UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

HENRIQUE MÜLLER DE QUEVEDO

**Determination of normative values for mechanical quantitative
sensory tests in the orofacial region**

**Determinação de valores normativos para testes quantitativos
sensoriais mecânicos na região orofacial**

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RESUMO

Determinação de valores normativos para testes quantitativos sensoriais mecânicos na região orofacial

Um novo conceito de tratamento de síndromes dolorosas baseada em mecanismos de dor é baseado na hipótese de que diferentes sinais clínicos refletem alterações em diversos mecanismos de geração de dor. Para analisar estes mecanismos, em 2006, o DFNS (German Research Network on Neuropathic Pain) criou um protocolo padronizado de testes quantitativos sensoriais (QST) para uma avaliação quantitativa de mecanismos de geração de dor, criando valores de referência para mão, pé e face (músculo masseter). No entanto, ainda há falta de valores de referência para alguns testes quantitativos em diversas importantes regiões orofaciais como o músculo temporal anterior e a mucosa oral. Este estudo buscou determinar valores normativos dos QSTs nessas regiões e avaliou a eficácia de um estímulo condicionante (CPM) na percepção da dor por meio de dois estímulos teste (PPT e MPT). 60 sujeitos saudáveis (30 homens/30 mulheres) foram examinados com os testes de sensibilidade tátil (MDT), limiar de dor mecânico (MPT), somação temporal (WUR), limiar de dor à pressão (PPT) e condicionamento modulatório da dor (CPM), afim de determinar valores normativos na população. Os pacientes foram examinados em sessão única por um único examinador treinado sob o protocolo desenvolvido pelo DFNS. Para avaliação estatística dos dados da CPM uma análise de variância (ANOVA) foi utilizada comparando os fatores sítio (2 níveis), tempo (2 níveis) e sexo (2 níveis) entre os dois estímulos teste (MPT e PPT). Os valores de referência para QST foram comparados por uma ANOVA multi-vias considerando os fatores sítio (3 níveis), lado (2 níveis), e sexo (2 níveis) ($\alpha=5\%$). MDT e MPT mostraram efeitos principais de sítio ($p<0,001$), em que a mucosa apresentou os maiores limiares para MDT e menos limiares para MPT, quando comparada à mão e temporal anterior. PPT demonstrou efeitos principais de sítio e sexo. Limiares de dor à pressão do músculo temporal foram menores comparados com a mão ($p<0,001$) e homens apresentaram maiores limiares que as mulheres em todos os sítios. O teste WUR não apresentou nenhum efeito de sexo, sítio ou lado examinado. Os dois estímulos teste da CPM (MPT e PPT) foram capazes de produzir maiores limiares

quando comparados aos estímulos não condicionados ($p < 0,001$). Um maior número significativo de sujeitos respondeu positivamente a estimulação CPM no músculo temporal ($p = 0,002$) para ambos estímulos teste. O estudo concluiu que o perfil sensorial avaliados por meio de QSTs pode ser influenciado pela região de exame e sexo. O efeito da CPM foi igualmente positivo para ambos estímulos teste. No entanto, seu grau de resposta depende da região avaliada.

Palavras chave: Dor facial. Neuralgia Facial. Limiar da Dor.

ABSTRACT

Determination of normative values for mechanical quantitative sensory tests in the orofacial region

Modern concepts for the treatment of pain patients are based on the hypothesis that different clinical signs and symptoms reflect different underlying pathophysiological mechanisms of pain generation. To analyze these mechanisms, in 2006, the DFNS (German Research Network on Neuropathic Pain) developed a standardized protocol of quantitative sensory testing (QST) for a quantitative evaluation of pain generating mechanisms, creating reference values for hand, foot and face (masseter muscle) sites. However, there is a lack of orofacial reference values for the temporalis muscle and maxillary gingiva. This study aimed to determine reference values for QST protocol in the orofacial region and evaluate the effectiveness of two test stimuli during conditioned pain modulation (CPM) test. Sixty participants (30 men/30 women) were examined through the tests of mechanical detection (MDT), mechanical pain (MPT), wind-up ratio (WUR), pressure pain threshold (PPT) and conditioned pain modulation (CPM), to determine reference values in healthy subjects. Individuals were examined in a single session by a trained examiner under the protocol developed by the DFNS (2006). The CPM statistical evaluation was done by a multi-way analysis of variance (ANOVA) within the factors site (2 levels), time (2 levels), and sex (2 levels); comparing the absolute values of MPT and PPT. QST reference values comparison was made by a multi-way within-subjects ANOVA performed considering the factors site (3 levels), side (2 levels) and sex (2 levels) ($\alpha=5\%$). MDT and MPT showed main effects of site ($p<0.001$), where the maxillary gingiva presented the highest thresholds for MDT and lowest MPT thresholds. In addition, PPT values of the anterior temporalis were lower than the hand ($p<0.001$). PPT ($p<0.001$) showed main effects of sex, where men presented higher thresholds. WUR did not show any main effects of sex, site or side. Both CPM test-stimulus (PPT and MPT) were capable of producing significantly higher thresholds during conditioning stimulus when compared to baseline thresholds ($p<0.001$). Temporalis CPM respondents were significantly higher ($p=0.002$) than hand respondents for both QSTs. The study concluded that orofacial QST profile of

healthy participants could be influenced by the test site and sex. The CPM does not differ considering PPT and MPT as test stimuli, but the test site can influence its effects.

Key words: Facial pain. Facial neuralgia. Pain Threshold.

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1 Introduction

1 INTRODUCTION

Modern concepts for the treatment of pain patients are based on the hypothesis that different clinical signs and symptoms reflect different underlying pathophysiological mechanisms of pain generation. The knowledge of how nociceptive impulses are produced and transmitted by the central nervous system (CNS) is essential to the understanding of how a patient is experiencing pain and the methods by which we can treat them (GREENSPAN, 2001).

