UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

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Evaluation of psychosocial, somatosensory and behavioral profiles of patients with chronic temporomandibular pain

Avaliação do perfil psicossocial, somatosensorial e comportamental de pacientes com dor crônica temporomandibular

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Orientador: Prof. Dr. Paulo César Rodrigues Conti

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RESUMO

Avaliação do perfil psicossocial, somatosensorial e comportamental de pacientes com dor crônica temporomandibular

Vários fatores têm sido avaliados para caracterizar padrões de normalidade em indivíduos saudáveis e variações relevantes em pacientes com disfunção temporomandibular crônica (DTM), para que possa ser realizado um diagnóstico mais preciso e um tratamento personalizado. Algumas variáveis que têm sido associadas a esse tipo de análise são questionários psicossociais, testes psicofísicos, capacidade endógena de modulação da dor e prática de atividade física. O objetivo deste estudo é investigar os efeitos inibitórios da modulação endógena de dor em indivíduos saudáveis e comparar à uma população com dor crônica temporomandibular. Também serão avaliadas suas relações com fatores associados, como perfis psicossociais e somatossensoriais, bem como níveis de atividade física. 311 indivíduos saudáveis e 68 pacientes com dor crônica temporomandibular com idades entre 18 e 50 anos foram incluídos neste estudo. Questionários foram aplicados para avaliação psicossocial e forneceram informações sobre ansiedade traço-estado (IDATE), catastrofização da dor, qualidade do sono (PITTSBURGH), nível de atividade física (IPAQ), qualidade do estilo de vida. A avaliação somatossensorial foi realizada no músculo temporal anterior do lado dominante dos indivíduos saudáveis e no lado da dor relatada para os pacientes com dor crônica de DTM. Os seguintes testes somatossensoriais foram realizados: limiar de dor mecânica (MPT), somação temporal (WUR), limiar de dor à pressão (LDP) e teste de modulação condicionada da dor (CPM). O teste Qui-quadrado foi utilizado para identificar possíveis associações entre as variáveis categóricas do estudo. As comparações entre as categorias do nível de atividade física foram feitas pelo teste de Kruskal-Wallis, seguido de Mann-Whitney com correção de Bonferroni. Uma regressão logística foi feita para avaliar as categorias binárias de presença de dor crônica e capacidade de modulação da dor (assumindo um ponto de corte de -10%). Todas as inferências estatísticas foram realizadas considerando um nível de significância de 5%. Pacientes com dor crônica temporomandibular apresentaram maiores valores para traços de ansiedade ($p=0,008$), catastrofização ($p<0,001$) e escores de Pittsburgh ($p=0,002$), bem como menores limiares de dor mecânica ($p=0,012$) e a pressão ($p<0,001$), também

relatando uma qualidade de estilo de vida inferior ($p<0,001$). A avaliação somatossensorial revelou limiares de dor mais baixos (MPT, PPT) para indivíduos com dor crônica. Valores semelhantes para a modulação da dor foram encontrados ao comparar pacientes saudáveis e com dor crônica temporomandibular. Ao analisar a frequência de atividade física dos indivíduos, se observou que diferentes níveis de atividade física não parecem alterar os níveis de modulação da dor, mas podem parecer ter um efeito positivo nos níveis de ansiedade, qualidade do sono e qualidade do estilo de vida. Níveis mais elevados de ansiedade, catastrofização e pior qualidade de sono e estilo de vida foram associados ao grupo de dor crônica. A avaliação somatossensorial revelou limiares de dor mais baixos para indivíduos com dor crônica.

Descritores: Exercício; síndrome da articulação temporomandibular; limiar da dor; Qualidade de vida.

ABSTRACT

Evaluation of psychosocial, somatosensory and behavioral profiles of patients with chronic temporomandibular pain

