Conditioned pain modulation (CPM)

experimental studies in the craniofacial region in healthy humans

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Conditioned pain modulation (CPM)

: experimental studies in the craniofacial region in healthy humans

Ph.D. thesis

by

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PREFACE

The present Ph.D. thesis is partly based on three research papers below, which are referred to in the text by Roman numerals. The studies have been accomplished at Experimental and Clinical Orofacial Pain Laboratory, Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark, in the period from 2009 to 2011.

I. Oono Y, Wang K, Svensson P, Arendt-Nielsen L. Conditioned pain modulation evoked by different intensities of mechanical stimuli applied to the craniofacial region in healthy men and women. Journal of Orofacial Pain 2011;25:364-375.

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II. Oono Y, Wang K, Svensson P, Arendt-Nielsen L. Conditioned pain modulation evoked by a mechanical craniofacial stimulus is not influenced by nociceptive stimulation of the temporomandibular joint. Journal of Orofacial Pain (accepted for publication, 2011).

III. Oono Y, Nie H, Matos RL, Wang K, Arendt-Nielsen L. The inter- and intra-individual variance in descending pain modulation evoked by different conditioning stimuli in healthy men. Scandinavian Journal of Pain 2011;2:162-169.

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Acknowledgements

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Yuka Oono; 31 July 2011, Aalborg, Denmark.

List of abbreviations:

C2: Second cervical nerve

C5: Fifth cervical nerve

CPM: Conditioned pain modulation

CPP: Cold pressor pain

CS: Conditioning stimulus

CTTH: Chronic tension-type headache

CV: Coefficient of variation

DNIC: Diffuse noxious inhibitory controls

Inter-CV: Inter-individual coefficient of variation

Intra-CV: Intra-individual coefficient of variation

L4: Fourth lumbar nerve

MAR: Right masseter muscles

NS: Nociceptive specific

PPT: Pressure pain thresholds

PPTol: Pressure pain tolerance thresholds

QST: Quantitative sensory testing

S1: First sacral nerve

SRD: Subnucleus reticularis dorsalis

TMJ: Temporomandibular joint

TMD: Temporomandibular disorders

TA: Tibialis anterior

Th1: First thoracic nerve

Th2: Second thoracic nerve

TS: Test stimulus

V: Trigeminal nerve (fifth cranial nerve)

V1: Ophthalmic (first) branch of the trigeminal nerve

V2: Maxillary (second) branch of the trigeminal nerve

V3: Mandibular (third) branch of the trigeminal nerve

Vc: Trigeminal subnucleus caudalis

VAS: Visual analogue scale

WDR: Wide dynamic range

1. INTRODUCTION

1.1. Background

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk, 1994)”.

Concerning an endogenous “pain inhibits pain” phenomenon, there is evidence that wide dynamic range (WDR) neurons (convergent neurons) are inhibited by nociceptive stimuli applied to areas of the body remote from the excitatory receptive fields (Le Bars, 2002). These phenomena are termed “diffuse noxious inhibitory controls (DNIC)” (Le Bars et al., 1979a,b). DNIC are triggered by the activities of most WDR and some nociceptive specific (NS) neurons in the spinal dorsal horn and trigeminal spinal tract nucleus, which are powerfully inhibited by stimulation of Aδ- and C-nociceptors in animals and humans (Le Bars, 2002). DNIC involve a supraspinal loop through the subnucleus reticularis dorsalis (SRD) in the medulla (Villanueva et al., 1988) and are observed in the intact but not in the spinal animal (Le Bars, 2002). It has recently been suggested that the DNIC-like effects in humans should be termed “Conditioned Pain Modulation (CPM)” (Yarnitsky et al., 2010).

Though there are many reports of CPM in the spinal region (Price and McHaffie, 1988; Willer et al., 1989; De Broucker et al., 1990; Le Bars et al., 1992), it has only been minimally investigated in the craniofacial region (Ellrich and Treede, 1998).

Recently, a systematic model for inducing experimentally evoked tonic head pain has been developed (Sowman et al., 2011). The model is a mechanical craniofacial compressive device which produces pain similar to chronic tension-type headache (CTTH) and the device enables systematic testing of CPM in healthy subjects (Sowman et al., 2011). A pain model with repetitive electrical stimulation of the temporomandibular joint (TMJ) has also been developed (Ayesh et al., 2007). This method is reliable and allows the generation of a constant painful input to the TMJ without tissue damage.

There is a clear relationship between the intensity of the conditioning stimulus (CS) and the strength of the resultant CPM (Le Bars et al., 1992; Villanueva and Le Bars, 1995). However, it is unclear whether CPM effects in the craniofacial region are intensity dependent in human.

DNIC, i.e. CPM, has initially been defined and tested with the CS applied to the extrasegmental region from the excitatory receptive fields (Le Bars et al., 1979a,b). Subsequently, the CPM effect with segmentally applied CS has been tested (Svensson et al., 1999a; Pud et al., 2005). Nevertheless, the interrelation between CPM effect and assessment sites has not yet been characterized.

Some of the recent animal and human experimental studies have shown that there are significant gender differences in the CPM responses (Staud et al., 2003; Ge et al., 2004; Serrao et al., 2004). However, other studies have failed to detect it (France and Suchowiecki, 1999; Baad-Hansen et al., 2005; Pud et al., 2005). The gender effect on the CPM is still unclear.

Therefore, one of the aims of this project was to investigate systematically whether 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 (study I).

There is growing evidence suggesting that CPM is attenuated in chronic pain patients suffering from temporomandibular disorders (TMD) (Maixner et al., 1995), fibromyalgia (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997), CTTH (Pielsticker et al., 2005), and migraine (Sandrini et al., 2006; Tommaso et al., 2007). Consideration of this fact has led us to propose the hypothesis that chronic craniofacial musculoskeletal pain conditions are associated with alterations in pain-modulatory processes reflected in CPM.

To test this hypothesis it was planned to evaluate whether experimental craniofacial pain (painful electrical stimulation of the TMJ) conditions reflect disturbed CPM mechanisms and the influence of gender on such CPM effects in the craniofacial region (study II).

The approximated median magnitude of the CPM effect is 29% (Pud et al., 2009). However, in this

report the data were derived from different test stimuli (TS) and CS applied to different assessment sites. Recent research (Yarnitsky et al., 2008) suggests that the evaluation of CPM may identify patients at risk of developing chronic pain. For further application of CPM as a diagnostic tool or for screening of analgesic compounds, the test-retest reliability and inter-individual variation in CPM should be determined.

Hence, it was also evaluated if there are significant differences for the subjects (inter-individual and intra-individual dependent) in inducing the CPM responses with different stimulus modalities at several assessment sites (study III).

The general hypotheses of the whole project are; 1) CPM evoked by tonic mechanical stimuli applied to the craniofacial region is intensity, assessment site and gender dependent, 2) experimental tonic craniofacial musculoskeletal pain triggers alterations in pain-modulatory processes, and 3) there are inter- and intra-individual variations in the CPM responses and this may vary with different techniques applied.

1.2. The aims of our own investigation

To reach the above goals, three experimental studies were performed (See Fig. 1).

The overall objectives of this project are:

1. To test if CPM evoked by tonic mechanical stimuli applied to the craniofacial region is intensity, assessment site and gender dependent.
2. To investigate the influence of experimental TMJ pain on CPM.
3. To evaluate the magnitude of CPM, and the inter- and intra-individual variation in CPM with different stimulus modalities.