Somatosensory assessment is routinely applied in a non-standardized manner and only in the last decade great efforts have been proposed to create a comprehensive and standardized protocol to quantify this assessment. In 2006, the DFNS (German Research Network on Neuropathic Pain) developed a standardized protocol of 13 quantitative sensory tests (QST) for a quantifiable evaluation of somatosensory profile, creating reference values for hand, foot and face (cheek region) (ROLKE; BARON; et al., 2006).

The effect of conditioned pain modulation has been commonly observed for centuries, this phenomenon is based on the paradigm that pain in one body region can mask pain in another body site. This effect was first named as diffuse noxious inhibitory controls (DNIC) and was widely tested on animal subjects (LEBARS; DICKENSON; BESSON, 1979). Human-based research, using 'pain inhibits pain' paradigms, has adopted the terms DNIC and HNCS (heterotopic noxious conditioning stimulation), incorporating the psychophysical domain, by describing behavior patterns. Trying to resolve this nomenclature ambiguity, the scientific community determined a consensus suggesting the term conditioned pain modulation (CPM) to describe psychophysical paradigms in which a conditioning stimulus is used to affect a test stimulus (YARNITSKY et al., 2010).

Recent studies speculate that an ongoing chronic pain may "exhaust" CPM mechanisms, causing a dysfunction increasing facilitation through the descending pathways. The evaluation of the conditioned pain modulation (CPM) can identify patients at risk of developing chronic pain and promote a personalized treatment to patients (YARNITSKY et al., 2012).

QSTs also have an important role on modern diagnostic methods for orofacial pain dysfunctions, and it is still a developing field. QSTs have been utilized to diagnose intraoral neuropathic dysfunctions such as atypical odontalgia, allodynia and hyperalgesia (PORPORATTI et al., 2015) and TMD disorders especially in the masticatory muscles. The aim of this study is to provide reference values and evaluate the CPM effect specifically to less studied orofacial regions such as the temporalis muscle and maxillary gingiva. These reference values may contribute to the diagnostic process and future research of several pain dysfunctions of the orofacial region.

2 Literature Review

2 LITERATURE REVIEW

2.1 QST normative data

Several methods can be used to assess patients with neuropathic pain. The most common and reliable are: questionnaires, electrodiagnostic studies, laser evoked potentials (LEP), functional neuroimaging, skin biopsy, and quantitative sensory testing (QST). In the diagnosis process, questionnaires are used to extend the patient medical history just as QSTs were created to extend traditional and more complex methods of neurological examinations of somatosensory functions (CRUCCU et al., 2004) (DWORKIN; SCHMADER, 2003).

Nerve fibers are divided according to their thickness, which is directly related to the speed at which nerve impulses are transmitted. The primary somatosensory afferent fibers are classified as type A, type C. Type A fibers are myelinated, and thicker, which gives them a greater stimuli transmission speed. A fibers are subdivided into alfa (13-20 μm), beta fibers (6-13 μm), and delta fibers (1-5 μm). Type C fibers are thinner (0.5-1 μm) and unmyelinated, transmitting slower impulses (0.5 to 2m/s). Different fibers are able to transmit different kinds of stimuli, alpha, beta and gamma fibers are responsible for proprioceptive and tactile stimuli, and type A delta and C type fibers are responsible for transmitting painful stimuli. Among the painful stimuli, the fastest are transmitted by type A delta fibers (needling, intense thermal stimuli of heat and cold), and slower stimuli such as deep pain are transmitted by type C fibers (chemical stimuli, itching and thermal heat and cold) (SYDNEY; CONTI, 2011) (JP., 2005). Modern concepts of pain treatment are based on the hypothesis that different clinical signs and symptoms reflect different mechanisms of pain generation. Experimental studies suggest that different mechanisms operate together or individually by determining the type of sensory response, correlating signs and symptoms with different physiological mechanisms (ROLKE; BARON; et al., 2006) (GREENSPAN, 2001).

There were a number of published papers testing QST procedures that allowed the evaluation of somatosensory function. However, when clinicians begun to use QSTs as diagnostic protocols, some obstacles still complicated the process. There was no general agreement on standard procedures for each test, some

sensory functions could be assessed in various ways and by different instruments, and still the same instrument could give different results if not properly standardized (YARNITSKY et al., 1995) (ROLKE; MAGERL; et al., 2006).

In 2002, the German Research Network on Neuropathic Pain (DFNS) was founded in order to establish a database of patients phenotypically characterized in various states of neuropathic pain. The DFNS developed a battery of 13 standardized QSTs, covering thermal tests of heat and cold perception, heat pain thresholds to cold and heat stimuli, mechanical detection thresholds to touch and vibration, painful sensitivity to mechanical pinprick stimuli, pressure, hyperalgesia, allodynia and temporal summation (ROLKE; BARON; et al., 2006) (MAIER et al., 2010).

To diagnose and treat patients based on underlying pain mechanisms, it is essential to characterize the somatosensory phenotype of each patient as accurately as possible. Svensson et. al (2004) (SVENSSON et al., 2004) evaluated quantitative sensory test methods (QSTs) used for the trigeminal region and concluded that QSTs were a useful tool for somatosensory evaluation, but still there is a lack of reference values and standardized protocols for various sites of the orofacial region (SVENSSON et al., 2004) (PIGG et al., 2010).

The focus of the present study was to evaluate only mechanical threshold tests, and determine their reference values in healthy subjects. The chosen QSTs were: Mechanical detection threshold (MDT), mechanical pain (MPT), pressure pain (PPT), temporal summation (WUR), and conditioned of pain modulation (CPM). According to Santos and Conti (2005) (SANTOS SILVA et al., 2005), reliable data on pressure pain thresholds (PPT) can be obtained by an algometer if factors such as the tip size, pressure, force speed, position and the degree of muscle contraction are controlled (MCMILLAN; NOLAN; KELLY, 1997) (SANTOS SILVA et al., 2005). In clinical practice, algometry can be performed using digital hand pressure, if the examiner is properly calibrated. PPT is capable of measuring pain pressure thresholds in both symptomatic and asymptomatic patients. With the use of the algometer, baseline values for pressure thresholds applied to orofacial muscles have been registered with acceptable reliability (FREDRIKSSON; ALSTERGREN; KOPP, 2000).