Several factors have been evaluated to characterize patterns of normality in healthy individuals and relevant variations in patients with chronic temporomandibular disorders (TMD), for a more accurate diagnosis and personalized treatment. Some variables that have been associated with this type of analysis are psychosocial questionnaires, psychophysical tests, endogenous pain modulation capacity, and the practice of physical activity. The objective of this study is to investigate the inhibitory effects of endogenous pain modulation in healthy subjects and a population with chronic TMD pain and its relationship with associated factors such as psychosocial and somatosensory profiles, as well as physical activity levels. 311 healthy individuals and 68 chronic TMD pain patients aged between 18 and 50 years were included in this study. Questionnaires were applied for psychosocial assessment and provided information on state-trait anxiety (STAI), pain catastrophizing (PCS), quality of sleep (PITTSBURGH), level of physical activity (IPAQ), lifestyle quality (FLC). The somatosensory evaluation was performed on the anterior temporalis muscle of the dominant side of the healthy individuals, and on the side of the reported pain for the chronic TMD pain patients. The following somatosensory test were performed: mechanical pain threshold (MPT), temporal summation (WUR), pressure pain threshold (PPT), and the conditioned pain modulation test (CPM). The Chi-square test was used to identify possible associations between the categorical variables of the study (on a nominal or ordinal scale), comparisons among categories of Physical activity level were made by the Kruskal-Wallis test, followed by Mann-Whitney with Bonferroni correction. A logistic regression was made to evaluate the binary categories of presence of chronic pain and pain modulation capability (assuming a -10% cutoff). All statistical inferences were performed considering a significance level of 5%. Chronic TMD pain patients presented higher values for anxiety traits ($p=0,008$), catastrophizing ($p<0,001$) and Pittsburgh scores ($p=0,002$) as well as lower mechanical ($p=0,012$) and pressure pain thresholds ($p<0,001$), and reported a lower lifestyle quality ($p<0,001$) than healthy individuals. Somatosensory evaluation revealed lower pain thresholds (MPT, PPT) for individuals with chronic pain. Similar values for

pain modulation were found when comparing healthy and chronic TMD pain patients and different levels of physical activity did not seem to alter pain modulation levels, but may seem to have a positive effect on anxiety levels, sleep quality, and lifestyle quality. Higher levels of anxiety, catastrophizing, and worse sleep and lifestyle quality were associated with the chronic pain group. Somatosensory evaluation revealed lower pain thresholds for individuals with chronic pain.

Key words: Facial pain. Exercise. Pain Threshold. Quality of life. Pain modulation.

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1 Introduction

1 INTRODUCTION

Temporomandibular disorder (TMD) is a condition that can lead to chronic pain in the face. TMD involves problems on both the temporomandibular joint (TMJ) and the muscles responsible for most oral functions, being the second main cause for seeking pain treatment in the dental clinic (DE LEEUW; KLASSER, 2013). As its diagnosis and correct treatment is multifactorial, several methods have been evaluated so that this type of pain can be better understood and treated. Methods such as the quantification of the sensory profile (QST tests), the psychosocial profile of each individual (questionnaires) and dynamic tests to assess the patients' endogenous pain modulatory systems (CPM) have been commonly chosen to better understand this process of pain chronicity. Another interesting factor to be investigated is the effect of physical exercise on hypoalgesia in orofacial pain. Due to the scarcity of studies on the topic, specifically in orofacial pain, it is still not possible to determine whether physical activity would have any influence on chronic pain in this region. In this sense, the real influence of physical activity on the response to painful sensory stimuli and on pain modulation in the orofacial region is still not fully elucidated. ROLKE; BARON; et al., 2006

Studies support the hypothesis that chronic pain can be facilitated by disorders in the endogenous pain modulating system (LAUTENBACHER; ROLLMAN, 1997) (KOSEK; HANSSON, 1997) or the presence of nociceptive stimuli with specific characteristics (e.g., high frequency) (STAUD; VIERCK; CANNON; MAUDERLI *et al.*, 2001). To study the mechanisms involved in the presence of chronic pain, psychophysical methods have been used, such as CPM and Wind-up (WU) (STAUD; ROBINSON; VIERCK; PRICE, 2003) (STAUD; CANNON; MAUDERLI; ROBINSON *et al.*, 2003). CPM, for example, favors the assessment of the functionality of the descending pain pathways. In this way, the presence of conditioning stimulus reduces experimental pain in healthy participants, but not in patients with chronic pain (LAUTENBACHER; ROLLMAN, 1997) (KOSEK; HANSSON, 1997). In this way, chronic pain maintenance can be related to a deficit of endogenous pain inhibition.

Other factors, such as gender and the patient's clinical condition, may be related to chronic pain development. It was seen that CPM was able to decrease temporal

summation only in men and not in women or patients with fibromyalgia (STAUD; ROBINSON; VIERCK; PRICE, 2003). Fibromyalgia patients have increased secondary pain induced by temporal summation (STAUD; VIERCK; CANNON; MAUDERLI *et al.*, 2001). This increase in WU has mechanisms that involve N-methyl-d-aspartate (NMDA) or substance P receptors, or intracellular pathways in neurons of the dorsal horn of the spinal cord (PRICE; DUBNER, 1977) (KELLSTEIN; PRICE; HAYES; MAYER, 1990). WU can contribute to hyperalgesia and persistent pain, and can be modulated by physical activities that can decrease the pain caused by WU in normal subjects, but not in patients with fibromyalgia (VIERCK; STAUD; PRICE; CANNON *et al.*, 2001).

This study aims to investigate the inhibitory effects of CPM in healthy subjects and a population with chronic TMD pain and its relationship with possible associated factors such as an active physical lifestyle, psychossocial, and somatosensory thresholds.