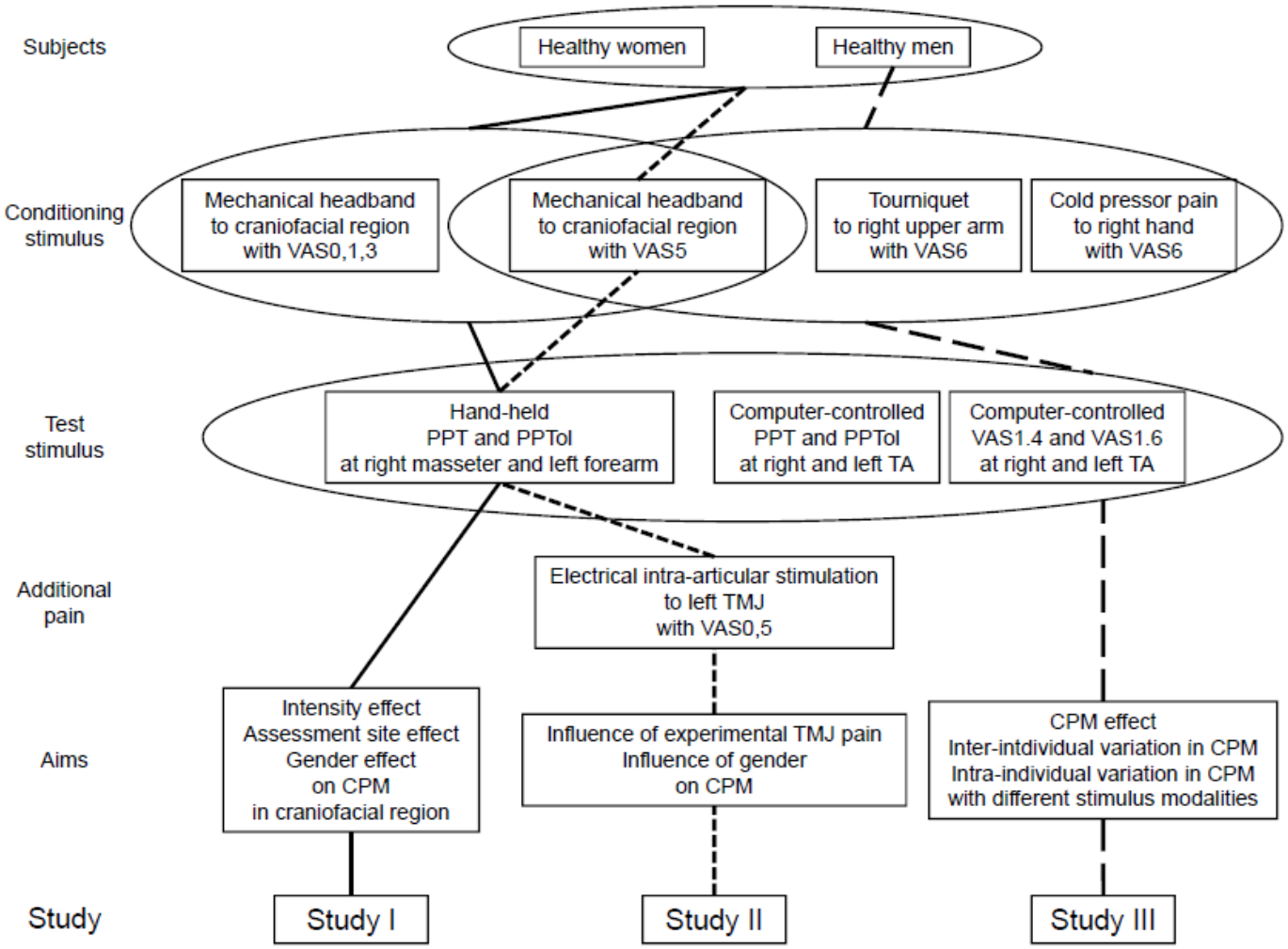

Figure 1. Diagram for experimental methodologies and aims in this project.

Headband: mechanical craniofacial compressive device, PPT: pressure pain thresholds, PPTol: pressure pain tolerance thresholds, VAS: visual analogue scale, TA: tibialis anterior, VAS1.4: pain intensity assessed on a VAS following 1.4 x PPT applied to TA, VAS1.6: pain intensity assessed on a VAS following 1.6 x PPT applied to TA, TMJ: temporomandibular joint, CPM: conditioned pain modulation. Solid line: study I, square dotted line: study II, long dashed line: study III.

2. EXPERIMENTAL PAIN MODELS IN CRANIOFACIAL REGION

2.1. Mechanical craniofacial pain

2.1.1. Nociceptive mechanism of mechanical craniofacial pain

In general, primary headache disorders tend to involve predominantly the ophthalmic (first) branch of the trigeminal nerve (V1) along with its physiological overlap with the high cervical input by way of the trigeminocervical complex (Bartsch and Goadsby, 2005). However, many primary headache disorders also involve the face, in effect the maxillary (second, V2) and mandibular (third, V3) branches of the trigeminal nerve (fifth cranial nerve: V) (Goadsby et al., 2009).

Cerebrovascular changes have been thought to be important for the initiation and maintenance of migraine and cluster-type headaches, although it is not clear that these changes play a significant role in tension-type headache (Moskowitz, 1990,1993; Connors, 1995; Strassman et al., 1996). Nevertheless, in all primary headaches, pain is perceived to come from within the cranium, and thus current theories suggest that activation of neural pathways that transmit input from the dura play an important role in headache (Strassman et al., 1996).

The first link in this neural pathway is the activation of unmyelinated (C) or thinly myelinated (Aδ) dural afferent fibers. Many dural afferent fibers appear to be polymodal nociceptors as they respond to noxious mechanical, thermal, and chemical stimuli applied to their receptive fields (Dostrovsky et al., 1991; Strassman et al., 1996; Bove and Moskowitz, 1997; Strassman and Raymond, 1999; Levy and Strassman, 2002a). The slowly adapting and graded response characteristics exhibited by dural afferent fibers to mechanical stimuli and the finding that they are commonly located in regions of the dura overlying meningeal blood vessels suggest that these fibers monitor information about cerebrovascular tone (Bove and Moskowitz, 1997; Levy and Strassman, 2002b). Mechanosensitivity in particular seems to be important in intracranial headaches as well as migraine (Levy and Strassman, 2002b).

2.1.2. Clinical craniofacial pain

The headache disorders are classified in the second edition of the International Classification of Headache Disorders by the Headache Classification Committee of the International Headache Society (Headache Classification Committee of the International Headache Society, 2004). The headache disorders are classified as being either primary, where the headache syndrome is itself the problem, or secondary, where the headache syndrome is driven by other pathological processes.

CTTH is a disorder evolving from episodic tension-type headache with daily or very frequent episodes of headache lasting minutes to days. The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, and it does not worsen with routine physical activity. There may be mild nausea, photophobia or phonophobia. Though the exact mechanisms of tension-type headache are not known, peripheral pain mechanisms are most likely to play a role in CTTH (Headache Classification Committee of the International Headache Society, 2004). Tension-type headaches, which are often associated with a feeling of muscle strain or spasm in the neck / shoulder or temporalis muscles and characterized by dull, aching, nonthrobbing pain that can be distributed unilaterally or bilaterally and referred to temporal, occipital, parietal, or frontal regions of the head, occur at a 50% higher rate in women (Taylor and Cleary 1989; Holroyd and Lipchik, 2000).

2.1.3. Experimental mechanical craniofacial pain model

Mechanical and cold headbands have been developed and have shown that craniofacial pain evoked by a mechanical or thermal headband may induce widespread CPM responses in healthy humans (Wang et al., 2010). The study was based on a compressive headband approach which had several limitations inherent in its mechanical design. These were mainly a result of the band design which limited the ability to direct and control forces. The irregular shape of the skull meant that pressure was applied unevenly around the skull and was directed primarily against prominent bony features.

Then the improved device, which can be fastened on 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, was developed (Sowman et al., 2011) (Fig. 2). A strain gauge force transducer is attached on the four probes and pressure can be adjusted over time using the visual analogue scale (VAS, 0-10 cm) feedback from the subject to maintain the pain intensity at a given level (target level). The tonic moderately-severe craniofacial pain triggered by this device was reported as dull, bilateral and like a strong headache similar to the quality of CTTH (Bigal and Lipton, 2005). The nociceptive input from the mechanical headband would be conducted via peripheral C-fibers including the temporalis muscle innervated by the mandibular branch of the trigeminal nerve (V3), the ventral part innervated by the ophthalmic branch of the trigeminal nerve (V1) and the dorsal part innervated by the second cervical nerve (C2). The device is a standardized mechanical tonic pain model for experimental evoking of tonic craniofacial pain and associated with robust CPM effects (Sowman et al., 2011). Therefore, we applied this device in studies I, II and III.

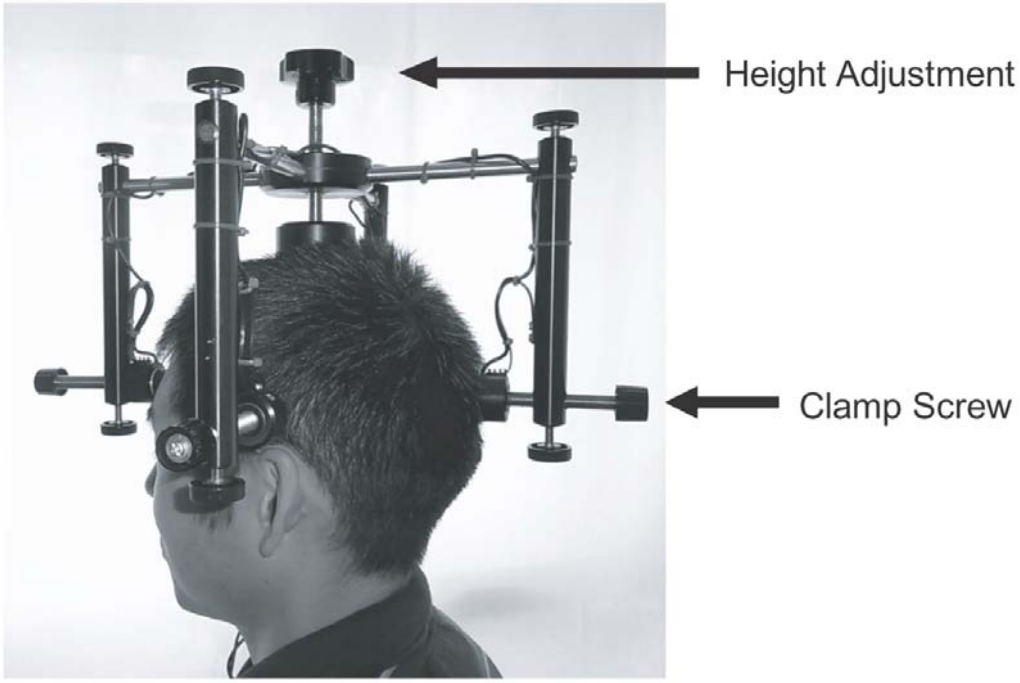

Figure 2. The compressive device for experimental craniofacial pain.