In this study, the MDT test was conducted according to the methodology described by Rolke et. al (ROLKE; MAGERL; et al., 2006). MDT assessment was obtained with von Frey monofilaments that were used to evaluate detection of type A-beta fibers through positive and negative responses to different thicknesses of the monofilaments (SYDNEY; CONTI, 2011).

A single brief mechanical stimulus to a body region can produce two successive sensations of pain in humans. The first sharp well-localized pain is followed by a second pain less localized that outlasts the initial stimulus. It has been shown that if mechanical stimuli are repeatedly delivered in an interval of less than 3 seconds, the second pain increases in intensity and duration (PRICE, 1972). This phenomenon is called temporal summation and can be evaluated through the wind up ratio QST (WUR). The psychophysical testing mechanism is an increase in magnitude and frequency of the central nervous system response when nociceptive neurons receive a repeated noxious stimulus. This test evaluates the increase in perceived pain intensity when noxious stimuli are repeated with a constant intensity under a short period (SVENSSON et al., 2011).

2.2 Conditioned pain modulation (CPM)

CPM has been commonly observed for centuries, this phenomenon is based on the principle that pain in one body region (conditioning stimulus) can mask pain in another body site (test stimulus). This effect was first named as diffuse noxious inhibitory controls (DNIC), but a recent consensus in the scientific community appointed the effect of DNIC in humans as conditioned pain modulation (CPM) (YARNITSKY, 2010) (KOSEK; HANSSON, 1997) (OONO et al., 2013).

CPM effects can vary depending on the conditioning stimulus, the magnitude and nature of the CS, and the stimulated nerve fibers (VILLANUEVA; LE BARS, 1995). Healthy individuals demonstrate that spinal nociceptive reflex is inhibited when their hand is immersed into a heated water bath at a noxious temperature, and that higher conditioning temperatures induce a greater CPM effect. The temperature can vary between 45°C to 47,5°C, depending on the individual's tolerance, and also CPM can be triggered with cold 6°C water, mechanical pressure, or chemical (muscular exercise under ischemia) (GRANOT et al., 2008).

A recent study by Oono (2013) (OONO et al., 2013) evaluated several conditioning stimuli and concluded that the cold stimulus is the conditioning stimulus that best triggers the CPM effect, when pressure pain threshold is used as a test stimulus. However, the author reports that further studies are still needed to evaluate the optimal conditioning stimulus for assessment of CPM (OONO et al., 2011). Lautenbacher (2007) (LAUTENBACHER; PRAGER; ROLLMAN, 2007) evaluated noxious stimuli conditions (water at 46.5°C) and non-noxious (water at 42°C) and concluded that noxious conditioning stimulation was able to increase the heat pain threshold using a focal heat test stimulus.

Yoono et. al. (2013) (OONO et al., 2013) examined the effects of CPM on the full QST protocol (13 tests) proposed by the DFNS (2006). The study adopted a 30-minute pressure-conditioning stimulus, and PPT was the only test amongst all QSTs that was significantly modulated and was considered the most sensitive measure to detect endogenous pain inhibitory mechanisms. This study aims to evaluate the effect of CPM on MPT and PPT tests and to determine reference values for MDT, MPT, WUR and PPT in healthy subjects.

3 Objectives

3 OBJECTIVES

Based on the reviewed literature, the objectives of this thesis are:

- 1) To determine reference values of mechanical quantitative sensory tests in the orofacial region for the temporalis muscle, and maxillary gingiva.
- 2) To compare the effectiveness of two test stimuli, i.e., mechanical pain threshold (MPT) and pressure pain threshold (PPT) in the conditioned pain modulation (CPM) response.

4. Materials and Methods

4 MATERIALS AND METHODS

4.1 Participants

Sixty healthy participants (30 women and 30 men) aged between 18 and 50 years were included in this study. They were faculty and student members of the Bauru School of Dentistry, University of São Paulo. None of the subjects reported any chronic pain conditions, e.g., neuropathic pain, temporomandibular disorder (TMD), headache, neck pain, low back pain or fibromyalgia, or previous injury to the assessed site. In addition, they were not making use of any pain medication that would interfere with the examination, e.g., non-steroidal anti-inflammatories (NSAIDs), analgesics, or medications that could affect the central nervous system, e.g., muscle relaxants or antidepressants. Prior to evaluation, the patient received an informed consent approved by the ethics committee of the Bauru School of Dentistry – USP, under the protocol 38674114.1.0000.5417. Individuals were examined in a single session by a single trained examiner.

4.2 Study design

The subject was sited comfortably in a chair in an upright position, and a brief questionnaire about personal information was filled. Prior to any of the QSTs, a training session was performed in which every test was thoroughly explained and at least one sample stimulus was done into a neutral site (opposite hand) for every QST. The examination was done randomly at the thenar eminence (dominant hand), temporalis muscle (bilateral), and maxillary gingiva (between the canine and premolar teeth) but followed a strict sequence according to the protocol described by the DFNS study (ROLKE; MAGERL; et al., 2006).

The protocol sequence was performed according to the DFNS recommendations, as follows: a) mechanical detection threshold (MDT) with the use of Von Frey filaments (model: Bio-VF-M); b) mechanical pain threshold (MPT) and wind up ratio (WUR), both done with an electronic Von Frey (somedic AB, Sweden);

c) pressure pain threshold, performed with an electronic algometer (somedic AB, Sweden). Finally, the conditioned pain threshold (CPM) was performed using a water bath (BM-02 Kacil, Brazil) as the conditioning stimulus (CS) and the sensebox kit MPT and PPT as the test stimuli (TS).