2 Literature Review

2 LITERATURE REVIEW

The international association for the study of pain (IASP) classifies pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. It is important to note that these neurobiological and psychological mechanisms involved in this experience are fluid and can be altered to obtain different pain outcomes. Some of these changes can lead to chronic pain, a condition that can damage not only biological mechanisms, but also social, emotional and professional aspects of patients' lives (RAJA; CARR; COHEN; FINNERUP *et al.*, 2020).

Chronic pain is defined as pain that persists past the normal time of healing and is present continuously or intermittently for at least three to six months. A significant part of this scenario is related to orofacial pain (OFP), which affects about 39 million adults (22%) in the United States (LIPTON; SHIP; LARACH-ROBINSON, 1993). Chronic orofacial pain (OFP) is the characteristic feature of a number of clinical conditions, such as temporomandibular joint disorder (TMD), burning mouth syndrome, atypical odontalgia and atypical facial pain that are difficult to diagnose and treat (DURHAM, EXLEY, WASSELL, & STEELE, 2007 ELRASHEED, WORTHINGTON, ARIYARATNAM, & DUXBURY, 2004; PFAFFENRATH, RATH, PÖLLMANN, & KEESER, 1993).

The descriptive epidemiology of chronic orofacial shows a strong association with psychosocial risk factors (AGGARWAL ET AL., 2008; BAIR ET AL., 2016; SLADE ET AL., 2016) and a co-occurrence with other long-term conditions like chronic widespread pain (CWP), irritable bowel syndrome (IBS) and chronic fatigue (CF) (AGGARWAL ET AL., 2006; BAIR ET AL., 2016; SLADE ET AL., 2016). A systematic review showed that psychosocial interventions were effective in improving long-term outcomes for patients with chronic orofacial pain. (AGGARWAL ET AL, 2011).

Several central nervous system (CNS) mechanisms have been implicated in chronic pain in general, and OFP specifically, including central sensitization, CNS neurotransmitter imbalances and somatosensory processing abnormalities. Endogenous inhibitory modulation of pain is a broad term that involves brain mechanisms capable of reducing or amplifying painful sensations (YARNITSKY,

2015). This upward mechanism was initially described in rats by Le Bars and consists of inhibiting the nociceptive response to a painful stimulus, concomitantly administered as a remote and test stimulus (YARNITSKY, 2015).

An endogenous pain modulation (EMP) is characterized by the CNS's ability to modulate nociceptive input from peripheral tissues as it ascends to the spinal cord/brainstem and the brain. EMP can increase or inhibit pain perception, its suggested that abnormal EPM could be part of chronic pain pathophysiology.

Pain modulation is also influenced by several factors such as: age, sex, ethnicity, menstrual cycle phase, psychological factors, ingestion of pharmacological substances, quality of sleep, conditioning stimulus site, expectation, suggestion and the placebo effect (LEWIS; RICE; MCNAIR, 2012; NIR; YARNITSKY, 2015; YARNITSKY, 2015;KENNEDY et al., 2016).

Different methods can be used to induce inhibition of nociceptive activity and may alter pain perception. These phenomena have been observed on human, animal, or in vitro studies. A classic example of pain modulation is the Gate Control Theory, where incoming peripheral stimuli and descending pathways can alter bottom-up signals and refining the ascending sensory information at early stages. (WALL, 1980) Different components of the gate control (segmental and supraspinal) had been investigated. Typically, segmental circuitries involve inhibitory modulation induced by large-diameter fibers that may reduce the nociceptive activity of spinal neurons. (YBROWN; HAMANN; MARTIN, 1973) This model provides a mechanism where innocuous stimuli can modulate nociceptive information. However, most protocols for the study of pain modulation are based on the hypothesis that "pain-inhibits-pain."

Suppression of pain by a second noxious stimulus has been studied using different methods. One of the most investigated phenomena is known as "diffuse noxious inhibitory control (DNIC). (LE BARS; DICKENSON; BESSON, 1979b) This principle demonstrated that second-order neurons, in the spinal cord, could have their activity reduced when another noxious stimulus was applied in remote regions of the body. (LE BARS; DICKENSON; BESSON, 1979a) There is a positive linear correlation between the intensity of the conditioning stimulus and the resulting inhibition of the painful test stimulus. (WILLER; DE BROUCKER; LE BARS, 1989) The inhibitory effects caused by DNIC have spinal and supraspinal components. (MCGARAUGHTY;

HENRY, 1997) (VILLANUEVA; LE BARS, 1995) (LE BARS; DICKENSON; BESSON, 1979a) (LE BARS; DICKENSON; BESSON, 1979b)