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.

2.2. Temporomandibular joint (TMJ) pain

2.2.1. Nociceptive mechanism of TMJ pain

The temporomandibular joint (TMJ) and masticatory muscles are supplied by Aδ- and C-fiber polymodal nociceptive afferents that may respond to a wide range of peripheral stimuli, including mechanical (e.g., heavy pressure) and algesic chemical (such as glutamate, hypertonic saline, capsaicin, and mustard oil) stimuli in TMJ and around muscles (Sessle, 2005; Cairns, 2007,2010). A noxious stimulus activates nociceptive Aδ- and C-fibers, which project to the trigeminal subnucleus caudalis (Vc), site for a critical brainstem relay in the TMJ-jaw muscle reflex pathway (Tsai et al., 1999). Although there is evidence of TMJ afferent projections to the superficial laminae of Vc (Capra, 1987; Hathaway et al., 1995), most Vc neurons that respond to TMJ stimulation are found in laminae V and VI (Broton et al., 1988). These input may project to higher levels of the brain (e.g., in the thalamus) or in the brain stem region such as reticular formation (Sessle, 2005).

2.2.2. Temporomandibular disorders (TMD)

Temporomandibular disorders (TMD) comprise a number of problems involving the structures of and around the TMJ, the masticatory musculature, or both (De Leeuw, 2008). Pain is one of the most common complaints associated with TMD and can be clinically expressed as masticatory muscle pain or as TMJ arthralgia (as in synovitis, capsulitis or osteoarthritis) (Benoliel and Sharav, 2008). Pain may occur spontaneously or may be associated with joint function and loading (e.g., during chewing, yawing or biting). TMD may also include symptoms of dysfunction (limitation of movement, interference during movement, internal derangements of the TMJ or locking of the joint). TMD pain may be, but is not necessarily, associated with such a dysfunction (De Laat, 2010).

Concerning diagnostic criteria of TMD, research diagnostic criteria (RDC-TMD) were established (Dworkin and LeResche, 1992) and translated into a clinical classification (Truelove et al., 1992). Three

subgroups (Myofascial pain (masticatory muscle pain); Anterior disc displacement; TMJ arthralgia, osteoarthritis and osteoarthrosis) have been distinguished and details can be accessed at the RDC-TMD website (http://www.rdc-tmdinternational.org).

2.2.3. Experimental TMJ pain model

When a cutaneous nerve is stimulated electrically, all three groups of cutaneous afferent fibers, i.e., Aβ-, Aδ- and C-fibers, are activated (Wagman and Price, 1969; Price and Wagman, 1970; Price et al., 1971; Gregor and Zimmermann, 1972; Menétrey et al., 1977), and the relative proportion of activation of individual fiber types depends on the stimulus intensity (Handwerker and Kobal, 1993). C-fibers have a higher activation threshold than Aδ-fibers.

Our group has also developed an experimental craniofacial pain model with repetitive electrical stimulation of the TMJ (Ayesh et al., 2007). Two unipolar needle electrodes were inserted into TMJ (Fig. 3). Then the experimental craniofacial pain was induced by repetitive electrical stimulation (0.5 ms duration, 5 Hz) to the TMJ to provide a constant painful input to the TMJ (Ayesh et al., 2007). This method is reliable and allows the generation of a constant painful input to the TMJ without tissue damage.

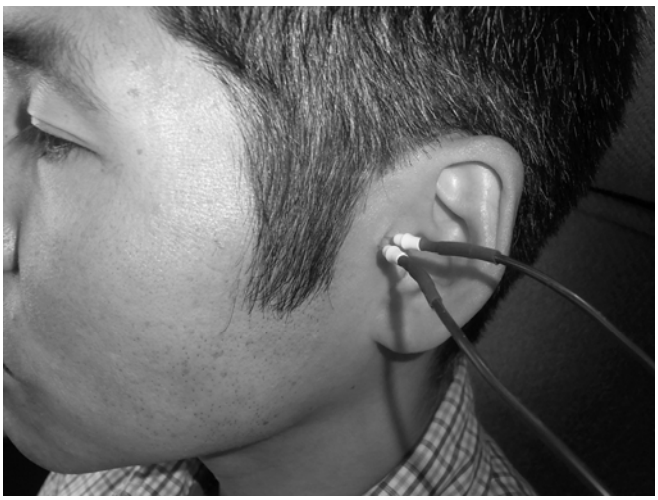

Figure 3. The experimental TMJ pain model.

Two unipolar needle electrodes were inserted into the left TMJ. Then the experimental TMJ pain was induced by repetitive electrical stimulation (0.5 ms duration, 5 Hz) to the TMJ.

3. CONDITIONED PAIN MODULATION (CPM)

Conditioned pain modulation (CPM) is the phenomenon through which the conditioning stimulus (CS) affects the test stimulus (TS) (Yarnitsky et al., 2010). This phenomenon reflects something that has been known in humans since ancient times, namely that one pain can mask another (Le Bars et al., 2001; Yarnitsky, 2010).

3.1. Methodological parameters

3.1.1. Test stimulus (TS)

To test CPM, various methodologies have been used (Pud et al., 2009) such as electrophysiological responses (e.g., somatosensory evoked brain potentials (Valeriani et al., 2005a,b; Oono et al., 2008), the spinal nociceptive flexion reflex (RIII reflex) (Willer et al., 1984; Serrao et al., 2004), blink reflex (Ellrich and Treede, 1998)) and pain thresholds (e.g., mechanical punctuate stimuli (Pud et al., 2005), pressure pain thresholds (Ge et al., 2004; Lautenbacher et al., 2008)).

The pressure pain threshold (PPT) is the measurement for testing of deep pain sensitivity, which is probably mediated through Aδ- or C-fibers (Mense, 1993). Though pressure stimulation applied on the skin could reflect the pain sensitivity of both the superficial and deep structures, it was shown that the deep-tissue nociceptors mediate a major component of the pressure-induced pain during pressure algometry (Graven-Nielsen et al., 2004).

Acute musculoskeletal pain is perceived to occur in response to stimulation of deep-tissue polymodal nociceptors related to Aδ- and C-afferent fibers (Mense, 1993), which can release sensitizing neuropeptides causing nociceptor sensitization and potentially hyperalgesia. Regarding specific mechanisms in musculoskeletal pain, additional information may be gained by quantitative sensory testing (QST) (Rolke et al., 2006) and quantitative assessment of pain.

Manually applied pressure stimulation of nociceptors in deep tissue (hand-held pressure algometry,

Fig. 4) is a validated technique for the assessment of pain sensitivity and is widely used (Jensen et al., 1986; Chesterton et al., 2007). The variability associated with manually applied pressure stimulation may be minimized through the use of computer-controlled pressure stimulation (computer-controlled pressure algometry, Fig. 5), which also allows for the measurement of stimulus-response functions that relate the pressure intensity with the pain response (VAS) (Graven-Nielsen et al., 2004). In pressure algometry, the stimulation probe is typically 1 cm^2 and the stimulated volume of tissue is relatively small.

Pressure pain thresholds (PPT) and pressure pain tolerance thresholds (PPTol) tend to give large and robust CPM responses (Ge et al., 2004; Arendt-Nielsen et al., 2008; Wang et al., 2010), and hence they were used as TS in the present project. Pressure pain thresholds (PPT and PPTol) are recorded from the right masseter muscles (MAR) and left forearm (flexor carpi radialis muscle) by a hand-held pressure algometer (Somedic, Sweden) (Fig. 4) with a constant application rate of 30 kPa/s and an algometer probe with an area of 1 cm^2 (Arendt-Nielsen et al., 2008) in studies I, II and III.

In study III, PPT and PPTol obtained by a computer-controlled pressure algometer (Aalborg University, Denmark) (Fig. 5) were also used as TS and recorded from the right and left tibialis anterior (TA) with a constant application rate of 30 kPa/s and an algometer probe with an area of 1 cm^2 (Graven-Nielsen et al., 2004). Additionally, the pain intensity which was assessed on a VAS (0-10 cm) following 1.4 and 1.6x PPT applied to TA (VAS1.4 and VAS1.6) was recorded to evaluate the reliability of TS modality.

Figure 4. Hand-held (manually applied) pressure algometer.

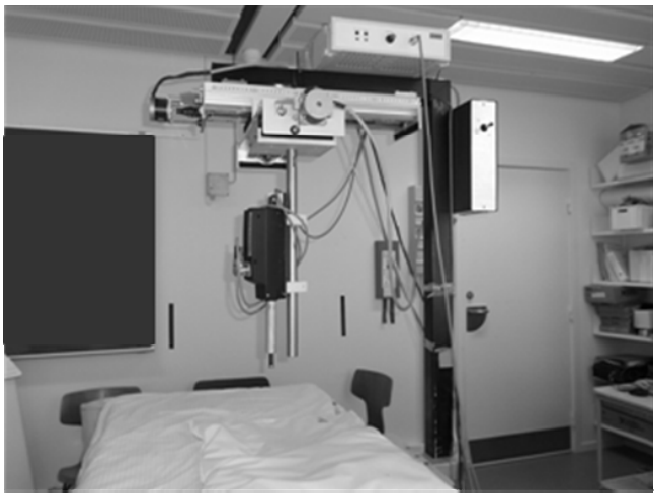

Figure 5. Computer-controlled pressure algometer.