4.3 Variables

For this study, five QSTs were chosen to assess somatosensory functions across a mechanical spectrum of primary afferents. A-beta fibers were evaluated by the mechanical detection threshold (MDT), A-delta fibers were assessed through the mechanical pain threshold (MDT), C fibers through pressure pain threshold (PPT). In addition, temporal summation was assessed by the wind-up ratio (WUR).

The test areas were: Temporalis muscle (bilaterally), maxillary gingiva, thenar eminence (hand). The order of test sites was randomly selected for each individual, but the QST tests always followed the same order, based the previously established QST protocol.

4.3.1 Mechanical detection threshold (MDT)

MDT was evaluated with a standardized set of von Frey monofilaments performing a standardized force between 0.008g and 300g until they bend (with 1-2 seconds contact). The von Frey's contact area has a rounded tip with 0.5mm diameter, avoiding sharp edges, which facilitate nociceptive activation. The evaluation was done through a "method of limits", starting from the finest filament (0.008g) applied perpendicularly on the site until the filament bends in an ascending scale until the patient feels the stimulus, then the stimulus is decreased until the patient stops feeling the stimulus. This up and down process was carried out 3 times (3 positive and negative responses) and the result is the geometric mean of these 3 series. During the whole process, subjects were asked to keep their eyes closed to avoid false positives. (ROLKE; BARON; et al., 2006) (ROLKE; MAGERL; et al., 2006) (OONO et al., 2013) (BAAD-HANSEN et al., 2013) (SVENSSON et al., 2011).

4.3.2 Mechanical pain threshold (MPT)

The mechanical pain threshold test (MPT) was evaluated using an electronic von Frey. This method has several differences when compared to the standard model using von Frey filaments (method of limits). The electronic von Frey produces a gradual continuous stimulus that ceases when the subject presses a button that signals the exact moment the individual starts to feel a noxious stimulus. This method has several advantages, such as the computer controlled gradual and constant stimulus increase, the diameter of the apparatus tip is always the same, and the process is much faster compared to the standard method of limits. The examination was held in the central portion of the anterior temporalis, thenar eminence and maxillary mucosa (premolar region). The tip of the electronic von Frey was applied perpendicularly to the chosen site and pressure was gradually increased always following the light mechanism of the apparatus that controls the constant gradual increase in pressure (25g/s). This process was carried out 3 times and the end result was the mean of these 3 series.

4.3.3 Wind up ratio (WUR)

Wind up ratio QST was used to evaluate the temporal summation of second pain phenomena. For this test, the electronic von Frey was used with a fixed pressure stimulus equivalent to +10% of the MPT threshold observed on the previous test. First, a single pinprick stimulation with the electronic von Frey tip is done and the patient is told to evaluate the pain rating on a digital VAS (sensebox, somedic ab; Sweden). Then, the VAS is reset and a series of 10 consecutive stimuli of the same intensity (1 per second applied within an area of 1cm²) is made and the subject rates the maximum experienced pain during the whole series on the same digital VAS. The examination will be performed at the anterior temporalis muscle (bilaterally), thenar eminence and the maxillary gingiva. Temporal summation (WUR) was calculated by dividing stimuli series pain rating by the pain rating of the single stimulus (ROLKE; BARON; et al., 2006).

4.3.4 Pressure pain threshold (PPT)

The PPT evaluation was held in the central portion of the anterior temporalis muscle and thenar eminence with a digital algometer (somedic AB, Sweden) that contains a flat circular tip of 1cm². The tip of the apparatus was positioned perpendicularly to the evaluation site and pressure was applied at a constant speed of 1kg/cm²/s until the subject pressed a button signaling the beginning of a noxious stimulus. The main advantage of the digital algometer is that the rate in which the pressure is increased is controlled by the computer and followed by the examiner by a set of lights that indicate the right pressure during the test. The green light indicates a correct applied pressure, as the blue and red light indicate a lack or excess of pressure, respectively. During the examination, the subject's head was firmly supported passively by the examiner. The test was done 3 times and the average of the 3 series was calculated to reach a final reference value for each site (ROLKE; BARON; et al., 2006; SANTOS SILVA et al., 2005; SVENSSON et al., 2011).

4.3.5 Conditioned pain modulation (CPM)

The chosen conditioning stimulus to induce CPM effect was a warm water recipient with controlled temperatures ranging between 45°C to 46.5°C, depending on individual tolerance. This protocol was previously tested by Niir (2011) (NIR et al., 2011) and confirmed to induce a CPM effect when test stimuli were performed simultaneously into a different body region. Prior to the test, subjects were asked to immerse their hand completely into a digitally controlled water bath (BM-02 Kacil, Brazil), with an initial temperature of 46.5°C for 15 seconds. Subjects were asked to rate their pain, if they reported a score higher or lower than 5-7 (0-10 scale), the water temperature was adjusted until the individual fell into that range of pain score. The water bath used for this study was digitally controlled, with a resolution of 0,1°C, and the water was maintained circulating by a submersed pump to keep the water at the same temperature across the whole recipient, as well as to keep the skin from conforming to the temperature (NIR et al., 2011).

The non-dominant hand of subjects was completely immersed in the water bath for about 75 seconds in a still position with the fingers wide apart, until the test stimulus was administered. Both MPT and PPT started at t=30s of the conditioning

stimulus on a randomized site and took about 45 seconds to complete. The test stimuli were administered one at a time, always starting with MPT, followed by PPT after a washout period of 3 minutes (NIR et al., 2011).

4.4 Statistical Analysis

Means and standard deviation (SD), median, minimum and maximum values as well as the 95% confidence interval of the mean were described for the MDT, MPT, WUR and PPT. In addition, all the quantitative variables were assessed for normal distribution using the Kolmogorov-Smirnov test and a log10 transformation was performed when the test results were significant, considering an alpha level of 5% ($p < 0.050$).