Spinal components of DNIC can be demonstrated in different approaches. For example, propriospinal mechanisms triggered by noxious inputs may be involved in segmental pain inhibition. These spinal circuitries decreased the activation of dorsal horn convergent neurons. (CADDEN; VILLANUEVA; CHITOUR; LE BARS, 1983) Other experiments have suggested contralateral segmental control in the neurons of the dorsal horn of the spinal cord. Furthermore, this modulation does not require the involvement of supraspinal pathways. (FITZGERALD, 1982) The DNIC supraspinal components were investigated using serotonin receptor blockers (Cinanserin and Metergoline) that decrease the inhibitory effects. Moreover, in the presence of 5-Hydroxytryptophan, a precursor for 5-HT synthesis, DNIC effects increased significantly. Those data together indicate that descending serotonergic pathways are involved in DNIC. (CHITOUR; DICKENSON; LE BARS, 1982)

DNIC has been studied in animals for decades. (SHROUT; FLEISS, 1979) In humans, it has been conventionally called Conditioned pain modulation (CPM). (LE BARS; DICKENSON; BESSON, 1979a) CPM paradigms initially assess the subject's baseline pain by the test stimulus. In the sequence, a conditioning stimulus is presented in a remote area, for example the subject is required to put his foot in a bucket with cold water. The perception of pain is retested at the same time (parallel paradigm), or after (sequential paradigm) the conditioning stimulus. (YARNITSKY; ARENDT-NIELSEN; BOUHASSIRA; EDWARDS *et al.*, 2010) CPM inhibition is not found in all study participants. There are also participants who report increased pain produced by the test stimulus. Although a study in healthy participants indicated that the median magnitude of CPM was 29%, there is no standardization of what would be a "normal range". (PUD; GRANOVSKY; YARNITSKY, 2009) Furthermore, there is evidence that inter-individual variability is large and that several factors may be involved in the CPM magnitude, such as age, sex, and probably other unknown variables. (EDWARDS; NESS; WEIGENT; FILLINGIM, 2003) (GE; MADELEINE; ARENDT-NIELSEN, 2004)

While CPM is based on a spatial filtration mechanism, other paradigms have alternative forms of action, such as temporal modulation such as Offset Analgesia. This dynamic quantitative sensory test represents a temporal inhibitory filtering

mechanism that amplifies the sensation of pain reduction in the face of a minimal reduction in the intensity of a noxious thermal stimulus. (BURSTEIN; NOSEDA; BORSOOK, 2015) During a small decrease of thermal stimuli intensity, subjects usually perceive no pain or pronounced reduction in the perceived pain, disproportionately than the actual decrease in temperature. (BURSTEIN; NOSEDA; BORSOOK, 2015) Unlike CPM that has descending spinal modulatory effects, offset analgesia is mediated by brain-derived pain modulation. (BACKHAUS; JUNGHANNS; BROOCKS; RIEMANN *et al.*, 2002) (HERMANS; CALDERS; VAN OOSTERWIJCK; VERSCHELDE *et al.*, 2016) (KISLER; GRANOVSKY; COGHILL; SPRECHER *et al.*, 2018) Offset Analgesia is a new concept, and the information about its mechanisms is limited. However, a recent study suggested that aging is associated with decreasing the temporal inhibitory mechanisms underlying this phenomenon. (HODKINSON; VEGGEBERG; WILCOX; SCRIVANI *et al.*, 2015) Furthermore, Offset analgesia may have a somatotopic organization showing higher inhibitory effects on the trigeminal area. (SZIKSZAY; ADAMCZYK; CARVALHO; MAY *et al.*, 2020)

Somatosensory and psychosocial evaluations have been shown to be of equal importance as methods to assess patients with orofacial 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; ANAND; ATTAL; GARCIA-LARREA *et al.*, 2004) (DWORKIN; SCHMADER, 2003).

Chronic pain and poor sleep quality have been described as a 2-way relationship, poor sleep quality has the ability to increase painful processes and impair regenerative processes, which in turn ends up harming the quality of sleep even more, creating a species of destructive cycle. (CALL-SCHMIDT; RICHARDSON, 2003).

Catastrophic thinking in relation to pain has been increasingly referred as a risk factor for pain chronicity. Catastrophizing may not only contribute to heightened levels of pain and emotional distress, but also increase the chance to extend the period of time in which the patient experiences pain (KHAN; AHMED; BLAKEWAY; SKAPINAKIS *et al.*, 2011). Pavlin et al (2004), found that high catastrophizing scores predicted the degree of pain that individuals experienced following surgery, and

contributed to a higher level of disability weeks after the surgery procedure. Michael Forsythe and his colleagues at Dalhousie University (FORSYTHE ET AL., 2008) followed a group of arthritis patients for two years following knee replacement surgery.

