muscles has been reported in spinal dorsal horn neurons.[52] Furthermore, convergence from trigeminal and cervical afferent inputs (cutaneous, musculoskeletal [temporalis, masseter, neck muscle]) has been demonstrated in nociceptive neurons of the first cervical (C1) dorsal horn and trigeminal subnucleus caudalis.[5,53,54] The nociceptive inputs from the test stimuli applied to the MAR and flexor carpi radialis muscle will lead to activation of nociceptive-specific and wide-dynamic-range (convergent) neurons in the trigeminal subnucleus caudalis or spinal dorsal horn. The nociceptive input from the mechanical headband would also result in the activation of the corresponding segmental pools of both these types of neurons in the trigeminal subnucleus caudalis. These signals might reach the other brain centers involving the caudal-most part of the medulla, including the subnucleus reticularis dorsalis, and could access descending pathways in the dorsolateral funiculi.[7] Accordingly, CPM may cause inhibition of activity in nociceptive neurons in the trigeminal subnucleus caudalis[5,6] or spinal dorsal horn[4] to the same degree, respectively, supporting the human data in the present study.

Overall, the results from this study show that CPM is triggered by the segmental application of the CS and imply that the magnitude of CPM is not affected, even if the CS is applied segmentally instead of extrasegmentally. This was further supported by the correlations between relative changes (increases) in PPT values at both the forearm and MAR and the perceived intensity of the CS. Although the correlation at MAR was relatively weak compared to forearm, the site of measurement (extrasegmental or segmental) might have played a role regarding the weakness of this relation.

Gender Effects in CPM

This study showed no CPM gender differences, in agreement with some other studies.[24,25,27,45,55,56] However, other studies have found gender differences in the CPM.[21–23,49,57] Granot et al[46] showed that the CPM effect of thermal CS was greater in men than women. It has also been reported that women have greater CPM in the ovulatory phase, suggesting hormonal influences on CPM.[45,58] Hormonal influences on CPM could possibly contribute to the overall gender differences in pain perception, as well as the CPM evaluation with muscle pain, viz significantly lower PPT and PPTol values in women at various muscle sites, which were also demonstrated in the present study and in a previous study.[23] Menstrual cycle could also be an important factor

in the pain perception of women. Although the data on the menstrual cycle in women were not recorded in this study, this information would be valuable in future studies for elucidation of gender differences.

Clinical Implications and Conclusions

The craniofacial compressive device triggered a tonic pain similar to CTTH and made it possible to apply the target pain intensity over time. So far, it has been impossible to apply tonic mechanical pain in the craniofacial region in humans. The most important aspects of using this new model (mechanical stimulation to the craniofacial region) and applying these characteristics are that it would be helpful in exploring the endogenous pain modulatory mechanism in the craniofacial region, especially for musculoskeletal pain conditions such as TMD or CTTH. The findings of this study could also lead to prospective clinical applications.

In conclusion, this study showed that CPM evoked by mechanical stimulation of the craniofacial region is intensity-dependent but not assessment site (segmental [craniofacial]; extrasegmental [spinal])– or gender-dependent. Mechanical CS of the craniofacial region may be useful to test deficiencies or alterations in endogenous pain modulatory systems in conditions such as TMD or CTTH, and may be used for pharmacological screening of new compounds expected to interact with CPM.

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