3.1.2. Conditioning stimulus (CS)

To evoke the CPM effect in healthy humans, different laboratories apply different modalities of CS (Pud et al., 2009), such as thermal (cold (Arendt-Nielsen and Gotliebsen, 1992; Sandrini et al., 2006) and heat (Ellrich and Treede, 1998; Oono et al., 2008)), electrical (Motohashi and Umino, 2001), chemical (Valeriani et al., 2005a,b; Romaniello et al., 2002) and ischemic (Fujii et al., 2006).

The standardized mechanical pain model for experimental evoking of tonic craniofacial pain (Fig. 2) is suitable for the CS in the craniofacial region and is associated with robust CPM effects (Sowman et al., 2011). Therefore, this model was employed as CS and was applied with different target intensities (VAS0, VAS1, VAS3 and VAS5) in study I, and with an intensity above VAS5 in studies II and III (See 2.1.3. Experimental mechanical craniofacial pain model). The nociceptive input from the mechanical headband would be conducted via peripheral C-fibers.

In order to evaluate the inter- and intra-individual variation in CPM, ischemic stimulation to the right upper arm and cold stimulation to the right hand were used as CS in addition to mechanical craniofacial pain in study III.

The computer-controlled cuff algometry technique stimulates a larger volume of tissue. In cuff algometry, a tourniquet is inflated around an extremity and the pain response is measured on a VAS (Polianskis et al., 2001) (Fig. 6). In study III, ischemic muscle pain was induced by inflation of a 13 cm wide tourniquet applied around the right upper arm (innervated by C5-Th2) (VBM Medizintechnik GmbH, Germany). The lower rim of the tourniquet was 3 cm proximal to the cubital fossa. The cuff control unit (Aalborg University, Denmark) (Fig. 6) was programmed to maintain the pressure at 36 kPa (above the systolic pressure) throughout the inflation period. Ischemia predominantly activates C-fibers following arterial occlusion with an inflated tourniquet cuff and evokes pain because of tissue metabolic changes (decreased PO_2, decreased glycemia, increased lactate and potassium levels, increased PCO_2 and lowered pH) in the blood, muscle, nerves and other tissues (Wilgis and Maryland, 1971; Hagenouw et al., 1986;

Benzon et al., 1988; Hirst et al., 1990; Maclver and Taneilian, 1992; Crews et al., 1994; Estebe et al., 2000). During constant stimulation in response to an ischemic sensation, the large peripheral fibers (A-fibers) failed to conduct and the C-fiber firing was maintained (Melzack and Wall, 1965).

We also applied cold pressor pain (CPP) (2-4 °C) to the right hand (innervated by C5-Th1) according to our previous study (Arendt-Nielsen et al., 2008). CPP is a blended sensation evoked by activity in more than one type of afferent, including cold-specific channels (Mackenzie et al., 1975), high threshold cold receptors (LaMotte and Thalhammer, 1982), Aδ cutaneous (Georgopoulos, 1976,1977; LaMotte and Thalhammer, 1982; Simone et al., 1995) and vascular nociceptors (Fruhstorfer and Lindblom, 1983; Arndt and Klement, 1991; Klement and Arndt, 1992; Arndt et al., 1993), plus cutaneous (Bessou and Perl, 1969; Torebjörk and Hallin, 1974) and perivascular C-nociceptors (Campero et al., 1996).

Figure 6. The computer-controlled cuff algometry.

Electronic visual analogue scale is shown on the right side.

3.2. Effects of CPM

3.2.1. Intensity effects of CS

The effects of CPM are known to differ, depending on the magnitude and nature of the CS and the stimulated nerve fibers (Willer et al., 1984; Villanueva and Le Bars, 1985; Villanueva et al., 1989).

Willer et al. (1984) demonstrated in healthy volunteers that the spinal nociceptive flexion reflex (RIII reflex) elicited by right sural nerve stimulation was inhibited by the immersion of the left hand into a heated thermoregulated water bath at the nociceptive temperature, i.e. higher conditioning temperatures induced a more intense CPM effect, while non-nociceptive temperatures (40 to 44°C) were without CPM effect. In addition, they showed a highly significant linear relationship between the increase in these thresholds and the intensity of the CS in the 44 to 47.5°C range. Moreover, the data indicated that, whether induced by heat, cold (6°C), mechanical (painful pinch) or chemical (muscular exercise under ischemia) procedures, a painful CS strongly depresses, at spinal level, the nociceptive messages elicited from remote localized body areas. These intensity-dependent CPM effects have been reported by many researchers in the spinal region (Willer et al., 1989; Le Bars et al., 1992; Le Bars, 2002; Granot et al., 2008; Tousignant-Laflamme et al., 2008). However, they have not been reported in the craniofacial region in humans.

Table 1 is the raw data from study I, and Fig. 7 is the overall effect of relative PPT changes (A) and PPTol changes (B). In study I, the intensity-dependent CPM effect (VAS0: 3.3 ± 1.6%, VAS1: 2.5 ± 2.1%, VAS3: 11.8 ± 2.0%, VAS5: 32.6 ± 3.3% for PPT and VAS0: -2.2 ± 2.5%, VAS1: -4.8 ± 2.2%, VAS3: 4.3 ± 2.4%, VAS5: 11.2 ± 2.8% for PPTol) was systematically shown in the craniofacial region in healthy humans. The finding supports the previous reports in the spinal region in humans and in the trigeminal region in animals (Willer et al., 1984; Le Bars and Willer, 2002).

Table 1

CPM effect (%) with different intensities of CS (mechanical craniofacial pain) during application of CS (raw data from study I).

		VAS0		VAS1		VAS3		VAS5	
Parameter	Assessment site	Men	Women	Men	Women	Men	Women	Men	Women
PPT	Masseter	6.0 ± 3.8	2.7 ± 3.9	-0.2 ± 4.3	2.2 ± 3.9	9.9 ± 4.3	11.4 ± 4.1	34.7 ± 7.6	23.1± 5.0
	Forearm	3.0 ± 2.8	1.7 ± 2.3	2.4 ± 3.9	5.6 ± 4.6	12.0 ± 4.2	13.9 ± 3.7	40.5 ± 7.9	32.2 ± 5.0
PPTol	Masseter	-0.7 ± 5.5	2.8 ± 6.5	-8.8 ± 3.6	-1.8 ± 5.6	2.7 ± 5.0	4.6 ± 5.1	7.7 ± 7.2	15.3 ± 5.0
	Forearm	-6.7 ± 3.1	-4.4 ± 3.9	-7.9 ± 3.1	-0.5 ± 4.7	-0.7 ± 4.0	10.5 ± 4.9	14.1 ± 5.2	7.8 ± 4.3

N = 40 (Men = 20, Women = 20); Mean ± SE (%).

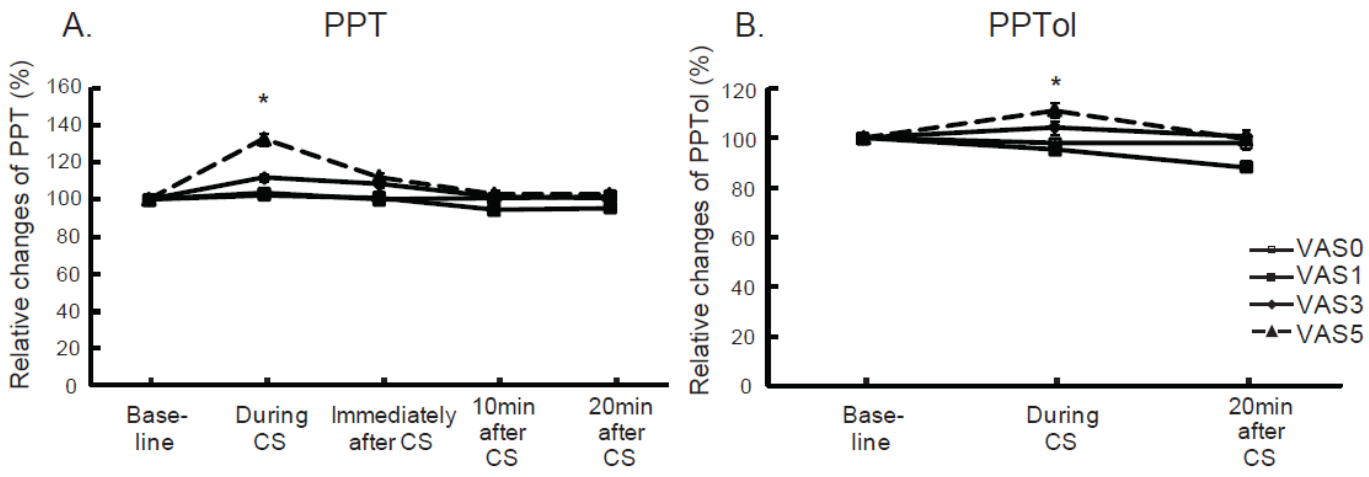

Figure 7. Relative changes of the pressure pain thresholds (PPT) values (A) and pressure pain tolerance thresholds (PPTol) values (B) (%, mean ± standard errors of mean) in the four sessions (target intensity of conditioning stimulus (CS); VAS0, VAS1, VAS3 or VAS5) from all the subjects (n = 40; men = 20, women = 20).