One of key factors to understand how a patient is experiencing pain is to have a knowledge of how impulses are produced and transmitted by the central nervous system (CNS). Mechanisms such as these are exceedingly difficult to assess from a clinical perspective, and for a long time the tools for these types of evaluation were not available. Somatosensory assessment began to be applied in clinical practice mostly in a non-standardized manner, although in the last decade great efforts have been proposed to create a comprehensive and standardized protocol to quantify this assessment. The development of a standardized protocol by the German Research Network on Neuropathic Pain (DFNS) began on 2006 with the standardization 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).

3 Objectives

3 OBJECTIVES

General objective:

To investigate the inhibitory effects of CPM in healthy subjects and a population with chronic TMD pain and its relationship with associated factors.

Specific objectives:

Based on the reviewed literature, the following specific objectives were assessed:

1- Investigate the effects of psychosocial factors (anxiety, catastrophizing, quality of sleep, lifestyle choices) on pain perception, CPM, and the presence of chronic pain.

2- Assess the somatosensory factors (Mechanical pain and pressure pain thresholds, temporal summation, and endogenous pain modulation) at chronic pain patients and healthy subjects.

3- Evaluate an active physical lifestyle's role in the psychosocial and somatosensory mechanisms, both on healthy individuals and chronic pain patients.

4- Identify a possible sensory and psychological profile of individuals with an active endogenous pain modulation system.

5- Compare within and between subjects the activation of the endogenous pain modulation system using three different induction protocols (Warm water bath, cold water bath, and the Q-Sense System).

4.Materials and Methods

4 MATERIALS AND METHODS

4.1 Participants

Three hundred and seventy-nine participants (311 healthy individuals and 68 chronic temporomandibular pain patients) aged between 18 and 50 years were included in this study. All participants were previously informed of the risks, benefits and objectives of this research and were freely invited to participate. Subjects were subsequently asked to sign an informed consent approved by the ethics committee of the Bauru School of Dentistry – USP.

4.1.1 Healthy Subjects

Data from heathy individuals were collected from 3 different study samples (totaling 311 subjects) made by the same research group (Bauru Orofacial Pain Group) by 5 different examiners using the same protocol (with the exception of the CPM test), questionnaires, and sensory equipment. Individuals were either faculty or student members of the Bauru School of Dentistry, University of São Paulo or residents from the city of Bauru, SP. None of the healthy individuals 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. Nor were they using any medication (non-steroidal anti-inflammatories, analgesics, or medications that could affect the central nervous system) that could interfere with pain sensation and experience.

4.1.2 Chronic pain patients

Sixty-eight chronic pain patients were recruited at the Dental Education Institute of Bauru (IEO) at the TMJ & Orofacial Pain Specialty Course. Patients presented chronic painful TMD (more than 6 months of pain) and met the classification criteria of the RDC / TMD (LERESCHE; DWORKIN; WILSON; EHRLICH, 1992), being classified in at least one or more criteria related to muscle pain and/or joint pain. Patients with asymptomatic articular disk displacement disorders or recent acute pain will not be considered in this group. The rest of the exclusion criteria will be the same as

previously described for asymptomatic individuals, except for the presence of chronic pain.

4.3 Variables

Psychosocial and somatosensory were evaluated in this study. Questionnaires were applied for psychosocial assessment and provided information on state and trait anxiety, pain catastrophizing, quality of sleep, physical activity, quality of life and lifestyle. The somatosensory evaluation was performed on the anterior temporalis muscle of the dominant side of the healthy individuals, and on the side of the reported pain for the chronic temporomandibular pain patients. The following tests were performed: mechanical pain threshold (MPT), temporal summation (WUR), pressure pain threshold (PPT), and the conditioned pain modulation test (CPM).

4.3.1 Mechanical pain threshold (MPT)

This test consists of using monofilaments to determine the pinprick pain threshold. The research tool used for this test was a kit of 20 Nylon Von Frey monofilaments of different diameters, calibrated to exert specific forces that increase as the monofilament caliber increases. The force applied by the monofilament can vary from 0.008 g/mm^2 to 300g/mm^2. Each monofilament will be applied perpendicularly to the region to be evaluated and light pressure will be applied until the filament bends. The filaments are applied in an upwards sequence until the patient reports a light pain, at which moment the examiner begins to decrease the applied force until the pain is no longer felt. This process is repeated 5 times and its result is determined by the geometric mean between the positives and negative responses (ROLKE, 2006; SVENSSON, 2011).

4.3.2 Wind up ratio (WUR)

Wind up ratio QST was used to evaluate the temporal summation of second pain phenomena. This test was also performed with calibrated Von Frey Filaments, exerting a light pinprick pain on the skin surface of the anterior temporalis muscle, and the patient reported a numerical pain rating scale (NRS) between 0 and 10. Subsequently, a sequence of 10 pinprick stimuli with the same force are applied and

the individual was asked to report a new NRS. Temporal summation was then calculated by dividing stimuli series pain rating by the pain rating of the single stimulus (ROLKE; BARON; MAIER; TOLLE *et al.*, 2006).