Multi-way analysis of variance (ANOVA) was performed as following: a) the within factor site (3 levels) and between factor sex (2 levels) and b) the within factor side (2 levels) and between factor sex (2 levels) were established to compare the MDT, MPT and WUR (absolute values after log10 transformation), and the PPT (absolute values). When appropriate, post hoc analyses were performed using Tukey's Honestly Statistical Difference (HSD). The significance level was set at 5% ($p = 0.050$).

The CPM effect was calculated by subtracting the conditioned MPT and PPT by its respective baseline. Negative values indicate an inhibitory CPM effect, meaning loss of somatosensory function (YARNITSKY et al., 2015). Moreover, the proportion of difference from baseline was also computed according to the formula $[(\text{difference}/\text{baseline}) \times 100]$. Multi-way analysis of variance (ANOVA) with the within factors site (2 levels) and time (2 levels) and between factor sex (2 levels) was performed to compare the absolute values after log10 transformation of the MPT and the absolute values of PPT. In addition, subjects were divided as CPM responders and non-responders using a 10% cutoff limit, as proposed by Oono (2011) (OONO et al., 2011). Subjects who had a decrease in threshold or did not have at least a 10% increase during the conditioning stimulus were classified as CPM non-responders. Then, the Cochran Q test followed by post-hoc McNemar test were performed to compare the proportion of responders and non-responders among different sites,

sides and test stimuli. In order to control for multiple comparisons, a Bonferroni correction adjusted the significance value for 0.7% ($p = 0.007$).

5 Results

5 RESULTS

5.1 Participants

The 60 participants were evenly distributed within genders (30M/30F); all were adults aging between 20 and 47, with an average age of 27 years old. 96.6% of subjects were right-handed, 21.6% declared to have headaches at least once a week, 51.7% reported sleep or awake bruxism and 15% reported facial muscular tiredness in the morning. All subjects were examined in a single session and there was no refusal to any of the tests.

5.2 Descriptive QST data

Table 1 shows the descriptive data of each QST.

Table 1 – Descriptive analysis of QSTs absolute values.

Site	MDT (g)				MPT (g)				WUR (series/single VAS)				PPT (kg/cm ²)		
	Right Temp.	Left Temp.	Gingiva	Hand	Right Temp.	Left Temp.	Gingiva	Hand	Right Temp.	Left Temp.	Gingiva	Hand	Right Temp.	Left Temp.	Hand
Mean	0.047	0.047	0.613	0.046	99.6	103.1	67.3	87.3	2.47	2.42	2.29	2.57	2.85	2.81	5.10
Median	0.013	0.014	0.455	0.027	92.4	85.5	49.3	77.7	2.16	2.20	1.98	2.10	2.69	2.74	4.93
Standard Deviation	0.111	0.145	0.563	0.082	47.2	58.3	46.8	46.4	1.18	1.23	1.35	1.38	0.91	0.90	1.52
Minimum	0.005	0.006	0.022	0.010	31.8	33.7	18.1	29.6	0.78	0.94	0.67	1.18	1.19	1.08	2.00
Maximum	0.683	1.027	2.374	0.553	231.0	293.0	241.3	252.5	5.81	8.00	7.57	7.25	5.52	5.45	10.74
Confidence Lv. +95%	0.029	0.037	0.145	0.021	12.2	15.0	12.1	12.0	0.30	0.32	0.35	0.36	0.24	0.23	0.39

5.3 Absolute QST reference ranges

Absolute reference ranges for mechanical detection threshold (MDT), mechanical pain threshold (MPT), wind up ratio (WUR), and pain pressure threshold (PPT) are represented as box-plot graphics (Figure 1).

Figure 1 – Absolute QST reference ranges from 3 body regions across all genders (n=60). Shaded areas represent the first and third quartile, in which 50% of subjects' thresholds were found, the line between both quartiles represents the median, and the upper and lower lines show the maximum and minimal thresholds for each QST test, respectively.

5.3 Data ranges for the detection of sensory loss/gain

Full range of available threshold data is shown in fig.2 y-axis.

Figure 2 – Absolute QST reference ranges are presented over different body regions across all age groups and gender (n=60). Absolute QST data are presented as means (dots) $\pm$ 95% confidence intervals reflecting the reference range in healthy human subjects. Grey bars indicate the measurable range of plus and minus signs for each QST parameter. The full range of the y-axis was limited by the danger of causing tissue damage or the maximum stimulus available of the devices. A plus sign signifies gain of sensory function (reduced threshold or increased rating), a minus sign loss of sensory function.

5.4 Mechanical detection threshold (MDT)

There were main effects of site ($F=318.53$, $p<0.001$). The highest thresholds were found in the gingival mucosa (Tukey: $p<0.001$), and hand thresholds values were higher when compared to temporalis muscle (Tukey: $p=0.007$). Neither main effects of side ($F=0.05$, $p=0.811$) nor main effects of gender ($F=2.75$, $p=0.102$) differences were found.

5.5 Mechanical pain threshold (MPT)

There were main effects of site ($F=29.93$, $p<0.001$) and gender ($F=9.73$, $p=0.002$). The lowest threshold values were found in the maxillary gingiva (Tukey: $p<0.001$) and there was no significant difference between hand and temporalis (Tukey: $p=0.054$). Women showed significantly lower threshold values for MPT (Tukey: $p=0.002$). There were no side-to-side differences in the temporalis muscle ($F=0.01$, $p=0.910$).

5.6 Wind up ratio (WUR)

There were no main effects of site ($F=1.18$, $p=0.167$), side ($F=0.06$, $p=0.792$) or gender ($F=0.04$, $p=0.830$).

5.7 Pressure pain threshold

There were main effects of site ($F=359.38$, $p<0.001$). Significant lower thresholds were found at the temporalis compared to the hand (Tukey: $p<0.001$). There were also main effects of gender ($F=24.51$, $p<0.001$). Men showed higher thresholds values for all sites ($F=24.51$, $p<0.001$). In addition, the lowest pressure pain threshold was observed at women's temporalis (Tukey: $p<0.021$), while the highest thresholds were found at men's thenar eminence (Tukey: $p<0.001$).