The increases are the mean values for two assessment sites (masseter and forearm). *Indicates a significant increase of normalized PPT values with CS of VAS5 compared to all other intensities of the CS during the application of CS ($P < 0.001$), and indicates a significant increase of normalized PPTol values with CS of VAS5 compared to VAS 0 and VAS1 during the application of CS ($P < 0.001$) (overall effect from four-way ANOVA and post-hoc tests) (from study I).

3.2.2. Assessment site effects on CPM

For the CPM effect there is no consensus concerning the distance between the TS and CS, that is CS localization and its efficacy in attenuating the perceived intensity of the TS. According to Le Bars et al. (1989) the distance between the TS and CS is not a critical factor for the strength of the inhibition. Daniziger et al. (1998) reported that the application of noxious conditioning electrical stimuli, whether segmentally or extrasegmentally, produced powerful and long-lasting inhibitory effects, especially with the extrasegmental paradigm.

Contrary to these reports, Defrin et al. (2010) revealed that CPM cannot occur at a small separation distance, but it occurs and is stronger at larger separation distances. They conclude that the CPM is affected by the distance between two noxious stimuli.

According to our study with CS to the craniofacial region (innervated by V1, V3 and C2) (study I), there were no significant differences in the magnitude of CPM even though the TS were applied to the segmental (masseter muscle, innervated by V3) or extrasegmental (forearm, innervated by C5-Th1) region to the CS. These observations implicate that the magnitude of CPM is not affected, even if the CS is applied segmentally instead of extrasegmentally. This was furthermore supported by the correlations between relative changes (increases) in PPT values at both the forearm and masseter muscle and the perceived intensity of the CS. These findings are consistent with the previous report (Le Bars et al. 1989, Danziger et al., 1998). However, in study III, the magnitude of CPM was bigger in the recording from TA (innervated by L4-S1) compared to the recordings from masseter (innervated by V3) and forearm (innervated by C5-Th1) when it was assessed with PPT as the TS and was evoked by the CS applied to the right hand (innervated by C5-Th1), right upper arm (innervated by C5-Th2) and craniofacial region (innervated by V1, V3, C2). The differences in the CPM effects among the assessment sites might partly be related to the method of evaluation (the hand-held or computer-controlled algometer) but also the size of the muscle could influence the response.

3.2.3. Gender effects on CPM

Gender differences in pain perception have been well established. In most studies, women report more intense pain, more frequent pain and pain of longer duration than men (Unruh, 1996). Greater pain sensitivity in women compared to men occurs in the peripheral actions of glutamate (Cairns et al., 2001) and morphine (Sessle, 2000), suggesting that peripherally based physiological mechanisms may contribute to the gender differences in the pain conditions (Cairns et al., 2001; Sessle, 2005).

The gender differences in CPM effects are still controversial. According to the recent review (Popescu et al., 2010) the majority of the studies using pain report find significantly more efficient CPM in men than women (mean women/men ratio = 0.54). They conclude that gender differences in the CPM effect depend on both the experimental methodology and the modes of measurement of the effect.

Moreover, hormonal influence on the CPM has been suggested. In other words the CPM effects of women differ with menstrual phase (Tousignant-Laflamme et al., 2008; Tousignant-Laflamme and Marchand, 2009). In addition, the menstrual phase may also influence the pain response with lower pain threshold during the luteal phase compared with the follicular phase (Hapidou and De Catanzaro, 1988).

In our studies (studies I and II) there were no gender differences in CPM in agreement with other previous studies (France and Suchowiecki, 1999; Baad-Hansen et al., 2005; Pud et al., 2005; Quiton and Greenspan, 2007; Tousignant-Laflamme et al., 2008; Wang et al., 2010). Though the data on the menstrual cycle in women were not recorded in our studies, 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 which were also demonstrated in our studies (studies I and II) and in a previous study (Arendt-Nielsen et al., 2008).

3.3. Variation in CPM

To date not many studies have focused on the variation in CPM. A previous study (Granot et al., 2008) mentioned that the CPM effect is relatively free of individual variability. To our knowledge study III is the first investigation to evaluate the CPM effects comparing three different CS modalities together with several assessment sites.

Two factors affect variance in CPM; the factor from methodological matters and the factor from individual differences. Concerning individual factors, the inter-individual variation and the intra-individual variation should be considered.

To evaluate the inter-individual variation, the inter-individual coefficient of variation (inter-CV) was calculated as standard deviation/mean × 100 (%). For evaluation of the intra-individual variation, the intra-individual coefficient of variation (intra-CV) was calculated as intra-CV = $\left(\sqrt{\left[\left(\sum d^2\right)/2n\right]}\right)/x \times 100$ (%), in which d is the difference between two results obtained from one subject, n is the number of subjects, and x is the mean of the results obtained from all the subjects (Spetalen et al., 2004).

3.3.1. Methodological factors

Immersion of the body part in cold water produces arterial pressor responses (Weise et al., 1993). Besides, an inverse relationship between blood pressure levels and pain intensity has been demonstrated by CPP (Duschek et al., 2007). From that point of view, hot water seems to be a more appropriate model for tonic pain compared to CPP (Streff et al., 2010). On the other hand, CPP, ischemic pain and mechanical pressure have excellent reliability and validity as well as thermal pain (Edens and Gil, 1995).

A recent review highlights the methodological variation in inducing CPM effects between different studies (Pud et al., 2009), and the approximated CPM effect in numerous studies is 29%. However, it is also pointed out that the difference in pain parameters should be taken into account and there is a limit of generalization of conclusions from one study to another. Concerning TS, the review (Pud et al., 2009) reports

that the approximated median magnitude of the CPM effect measured by the suprathreshold test-pain reduction was 29% (ranging from 10% to 55%); the increase in the test-pain thresholds was 25% (ranging from 3% to 100%); and the change in the neurophysiological measures was 28.5% (ranging from 10% to 60%). They suggest that due to the high variation in the studies which measured the changes by test-pain thresholds, continued use of test-pain thresholds in future studies may be questionable.

Table 2 shows the CPM effect in this project (studies I, II and III). In our project, the averaged CPM effect from all the data (with CS of VAS5 in study I and without electrical TMJ stimulation in study II) was 27.1%, which is almost equal to the value in the literature (Pud et al., 2009). Regarding the modalities of TS, the CPM effect measured by the increase in the test-pain thresholds (PPT) was 33.5% (ranging from 10.1% to 66.3%); the increase in the test-pain tolerance thresholds (PPTol) was 19.5% (ranging from 7.7% to 32.6%); and the reduction in the pain intensity (VAS) was 30.7% (ranging from 21.3% to 41.5%).

Undoubtedly, the factor from PPT testing is notable for the variance in CPM. However, previous studies reported that the test-retest reliability of the PPT technique can be guaranteed (Cathcart and Pritchard, 2006; Cathcart et al., 2009). Furthermore, the inter-individual CV for PPT measured by a hand-held algometer was 28% for women and 33% for men, and the intra-individual CV based on repeated PPT measurements with a 1 week interval was 14% (Brennum et al, 1989). From our investigation, the range of the CPM effect with test-pain thresholds (10.1-66.3%) was similar to the values derived from neurophysiolological measurement (10-60%) in the above-mentioned review (Pud et al., 2009). Therefore, we believe that PPT is reliable and useful to evaluate the CPM effect.

Study III demonstrated that the CPP caused the significantly strongest CPM effect (43.6 ± 6.2%) compared to the tourniquet (31.0 ± 3.7%) and headband (20.5 ± 3.4%) in PPT. Concerning VAS1.6, the CPM effect with CPP (37.2 ± 4.4%) was larger than with tourniquet (33.2 ± 5.4%) and headband (21.3 ± 3.2%).

From the point of view of the assessment sites, CPM effect recorded from TA was significantly

larger (46.6 ± 4.7%) compared to the masseter (17.8 ± 2.2%) and forearm (15.3 ± 2.0%) in PPT.

Overall, the CPM induced by CPP elicits the strongest responses (43.6%), and the leg as the assessment site results in the largest responses when assessed by pressure pain thresholds.

Table 2

CPM effect (%) in this project.

			Study I		Study II		Study III			
			Headband		Headband		Headband	Tourniquet	CPP	
			VAS5		VAS5 without TMJ stimulation		VAS5	VAS6	VAS6	
Parameter	Algometer	Assessment site	Men	Women	Men	Women	Men	Men	Men	Mean
PPT	Hand-held	Masseter	34.7 ± 7.6	23.1± 5.0	41.1 ± 5.1	53.3 ± 8.3	10.1 ± 2.7	20.7 ± 3.4	23.3 ± 4.3	29.5
		Forearm	40.5 ± 7.9	32.2 ± 5.0	61.2 ± 7.7	45.6 ± 7.1	13.8 ± 4.7	15.1 ± 2.6	16.7 ± 2.8	32.2
PPTol	Hand-held	Masseter	7.7 ± 7.2	15.3 ± 5.0	12.5 ± 5.0	26.7 ± 7.7	24.4 ± 4.9	20.5 ± 3.7	32.6 ± 4.6	20.0
		Forearm	14.1 ± 5.2	7.8 ± 4.3	18.8 ± 5.1	27.5 ± 9.5	15.0 ± 3.4	24.7 ± 4.9	19.8 ± 2.4	18.2
PPT	Computer-controlled	TA	–	–	–	–	29.1 ± 5.7	43.4 ± 5.8	66.3 ± 10.0	46.3
PPTol	Computer-controlled	TA	–	–	–	–	18.7 ± 4.8	20.2 ± 2.7	24.6 ± 2.3	21.2
VAS1.4	Computer-controlled	TA	–	–	–	–	24.0 ± 3.8	26.7 ± 5.1	41.5 ± 5.3	30.7
VAS1.6	Computer-controlled	TA	–	–	–	–	21.3 ± 3.2	33.2 ± 5.4	37.2 ± 4.4	30.6

N = 40 (Men = 20, Women = 20) in studies I and II, and N = 12 for masseter and forearm and N = 24 for TA before the exclusion of non-responders in study III.