4.3.3 Pressure pain threshold (PPT)

The PPT evaluation was held in the central portion of the anterior temporalis muscle with a flat circular tip of 1cm^2, made with a digital algometer (KRATOS, Brazil). The tip of the apparatus was positioned perpendicularly to the evaluation site and pressure was applied at a constant speed of 1kg/cm^2/s until the subject pressed a button signaling the beginning of a noxious stimulus. This test sequence was performed 3 times and the average of the 3 series was calculated to reach a final reference value for each site (ROLKE; BARON; MAIER; TOLLE *et al.*, 2006; SANTOS SILVA; CONTI; LAURIS; DA SILVA *et al.*, 2005; SVENSSON; BAAD-HANSEN; PIGG; LIST *et al.*, 2011).

4.3.4 Conditioned pain modulation (CPM)

The evaluation of conditioned pain modulation was performed with 3 different conditioning stimuli (CS) throughout the sample of this study. As each data set was collected by a separate examiner at different point in time, the performed CPM protocol varied throughout each data collection and will be described below:

a. Warm water bath conditioning stimulus (n=190): This protocol was previously tested by Niir (NIR; GRANOVSKY; YARNITSKY; SPRECHER *et al.*, 2011) and confirmed to induce a CPM effect when test stimuli were performed simultaneously into a different body region. Firstly, the water temperature at the electronic water bath (Kacil- Brazil) was adjusted until the individual reported a pain score range between 5 and 7 on the NRS. The warm water bath was kept between 45°C and 47,5°C depending on the endured moderate pain of the individual. Circulation of the warm water was maintained by a submerged water pump to keep the water at the same temperature across the whole recipient, as well as to keep water bubbles from forming around the skin (NIR; GRANOVSKY; YARNITSKY; SPRECHER *et al.*, 2011). The non-dominant hand of the individuals

was completely immersed in the water bath for 45 seconds in a still position with the fingers wide apart, until the test stimulus with a digital algometer was administered after 45s of conditioning stimulus. (NIR; GRANOVSKY; YARNITSKY; SPRECHER *et al.*, 2011).

b. Cold water bath conditioning stimulus (n=151): For this test, a bucket of water with ice at 10-12 ºC was used to submerge the contralateral hand of the test subject and cause a moderate noxious conditioning cold stimulus. The conditioning stimulus was maintained for one minute and PPT was assessed with a digital algometer (on the same site as the baseline assessment). The difference in pain threshold between the first PPT and the PPT after the conditioning process, was counted as a percentage of pain modulation.

c. Q-sense CPM System (Medoc, Ltda, Israel) (n=30): Q Sense is portable device with a double thermode system that applies the Test Stimulus (TS) and conditioning Stimulus (CS) simultaneously according to pre-programed setups. The test stimulus (TS) is applied to the non-dominant forearm region and the conditioning stimulus is applied to the chosen test region. Firstly, a temperature that causes a pain intensity of at least 50/70 (NRS) is established. Then, a TS with duration of 45 seconds is applied and during this period the participant records the pain intensity of the CS continuously using a computerized visual analog scale (NRS). In the last 25 seconds of application of CS, TS is applied at a temperature of 0.5 ºC higher than the CS. The difference between the NRS during the periods of dual stimulation (CS and TS) and simple stimulation (CS only) is be considered as the CPM value. For the equivalent comparison among the 3 types of CPM, all CPM results were calculated as a percentage of pain modulation and the final CPM result was recorded as a percentage increase/decrease between the initial and final NRS.

4.3.5 Level of physical activity (IPAQ)

The level of physical activity of each individual was classified according to the International Physical Activity Questionnaire (IPAQ), an instrument for measuring the level of physical activity translated and validated by Matsudo et al. (MATSUDO, 2011).

Subjects were classified as “highly active” when fulfilled the recommendations of the item (a) vigorous activity: ≥ 5 days/week and ≥ 30 minutes per session; item (b) “Moderate activity” included individuals that practiced physical activity 2-3 times a week, with at least 30 minutes per session; item (c) “Sedentary” included participants who reported just going for short walks or less and those who practiced these physical activities for less than three months continuously.

The classification of chronic orofacial pain patients in relation to the physical activity level presented some methodological limitations. Very few pain patients (that sought help at the clinical TMD course) had an active physical lifestyle and no patients reported a “highly active” physical lifestyle. This uneven distribution was largely due to their persistent pain, that has been known to cause social, physical, and emotional limitation. Considering these limitations, the variable “level of physical activity” was categorized in two ways. Firstly, considering the whole sample (healthy and pain patients), in three levels: Sedentary (G1), Moderate activity (G2) e Vigorous Activity (G3). Secondly, to evaluate the effectiveness of physical activity in healthy and pain subjects, the data were divided into 5 groups: Healthy sedentary (G1), Healthy Moderate Activity (G2), Healthy Vigorous Activity (G3), Pain Sedentary (G4) and Pain Moderate Activity (G5).