5.8 CPM absolute values

Table 2 presents the descriptive data for the MPT test stimulus and table 3 represents data for PPT. Negative mean/median values for the CPM effect indicate loss of function from mechanical receptors, thus indicating an increase in the overall pain threshold.

Table 2 – Data description for MPT across all body regions

	Right Temporalis				Left Temporalis				Hand			
	Base (g)	CS (g)	CPM (g)	CPM (%)	Base (g)	CS (g)	CPM (g)	CPM (%)	Base (g)	Test (g)	CPM (g)	CPM (%)
Mean	99.6	155.8	-56.2	-68.6	103.1	158.8	-55.8	-67.4	87.3	121.6	-34.4	-56.4
Standard Error	6.1	9.8	8.0	10.7	7.5	10.8	8.7	8.7	6.0	8.0	6.8	10.4
Median	92.4	143.0	-50.1	-51.9	85.5	138.0	-44.7	-60.9	77.7	104.0	-23.7	-41.8
Standard Deviation	47.2	75.8	61.9	82.6	58.3	83.4	67.5	67.4	46.4	61.9	52.7	80.5
Minimum	31.8	30.0	-250.2	-411.5	33.7	23.0	-276.9	-282.3	29.6	28.0	-168.8	-347.7
Maximum	231.0	345.0	75.0	54.0	293.0	375.0	137.0	46.8	252.5	329.0	62.5	39.6
Confidence Level (95.0%) +/-	12.2	19.6	16.0	21.3	15.0	21.6	17.4	17.4	12.0	16.0	13.6	20.8

Table 3 – Data description for PPT across all body regions

	Right Temporalis				Left Temporalis				Hand			
	Base (kg/cm ²)	CS (kg/cm ²)	CPM (kg/cm ²)	CPM (%)	Base (kg/cm ²)	CS (kg/cm ²)	CPM (kg/cm ²)	CPM (%)	Base (kg/cm ²)	CS (kg/cm ²)	CPM (kg/cm ²)	CPM (%)
Mean	2.85	3.60	-0.75	-29.5	2.81	3.51	-0.71	-29.0	5.10	6.11	-1.01	-23.3
Standard Error	0.12	0.15	0.09	3.9	0.12	0.14	0.09	3.8	0.20	0.25	0.19	4.1
Median	2.69	3.47	-0.58	-23.6	2.74	3.38	-0.56	-23.4	4.93	5.83	-0.99	-18.6
Standard Deviation	0.91	1.16	0.71	30.1	0.90	1.09	0.71	29.2	1.52	1.90	1.44	32.0
Minimum	1.19	1.71	-2.89	-131.1	1.08	1.77	-2.68	-118.6	2.00	2.38	-6.81	-142.2
Maximum	5.52	7.82	0.96	25.0	5.45	6.39	0.81	30.9	10.74	11.60	4.22	63.9
Confidence Level (95.0%) +/-	0.24	0.30	0.18	7.8	0.23	0.28	0.18	7.5	0.39	0.49	0.37	8.3

5.9 CPM effects for MPT and PPT

Figure 3 represents the graphical representation of the CPM effect for both test stimuli. Both showed main effects of site ($Q=41.55$, $p<0.001$). Temporalis conditioned threshold was significantly higher (Tukey: $p<0.001$) than the hand threshold, although no temporalis side differences ($p>0.05$) were encountered. The conditioned threshold was significantly higher (Tukey: $p<0.001$) than the baseline threshold for both stimuli. In addition, male participants had higher hand baseline and conditioned thresholds than female subjects, but the same difference was not found for the temporalis muscle.

Figure 3 – Graphical representation of absolute values and standard deviation for baseline thresholds and modulated test stimuli. Baseline threshold represented in blue colored columns followed by test stimulus thresholds in orange colored columns. Different letters represent statistical differences ($p < 0.05$).

5.10 CPM responders vs non-responders

Subjects were divided into CPM responders and CPM non-responders by a 10% cutoff (Figure 4). During MPT stimulus, 83.3% had a positive CPM response for the temporalis, and 60% for the hand site. PPT test showed a 76.6% positive response for the temporalis, while 66.6% of subjects were positive for the hand site. Temporalis CPM responders were significantly higher than hand responders for both QSTs ($p = 0.002$). No side differences between temporalis side and between MPT and PPT positive respondents were observed ($p > 0.007$).

Figure 4 – Graphical representation of the number of CPM respondents to each QST/site during CS. Different letters represent statistical differences ($p < 0.007$).

6 Discussion

6 DISCUSSION

The main findings of this cross-sectional assessment of mechanical quantitative sensory tests were: a) reference values for mechanical QSTs (MDT, MPT, WUR, PPT) were obtained for 3 sites of the orofacial region. b) evaluation of the conditioned pain modulation (CPM) through two different test stimuli (MPT and PPT) showed that both QSTs were capable of producing similar and effective results with a warm water (46°C) conditioning stimulus.

The temporalis muscle and oral mucosa are two poorly explored important sites that only a few studies have researched (PIGG et al., 2010) (SANTOS SILVA et al., 2005) (PORPORATTI et al., 2015), leaving a lack of reference values for mechanical QST in these areas. In addition, there is still much debate to which QST is the best test stimulus to assess the CPM effect (YARNITSKY et al., 2015).

Within the orofacial region, the masseter muscle was not evaluated due to the vast number of studies that had already determined its QST reference values. The focus of our study were less researched regions such as the anterior temporalis muscle and maxillary gingiva. Only the temporalis was bilaterally assessed due to a previous research (SANTOS SILVA et al., 2005) that found differences in pain pressure thresholds between sides. Hand and gingiva sites values had already been determined by several studies (KOMIYAMA; DE LAAT, 2005; ROLKE; MAGERL; et al., 2006; SVENSSON et al., 2011) and no side differences were reported. Our study focused only on mechanical thresholds and test stimulus because of the available research time and apparatus restraints. Mechanical stimuli were chosen because of their greater availability in clinical practice, and their reference values would be more broadly used by clinicians.