Mean ± SE (%).

3.3.2. Inter-individual variation in CPM

Our investigation (study III) showed that in general the CPP causes a smaller inter-CV (41.4-60.1%) than the tourniquet and headband.

Gender differences (Ge et al., 2004) and age differences (Washington et al., 2000; Edwards et al., 2003) could affect CPM responses. Only one article has reported the test-retest reliability of CPM with intraclass correlations (ICCs) and coefficient of repeatability (CR) using occlusion cuff (CS) in humans, and it concludes that there are no significant differences in the CPM effect across test-retest occasions (Cathcart et al., 2009). However, the cuff resulted in a large inter-individual variation (CR was 1.69), which is consistent with our result that in general the cuff has larger inter-individual variation than CPP.

3.3.3. Intra-individual variation in CPM

The possible influential factor on the intra-individual variation in CPM is habituation (Treister et al., 2010). To minimize the intra-individual variation, it is better to evaluate CPM with the same examiner (Antonaci et al., 1998).

Our experiment (study III) was performed by the same examiner. The smallest threshold variability was obtained from the assessment sites at the masseter or the forearm regardless of the CS (35.2-40.1%). For pain ratings, the smallest intra-individual variability was obtained with CPP (27.0%). There was a general pattern that the CPP leads to smaller intra-CV (27.0-42.4%).

3.3.4. Clinical implications

Impairments of CPM in chronic pain conditions, such as fibromyalgia (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997), irritable bowel syndrome (Wilder-Smith et al., 2004), migraine (Sandrini et al., 2006) and CTTH (Pielsticker et al., 2005), have been reported. It can be speculated that the ongoing chronic pain may “exhaust” CPM, leading to dysfunction of CPM or causing an increased facilitation

through the descending pathways. An alternative explanation for the relation between chronic pain and impairment of CPM is that less efficient CPM might be a risk factor for acquisition of chronic pain in these patients. To support the latter option, recent research (Yarnitsky et al., 2008) shows that the pre-operative evaluation of CPM may identify patients at the risk of developing chronic pain. For further application of CPM as a diagnostic tool or for screening of analgesic compounds the test-retest reliability and inter-individual variation in CPM should be determined.

From the findings of study III, the experimental paradigm with the CPP as the CS and PPT as the TS is the most reliable to evaluate CPM.

3.4. Central mechanism of CPM

As mentioned in the introduction, CPM, formerly termed DNIC, is the phenomenon whereby the activities of nociceptive (WDR and NS) neurons are powerfully inhibited by the application of noxious CS to any body areas distant from their excitatory receptive fields (Le Bars, 2002). This inhibition is triggered by noxious stimuli and affects nociceptive neurons within the spinal cord and the trigeminal system (Villanueva and Le Bars, 1985; Hu, 1990; Le Bars et al., 1995; Meng et al., 1997).

CPM is a spinal-supraspinal feedback loop which modulates spinal neuronal activity (Le Bars et al., 1995). A painful stimulation to a region of the body activates spinal dorsal horn neurons or neurons in the trigeminal spinal tract nucleus and sends an excitatory signal (through the ventrolateral quadrant for spinal dorsal horn neurons) towards higher centers, including the lower brainstem, especially SRD (within the caudal-most aspect of the medulla). This signal activates CPM, which inhibits spinal and trigeminal nociceptive neurons through the dorsolateral funiculi (Le Bars et al., 1995, Le Bars and Willer, 2002).

According to the review (Villanueva et al., 1996), the SRD plays a specific role in processing cutaneous and visceral nociceptive inputs, particularly in CPM. From a general point of view, the reciprocal connections between the caudal medulla and spinal cord suggest that this area is an important link in the

feedback loops which regulate spinal outflow. Moreover, the existence of SRD-thalamic connections put a new light on the role of spino-reticulo-thalamic circuits in pain transmission.

Taken together, the inhibitions are mediated by a spino-bulbo-spinal loop, the ascending part of which is composed of the spinoreticular tract and synaptic relays in the brainstem (Le Bars and Willer, 2002).

Concerning the endogenous mechanism of CPM, CPM - whether tested on WDR neurons in animals or the nociceptive RIII reflex in man - is blocked by naloxone (Le Bars et al., 1981; Willer et al., 1990). This fact implies that there is at least one opioidergic link in this loop both in the rat and in man (Le Bars et al., 1981; Willer et al., 1990).

Recent animal studies have also shown that systemic or local (close to the nucleus raphe magnus: RMg) administration of an α1-adrenoceptor agonist, phenylephrine (PE), and systemic administration of a selective α2-adrenoceptor agonist, dexmedetomidine (DEX), inhibit DNIC (Sanada et al., 2009; Makino et al., 2010). These findings suggest that adrenergic neurons are involved in DNIC.

3.4.1. CPM in healthy humans

Following animal DNIC studies, CPM has been focused on healthy humans. Price and McHaffie (1988) observed that the pain elicited by intense electrical stimulation of the ankle area was decreased by noxious thermal CS of the skin of either the dorsal surface of the contralateral foot or the abdominal region. Roby-Brami et al. (1987) reported that the RIII reflex was inhibited by nociceptive electrical stimuli applied to the fingers. Terkelsen et al. (2001) showed CPM as the inhibition of the nociceptive withdrawal reflex by CPP.

CPM is activated by conditioning stimulus. In addition, CPM is also affected by psychological factors, such as attention and distraction (Fernandez and Turk, 1989; Quiton and Greenspan, 2007; Defrin et al., 2010). Both distraction and stress can reduce pain (Fernandez and Turk, 1989) and contribute to pain-evoked hypoalgesia. Also factors such as task difficulty and the environmental demands (emotional

arousal) are implicated in moderating the interruptive function of pain (Eccleston and Crombez, 1999).

3.4.2. CPM in craniofacial region

Animal studies demonstrate that the trigeminal subnuclei caudalis and oralis are involved in the DNIC effect (Dickenson et al., 1980; Dallel et al., 1990; Hu, 1990). Subsequently, the CPM effect in the craniofacial region has been reported in humans (Svensson et al., 1999a,b; Mason et al., 2007; Oono et al., 2008). Ellrich and Treede (1998) reported that the blink reflex caused by electrical stimulation of the supraorbital nerve was reduced when heat stimulation was administered to the ipsilateral or contralateral forearm or the ipsilateral foot bottom.

From study I it is systematically demonstrated in healthy humans that CPM is triggered in the craniofacial region by the application of mechanical stimulus.

The nociceptive input from the mechanical headband would result in the activation of the corresponding segmental pools of both NS and WDR neurons in the trigeminal subnucleus caudalis. These signals might reach the other brain centers involving the caudal-most part of the medulla, including the SRD, and could access descending pathways in the dorsolateral funiculi (Le Bars, 2002). Accordingly, CPM may cause inhibition of activity in nociceptive neurons in the trigeminal subnucleus caudalis (Hu, 1990; Raboisson et al., 1995) or the spinal dorsal horn (Le Bars et al., 1979a) to the same degree corresponding to the intensity of the CS, that is, the CPM effect in a CS intensity dependent manner without assessment site difference (segmental: craniofacial / extrasegmental: spinal).

Overall, we report here, for the first time, that the CPM effect in the craniofacial region in humans is CS intensity dependent consistent with a previous animal report (Bouhassira et al., 1987) but not assessment site or gender dependent.

3.5. Modulation of CPM by experimental TMJ pain

3.5.1. Influence of experimental pain on CPM

According to the report from Arendt-Nielsen et al. (2008), the two concomitantly applied CS (CPP to the hand and muscle pain to the TA) evoke less CPM despite higher perceived pain intensity by the subjects.

On the other hand, in study II, the concomitantly evoked pain (mechanical craniofacial pain and electrical TMJ pain) did not impair CPM effects (Table 3, Fig. 8). The differences in the methodological matters (the assessment site for TS, the stimulated site for CS and the nature of the CS) might affect these inconsistent results.

Interestingly, in study II, the TMJ pain values (VAS-TMJ, painful) tended to decrease during the application of CS (Fig. 9). This observation suggests that the CS triggered the CPM effects on both the TS and the TMJ stimulation. Moreover, the CS pain values in the painful session (VAS-CS, painful: VAS-TMJ = 5) were significantly lower than in the control session (VAS-CS, control: VAS-TMJ = 0, only with insertion of the needle electrodes and without electrical stimulation). This fact also implies that the painful TMJ stimulation triggered a CPM effect on the CS. These phenomena indicate a bidirectional mechanism of CPM which, to our knowledge, has not been reported before.