4.3.6 State-trait Anxiety Inventory (STAI).

The inventory evaluates state and trait of anxiety in individual questionnaires, each of which consists of 20 items. It is a self-report instrument with scores for individual items ranging from 1 (‘‘almost never’’) to 4 (‘‘almost always’’). The total score ranges from 20 to 80 for each scale. For analysis purposes, these scales do not have defined cut points. It was explained to the subject that the instrument was divided into two parts (“State” - how the individual felt at that exact moment of the test application and “Trait” - how he normally feels every day). The individual needed to mark an x in the chosen option, and it was clarified that the questions did not had right or wrong answers. The options were: 4: very much; 3: quite; 2: a little; 1: absolutely not. The instrument used was translated and validated for Portuguese by Biaggio and Natalício (1979) and developed by Spielberger et al. (1970).

4.3.7 Pain Catastrophizing Scale (PCS)

PCS is an instrument developed as comprehensive evaluation that encompasses different perspectives on catastrophizing including pain. It is a self-administered questionnaire composed of 13 items, in which the patient reports the degree in which he has any thoughts or feelings described in the questionnaire, always respecting a 5-point graduation. The instrument is composed of three subscales: hopelessness, magnification and rumination. Participants were asked to answer the questions in accordance with the thoughts and feelings developed when affected by pain, independently of having or not pain at the moment of examination. The scores vary between 0 and 52 points, and higher scores translates to higher levels of pain catastrophizing.

4.3.8 Fantastic Lifestyle Checklist

This instrument developed by Wilson e Ciliska (WILSON, 1984), is composed of 25 questions covering nine domains: 1) family and friends, 2) physical activity, 3) nutrition, 4) cigarettes and drugs, 5) alcohol, 6) sleep, use of seat belt, stress and safe sex, 7) standard of behavior, 8) introspection and 9) work, as well as satisfaction with the profession. The questions are in the form of a Likert scale and the sum of all points allows to reach a total score that classifies individuals into five categories which are: "Excellent" (85 to 100 points), "Very good" (70 to 84 points), "Good" (55 to 69 points), "Regular" (35 to 54 points) points) and "Needs improvement" (0 to 34 points). The lesser the score, the bigger the lifestyle change should be. Higher scores indicate that lifestyle choices are greatly promoting health and well-being. It is desirable that healthy patients reach a score between 55 and 69 points, a classification considered as “good” by the authors (WILHELM; HANDLEY; REDDY, 2016).

4.3.9 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-administered tool used to assess sleep quality and possible disorders over a 1-month time interval. It was developed by Buysse et al. (BUYSSE; REYNOLDS; MONK; BERMAN *et al.*, 1989) and validated in Brazil, in an adult population, by Bertolazi et al. (2011). 19 questions are categorized into 7 components, ranging from 0 to 3. The PSQI components are as follows: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleeping medication (C6) and daytime dysfunction (C7). The

sum of scores for these 7 components yields one global score, which ranges from 0 to 21, where higher scores indicate worst sleep quality. A global PSQI score greater than 5 indicates major difficulties in at least 2 components or moderate difficulties in more than 3 components (BERTOLAZI; FAGONDES; HOFF; DARTORA *et al.*, 2011).

4.4 Statistical Analysis

Data were analyzed using descriptive statistics, with frequency tables, measures of central tendency and dispersion. Variables were analyzed using the Kolmogorov-Smirnov test, where they were classified as not having a normal distribution. In this case, non-parametric tests were used for statistical inference.

The Chi-square test was used to identify possible associations between the categorical variables of the study (on a nominal or ordinal scale), such as gender, pain modulation, physical activity level and chronic pain. To identify significant differences between these categories in relation to STAI, Catastrophizing, Pittsburg, Fantastic Lifestyle Checklist, Pain Modulation (CPM), Temporal summation (WUR) and Pressure Pain Threshold (PPT), the Mann-Whitney test was applied for comparisons between the categories Sex, Pain modulation and Presence of Chronic Pain, as they are measured as binary response variables.

For comparisons among categories of Physical activity level, the Kruskal-Wallis test was applied, followed by Mann-Whitney with Bonferroni correction, where significant differences were indicated.

Considering the binary categories of presence of chronic pain and pain modulation capability, a logistic regression was made to establish associations between these categories and the quantitative variables of the study (STAI, Catastrophizing, Pittsburg, Lifestyle, pain modulation level, temporal summation, and pressure pain threshold.