6.1 Mechanical detection threshold (MDT)

Data for MDT, MPT and WUR were not normally distributed due to natural biological variations in response to QSTs. Similar researches (ROLKE; MAGERL; et al., 2006) (SVENSSON et al., 2011) that attempted to obtain reference values for these tests also found non-normalized values that had to undergo log-transformation

in order to achieve normal distribution. Significant differences ($p < 0.01$) for MDT among body regions were found, the gingival mucosa showed higher detection thresholds ($p < 0.001$), followed by hand, that also showed a higher threshold when compared to the temporalis muscle. A similar study (KOMIYAMA; DE LAAT, 2005) analyzed tactile detection at the maxillary gingiva, cheek skin, tongue tip, and thenar skin and also found higher threshold values for the gingiva compared to all other sites. This finding suggests that the gingival mucosa is less responsive to tactile detection than other areas.

The fact that hand threshold was higher than temporalis might be explained by the characteristics of the thenar skin that is usually more exposed to environmental influences, thus exhibit a significant thickening of the epidermis resulting in higher mechanical resistance (HOLBROOK; ODLAND, 1974). No side (temporalis) and gender differences were observed ($p > 0.05$), a result also observed by other similar studies (KOMIYAMA; DE LAAT, 2005) (ROLKE; BARON; et al., 2006).

6.2 Mechanical pain threshold (MPT)

Given the difference between the standard MPT test with von Frey filaments and the electronic von Frey, some studies have evaluated their efficacy and reliability. Tena et. al. (2012) (TENA et al., 2012) evaluated these two methods comparing their reproducibility, reliability and time required for testing and found that both tests showed good reliability, although the electronic von Frey showed a better reproducibility and took half the time to be completed. The advantage of the electronic von Frey used by our study (somedic AB, Sweden) was that it provided a continuous stimulus with a computer controlled steady increase in pressure (g), in which the pinprick pain threshold was set by the pressing of a button controlled by the participant.

MPT data had a relatively large somatosensory variation amongst subjects, with mean/SD values of 101.5g (± 52.7), 67.3g (± 46.8), and 87.3g (± 46.4) for temporalis, gingiva and hand, respectively. These somatosensory deviations among healthy subjects it is a common data trait also observed by other QST studies (BAAD-HANSEN et al., 2013). Maier et. al. (2010) (MAIER et al., 2010) also found

threshold deviations in 36.2% of the healthy reference group, showing that healthy subjects present at least 1 threshold value outside the 95% CI (for the 13-test QST protocol). Porporatti et al, (PORPORATTI et al., 2015) compared 4 intraoral QST values between healthy and acute pulpitis patients (IT) and concluded that the MPT is the most accurate QST to discriminate the diagnostic differences between IT and healthy individuals. These results stress the importance that QST evaluation should always be combined with a thorough clinical examination and other supplementary tests (BAAD-HANSEN et al., 2013).

Contrary to the detection threshold, the maxillary gingiva showed significantly lower threshold for mechanical pain ($p < 0.05$) compared to the temporalis muscle and hand, which did not show statistical differences between them ($p > 0.05$). These results indicate that the maxillary gingiva is less responsive to tactile sensation but more sensitive to mechanical pain stimuli, when compared to extra oral sites such as hand and temporalis. This maxillary gingiva pattern was also observed by other QST studies (KOMIYAMA; DE LAAT, 2005) (PORPORATTI et al., 2015).

Our study observed significantly lower MPT thresholds for women for all body regions ($p < 0.05$). The DFNS research group studies showed pronounced gender differences only for pain thresholds, these differences can be more likely explained by different central processing and are unlikely due to peripheral factors such as innervation density (ROLLMAN; LAUTENBACHER, 2001) (GARRETT et al., 2013).

6.3 Wind up ratio (WUR)

Temporal summation evaluated by the wind up ratio QST, did not show any gender, side, and site differences ($p > 0.05$). This is a common finding in several studies (ROLKE; MAGERL; et al., 2006) (PIGG et al., 2010) due to the nature of the QST test. Since WUR is a ratio, differences in region specific pinprick sensitivity are probably eliminated by having a similar proportion between numerator (series pain rating) and denominator (single pain rating). Temporal summation is a central nervous system phenomenon that may reflect the early stages of central sensitization (STAUD et al., 2004). Pigg (2010) (PIGG et al., 2010) showed poor WUR reliability in

healthy subjects, and argued that future studies examining WUR reliability in pain patients may determine if this variable is clinically important.

6.4 Pain Pressure Threshold

PPT was the QST that demonstrated the least somatosensory variation among healthy individuals, being the only test to exhibit normal distribution. Mean values for right temporalis ($2.85 \text{ kg/cm}^2 \pm 0.91$), left temporalis ($2.81 \text{ kg/cm}^2 \pm 0.90$), and hand ($5.10 \text{ kg/cm}^2 \pm 1.52$) showed main effects for site ($p < 0.001$), but not for side ($p > 0.05$). These results indicate that pressure thresholds are region specific with no side-to-side differences, a result also obtained by the DFNS reference protocol. Although the DFNS (2006) study obtained reference values for 13 QSTs on healthy individuals through a large sample (250 subjects), it only examined cheek, hand, and foot sites. Since QST values are region specific, our study chose to examine the temporalis muscle, a region that has fewer published papers focused on its QSTs reference values.

A study by Silva et. al. (2005) (SANTOS SILVA et al., 2005) examined PPT values for healthy ($n=49$) and TMD patients ($n=50$) for the temporalis and masseter muscle. The study found overall mean values for the temporalis muscle of 2.81 kgf/cm^2 (right) and 2.91 kgf/cm^2 (left), results that are very similar to the ones found by our study. In addition, Silva's study found significant side-to-side differences, a result that contradicts our data, and the majority QST studies (SVENSSON et al., 2011) (ROLKE; BARON; et al., 2006) (KOMIYAMA; DE LAAT, 2005).