Higher prevalence of many chronic muscle pain conditions in women has been reported (Cairns et al., 2001; Sessle, 2005). In addition, female reproductive hormones may play a role in craniofacial pain (LeResche et al., 1997).

Meanwhile, there were no gender differences in the CPM effect in our investigation (study II). The fact that the data on the menstrual cycle in women were not recorded in study II might affect these differences. The information on the menstrual cycle would be valuable for elucidation of gender differences in future studies.

Table 3

CPM effect (%) with and without TMJ pain during application of CS (raw data from study II).

		Control session (without TMJ pain)		Painful session (with TMJ pain)	
Parameter	Assessment site	Men	Women	Men	Women
PPT	Masseter	41.1 ± 5.1	53.3 ± 8.3	41.7 ± 9.3	48.3 ± 6.6
	Forearm	61.2 ± 7.7	45.6 ± 7.1	53.3 ± 8.3	53.6 ± 5.4
PPTol	Masseter	12.5 ± 5.0	26.7 ± 7.7	2.0 ± 4.6	23.4 ± 6.9
	Forearm	18.8 ± 5.1	27.5 ± 9.5	16.0 ± 6.9	29.2 ± 5.4

N = 40 (Men = 20, Women = 20); Mean ± SE (%).

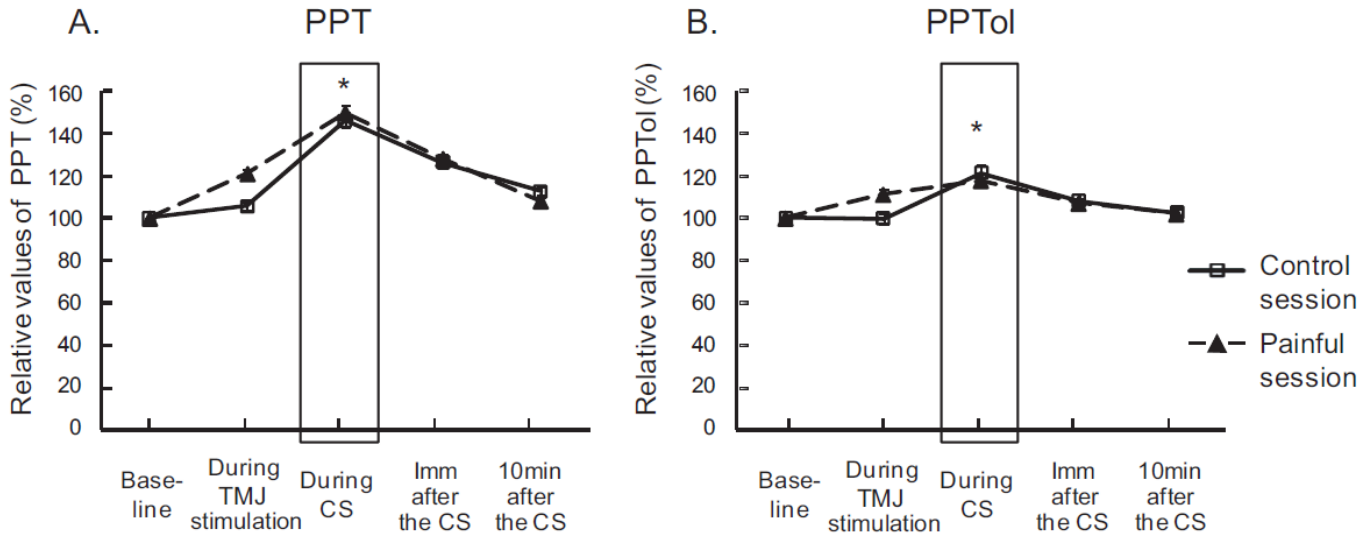

Figure 8. Relative values of the pressure pain thresholds (PPT) (A) and pressure pain tolerance thresholds (PPTol) (B) (%, mean ± standard errors of mean) in the control (without electrical TMJ stimulation) and the painful (with electrical TMJ stimulation) sessions from all the subjects (n = 40; men = 20, women = 20).

The increases are the mean values for two assessment sites (masseter and forearm). "During TMJ stimulation" represents "with insertion of the needles" in the control session and "with electrical TMJ stimulation" in the painful session. "During CS (conditioning stimulus)" represents "during conditioning and TMJ stimulation" and "Imm after the CS" represents "Immediately after the conditioning and TMJ stimulation". *Indicates significant increases of normalized PPT and PPTol values compared with baseline values ($P < 0.001$) in both sessions (overall effect from four-way ANOVA and post-hoc tests). There were no significant differences between sessions in the increment of PPT and PPTol during CS (from study II).

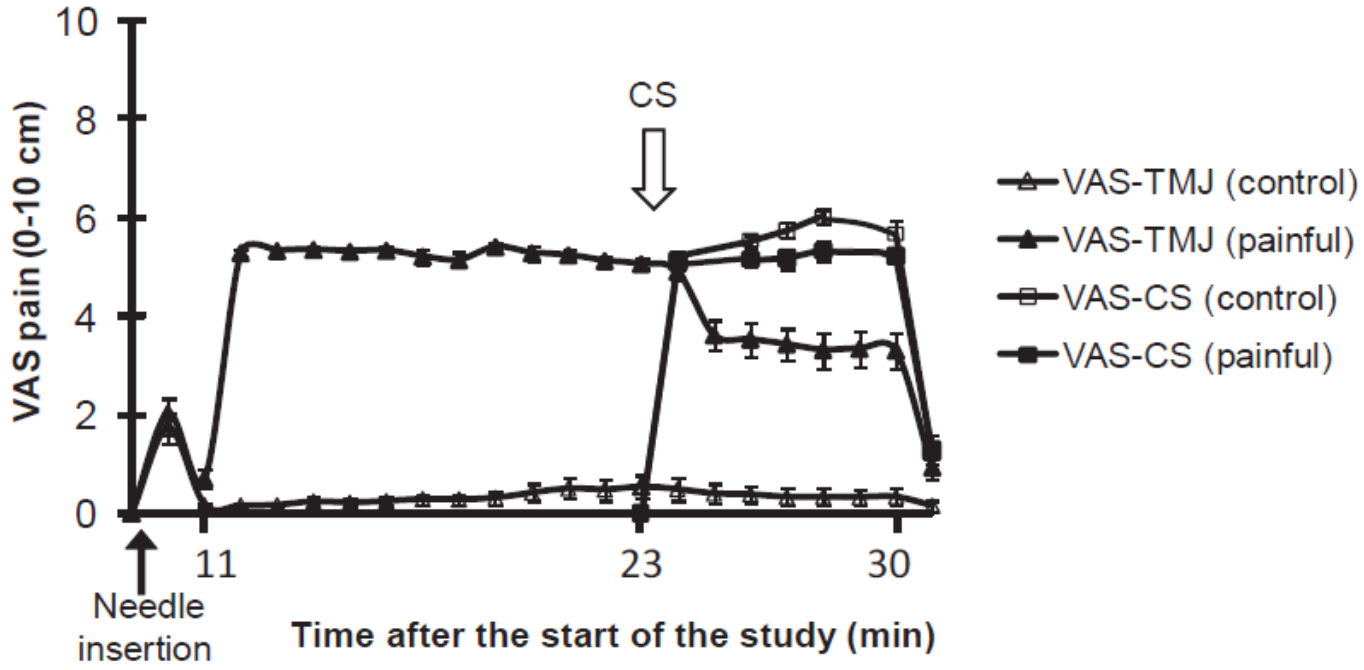

Figure 9. Continuous visual analogue scale (VAS) ratings of the pain intensity of the repetitive electrical temporomandibular joint (TMJ) stimulation in the painful session (VAS-TMJ, painful), the pain intensity of the needle electrodes in the control session (VAS-TMJ, control) and the pain intensity of the craniofacial compression (conditioning stimulus: CS) (VAS-CS) in two sessions (control: VAS-TMJ = 0, painful: VAS-TMJ = 5) from all the subjects (n = 40; men = 20, women = 20) (mean ± standard errors of mean).

The black arrow shows the needle insertion and the white arrow shows the application of mechanical craniofacial pain (CS). In the control session the VAS-TMJ pain values after the needle insertion was low (under VAS = 1) and stable. In the painful session the VAS-TMJ pain values tended to decrease during CS. The CS pain values in the painful session (VAS-CS, painful) were significantly lower (P = 0.008) than in the control session (VAS-CS, control) (from study II).

3.5.2. Clinical implications

Impairments of endogenous pain-modulatory pathways are implicated in clinical pain conditions.

Study II implies that two experimental painful stimuli may interact in a complex manner like in persistent pain conditions where changes in the balance between descending inhibition and facilitation may occur.

Study II also showed that acute experimental TMJ pain did not alter CPM effects evoked by tonic painful mechanical stimulation of the craniofacial region. Deficiencies in CPM effects in persistent pain conditions are therefore most likely more related to the duration of the clinical pain than the pain per se.

4. CONCLUSIONS AND PERSPECTIVES

The aims and conclusions from this project are shown in Fig. 10.

The conclusions from this project are:

1. The CPM effect in the craniofacial region is intensity dependent but not assessment site (segmental: craniofacial / extrasegmental: spinal) or gender dependent (study I).
2. The acute experimental TMJ pain does not alter the magnitude of the CPM effects in either gender, that is, deficiencies in CPM in persistent pain conditions are most likely more related to the duration of clinical pain than the pain per se (study II).
3. The cold pressor pain evokes the largest CPM, the leg as the assessment site results in the largest CPM responses, and the cold pressor pain causes the smallest inter- and intra-individual variation. The result implicates that the cold pressor pain is the most efficient conditioning stimulus to induce CPM when assessed by pressure pain thresholds (study III).

The present project showed that the mechanical compressive device and the experimental TMJ pain models are suitable for systematic elucidation of the pain-modulatory mechanism in the craniofacial region in humans. Moreover, this project provides information on the endogenous pain-modulatory mechanism in healthy humans; two experimental painful stimuli interact in a complex manner like in persistent pain conditions.

The general conclusions from this project are; 1) the CPM effect in the craniofacial region is dependent on the intensity of the conditioning stimulus without any assessment site or gender differences, 2) deficiencies in CPM in persistent pain conditions are most likely more related to the duration of clinical pain than the pain per se, and 3) the experimental paradigm with the cold pressor pain as the conditioning stimulus and pressure pain thresholds as the test stimulus is the most reliable method to evaluate CPM.

The clinical relevance of CPM assessments is not examined in this project. Therefore, future research on CPM with clinical pain patients would be of major value to elucidate the endogenous

pain-modulatory mechanism. Furthermore, it would be useful to explore and develop more reliable method to test CPM for experimental and clinical use, to evaluate endogenous pain-modulatory mechanism with CPM and to develop new and more efficient analgesic treatments which specifically interact with CPM in chronic pain patients.

Further investigation of the above mentioned studies on CPM will lead to the possible benefit of the many millions of people suffering from pain.

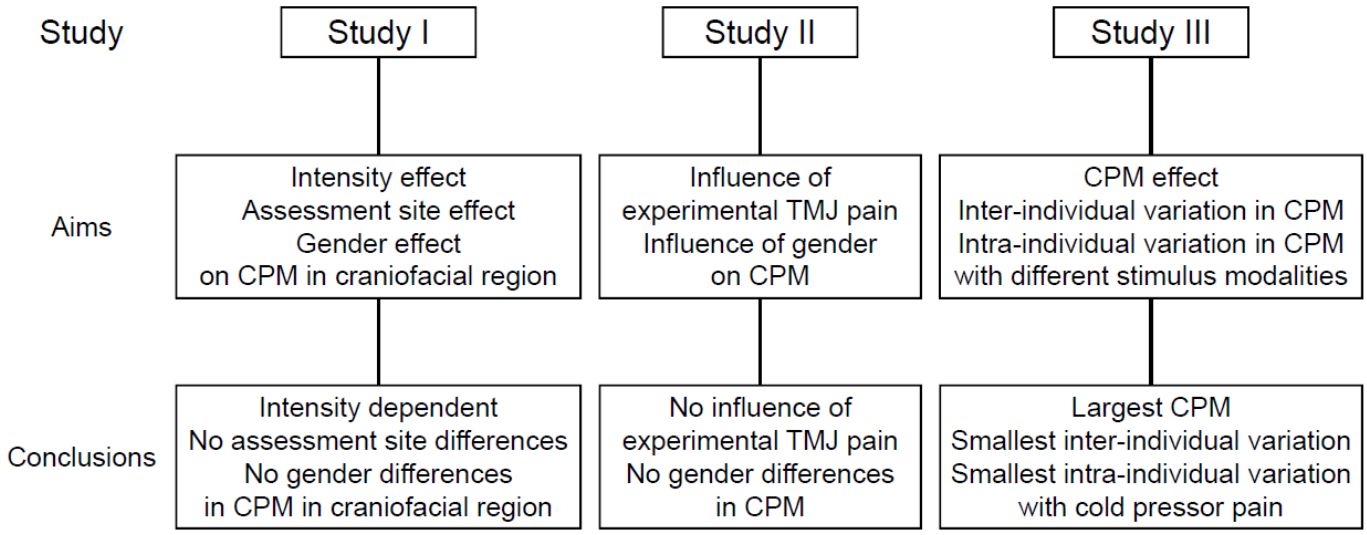

Figure 10. Diagram of the aims and conclusions in this project.

TMJ: temporomandibular joint, CPM: conditioned pain modulation.

5. ENGLISH SUMMARY

Conditioned pain modulation (CPM)

: experimental studies in the craniofacial region in healthy humans

This Ph.D. thesis is based on three research studies, which have been carried out in the period from 2009 to 2011 at Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark.

Conditioned pain modulation (CPM) in the craniofacial region in healthy humans has received little attention. Moreover, chronic craniofacial musculoskeletal pain conditions such as temporomandibular disorders (TMD) are associated with alternations in pain-modulatory processes reflected in CPM. Recent research suggests that the evaluation of CPM may identify patients at risk of developing chronic pain. For further application of CPM as a diagnostic tool or for screening of analgesic compounds, the test-retest reliability and inter-individual variation in CPM need to be studied.

The aims of this Ph.D. project were to investigate systematically if the CPM is intensity, assessment site (segmental: craniofacial region / extrasegmental: spinal region) and gender dependent in the craniofacial region (study I); if an ongoing experimental temporomandibular joint (TMJ) pain influences the CPM evoked by standardized mechanical craniofacial pain (study II), and to evaluate the inter- and intra-individual variation in CPM evoked by the different stimulus modalities (study III).

Study I showed for the first time that the CPM effect in the craniofacial region (evoked by mechanical stimulation) is intensity dependent but not assessment site (segmental: craniofacial region / extrasegmental: spinal region) or gender dependent. Study II indicated that acute experimental TMJ pain does not alter the magnitude of the CPM effects in either gender, suggesting that deficiencies in CPM in persistent pain conditions are most likely more related to the duration of clinical pain than the pain per se. In addition, study III showed that the cold pressor pain (CPP) evokes the largest CPM responses and leads to the

smallest inter- and intra-individual variation. The leg as the assessment site results in the largest CPM responses. These results implicate that the CPP is the most efficient conditioning stimulus to induce CPM when assessed by pressure pain thresholds.

In conclusion, the present work on CPM has provided new information on the pain modulation system. The results might be helpful to improve the knowledge of assessment, diagnosis and treatment of TMD and other craniofacial pain disorders.

6. DANISH SUMMARY

Betinget smertemodulation (CPM)

: eksperimentelle studier i den kraniofaciale region hos raske mennesker

Denne Ph.D.-afhandling er baseret på tre forskningsrapporter. Undersøgelserne er gennemført i perioden 2009-2011 på Center for Sanse-Motorisk Interaktion (SMI), Det Sundhedsvidenskabelige Fakultet, Aalborg Universitet, Danmark.

Betinget smertemodulation (CPM) i den kraniofaciale region hos raske mennesker er kun undersøgt lidt. Desuden er kroniske kraniofaciale muskuloskeletale smertetilstande, som f.eks. temporomandibulær dysfunktion (TMD), forbundet med vekslen i smerte-modulerende processer afspejlet i CPM. Nylige forskningsresultater har vist, at evalueringen af CPM kan identificere patienter med risiko for at udvikle kroniske smerter. For yderligere at kunne anvende CPM som et diagnostisk værktøj eller til screening af smertestillende stoffer skal test-retest pålidelighed og inter-individuelle variationer af CPM fastlægges.

Formålet med nærværende projekt er systematisk at undersøge, om CPM er intensitets-, vurderingssteds- (segmentær: kraniofaciale region / ekstra-segmentær: spinale region) og kønsafhængig i den kraniofaciale region (studie I); påvirkningen af eksperimentelle kæbeledssmerter på CPM fremkaldt ved hjælp af standardiserede mekanisk kraniofacial smerte samt (studie II), at vurdere inter- og intra-individuel variation af de forskellige stimuli-metoder til fremkaldelse af CPM (studie III).

Dette forskningsprojekt har som det første vist, at CPM-effekten i den kraniofaciale region (fremkaldt ved hjælp af mekanisk stimulation) er intensitetsafhængig, men ikke vurderingsteds- (segmentær: kraniofacial / ekstra-segmentær: spinal) eller kønsafhængig (studie I). Desuden viser forsøget, at akutte eksperimentelle kæbeledssmerter ikke ændrer styrken af CPM-effekterne hos nogen af de to køn, det vil sige at mangler i CPM i vedvarende smerter sandsynligvis er mere relateret til varigheden af den kliniske smerte end smerten i sig selv (studie II). Desuden viste studiet af den inter- og intra-individuel variation i CPM, at

kold pressorsmerte (CPP) fremkalder den største CPM, at benet som vurderingssted resulterer i de højeste CPM-reaktioner, og at CPP forårsager den mindste inter- og intra-variationskoefficient (CV). Resultatet indikerer, at CPP er den mest effektive konditioneringsstimulus til fremkaldelse af CPM, da den blev vurderet ved hjælp af tryksmertetærskler (studie III).

Dette CPM-studie har givet ny information om smertemodulationssystemet. Resultaterne kan være nyttige til forbedring af diagnosticering og behandling af kæbeledssmerter samt andre kraniofaciale smertelidelser.

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