Our study observed main effects of gender for PPT values ($p < 0.001$). Women presented lower pain pressure thresholds for all sites, a common result when comparing mechanical pain thresholds on most QST studies (BAAD-HANSEN et al., 2013; ROLKE; BARON; et al., 2006; SANTOS SILVA et al., 2005).

6.5 CPM effects

One of the objectives of this study was to evaluate the effects of conditioned pain modulation on mechanical pain thresholds (MPT and PPT). Oono et. al. (2013)

(OONO et al., 2013) examined the effects of CPM on the full QST protocol (13 tests) proposed by the DFNS (2006). That study adopted a 30-minute pressure-conditioning stimulus, while the full QST protocol was administered. PPT was the only test amongst all QSTs that was significantly modulated and may be the most sensitive test to detect endogenous pain inhibitory mechanisms. These and other findings suggest PPT as the primary test stimulus to evaluate CPM effects (OONO et al., 2013) (OONO et al., 2011). The studies of Niir and Nahman (NIR et al., 2011) (NAHMAN-AVERBUCH et al., 2014) used thermal stimuli as both conditioning and test stimulus. The conditioning stimulus for both studies was a noxious warm or cold water while focal heat (49°C) was applied at another body region. Both studies concluded that focal thermal stimulus is also an efficient way to measure CPM effects. In addition, Niir (2011) (NIR et al., 2011) tested various different conditioning temperatures (44.5°C, 45.5°C, 46°C) and concluded that the best range to induce CPM is between 45.5°C and 46°C, depending on the subject's tolerance.

Based on the supporting evidence (NIR et al., 2011) (OONO et al., 2013), our study used a noxious warm water bath, with temperatures ranging from 45°C to 46.5°C, as a conditioning stimulus. As test stimulus, PPT was chosen for its wide support in literature as the most reliable mechanical test stimulus for CPM. In addition, an alternative MPT protocol than the one presented by the DFNS was used as a potential test stimulus. The standard MPT test is a method of lower and upper limits, with varying von frey filaments (Optihair2-Set, Marstock) in an intermittent stimulus. The electronic von Frey used by our study (somedic AB, Sweden) provides a continuous stimulus with a computer controlled increase in pressure (g), in which the pinprick threshold is set by the pressing of a button.

Both PPT and MPT were capable of producing significantly higher thresholds during CS when compared to baseline thresholds ($p < 0.001$). To evaluate the effectiveness between both tests, the number of CPM responders ($>10\%$ of threshold increase) was compared between QSTs, gender, and site. Temporalis CPM responders were significantly higher ($p = 0.002$) than hand responders for both QSTs. No gender, MPT and PPT differences for positive responders were observed ($p > 0.007$). These results suggest that the temporalis muscle was significantly more

effective to provoke a CPM response, and a MPT determined by a continuous stimulus proved to be just as effective as PPT to evaluate CPM effects.

6.6 Interpretation of QST reference data

The clinical interpretation of raw QST data can be very challenging due to the variations of magnitude, scale, and measures among the many sensory tests available. The fact that each region presents different thresholds for the same test, as shown by our study when comparing temporalis, gingiva and hand, only complicates the overall evaluation of the raw data. The QST protocol used by our study was chosen to assess somatosensory functions across a mechanical spectrum of primary afferents. A-beta fibers were evaluated by the detection threshold (MDT); A-delta fibers were assessed through the pain detection threshold (MDT), C fibers through pain pressure (PPT), WUR and CPM tests respectively evaluated temporal summation and pain modulation phenomena.

Rolke et. al. (2006) proposed a graphical representation of mean values and confidence intervals for each test and site, which can be used to determine gain or loss of sensory function. On our study, all reference data was represented by figure 2, mean values for each region and the 95% confidence interval were represented between the grey bars, which demonstrate sensory gain/loss. The plus sign is used to represent a sensory gain (lower threshold) and a minus sign represent a somatosensory loss (higher thresholds). This type of graphical representation facilitates the clinical visualization of healthy or altered individual's threshold, simplifying the clinical diagnosis based on QST.

6.7 Limitations

The present study had the following methodological limitations: a) only the test sites were properly randomized for each individual, the order of the QST tests followed a fixed protocol established by the DFNS. This fixed protocol was developed to avoid interferences among tactile, pinprick and pressure tests, due to the nature of each stimulus and the type of assessed nerve fiber. b) the study was focused only in

obtaining reference values for the adult population (18-50). The DFNS study found consistent reference values within this age range, but values for a younger or older population may vary. c) this study did not analyze the psychological profile of each participant. Although the DFNS studies did not performed such evaluation, Rhudy and Meagher (2000) (RHUDY; MEAGHER, 2000) analyzed 60 healthy human subjects and concluded that emotions such as fear can inhibit and anxiety can enhance pain perception.

More studies are needed to establish a full range of QST reference values for each orofacial region and evaluate the relationship between pain thresholds and psychological variables. With a more complete quantitative mapping of somatosensory functions, more precise and predictive diagnostic methods can be developed for the orofacial region.

7 Conclusions

7 CONCLUSIONS

Based on the study described in this thesis, we conclude:

1. Reference values for mechanical thresholds were effectively obtained for most primary sensory afferents. This data allow us to obtain a somatosensory phenotype of a patient including minus and plus signs for tactile detection, mechanical cutaneous and deep pain, temporal summation and the establishment of conditioned pain modulation profile.
2. Maxillary gingiva is less susceptible to tactile stimulus but more susceptible to pinprick pain when compared to the temporalis and hand.
3. Higher thresholds for MPT and PPT were observed in men.
4. PPT and MPT were effective as test stimuli and the temporalis muscle was the most effective site to evaluate CPM effects.

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