The statistical inference was performed considering a significance level of 5% and the software used for the analyzes was SPSS V. 24.0.

5 Results

5 RESULTS

5.1 Descriptive data

The 379 participants were evenly distributed within genders (159M/220F); all were adults aging between 18 and 50, with an average age of 29 years old. From the sample studied, 311 (82%) were classified as healthy and 68 (18%) with chronic orofacial pain. 158 individuals presented data available concerning their level of physical activity evaluated by the IPAQ, 68 of which were chronic pain patients. Also, 190 individuals had their percentage of endogenous pain modulation (CPM) evaluated with the “warm water bath (46ºC)”, 159 subjects were applied the “cold water bath” (10-12ºC) conditioning stimulus, and 30 chronic pain patients were evaluated with the Q-sense CPM System (46ºC). All subjects were examined in a single session and there was no refusal to any of the tests.

Figure 1 - Sample distribution for each analyzed category.

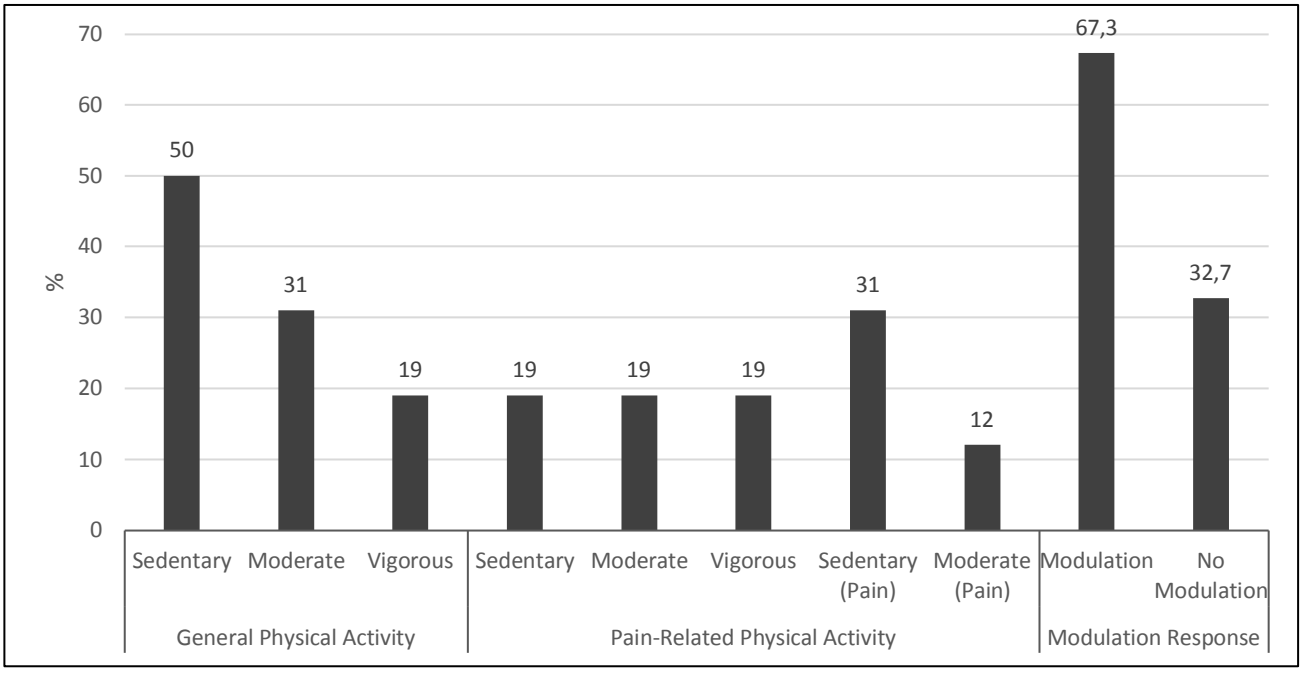

Table 1 shows descriptive data of each questionnaire and QST.

VARIABLES	N	Minimum	Maximum	Mean	Std. Deviation	Percentiles		
						25th	50th (Median)	75th
Trait-Anxiety	241	21	79	39,1	10,2	32	38	45,5
State-Anxiety	241	20	75	37,6	10,3	30	36	43

Pain Catastrophizing	158	3	49	21,3	10,7	12	21	29
Pittsburgh	158	1	17	6,3	2,6	5	6	8
Fantastic Lifestyle	120	21	90	68,3	13,5	59,1	71,5	78,8
MPT (g)	220	0,2	424,3	82,2	75,2	29,9	66,4	108,2
CPM (%)	379	-131,1	63,8	-21,2	25,4	-34,8	-20,0	-5,5
WUR (series/single VAS)	258	0,5	12,5	2,3	1,3	1,4	2,0	2,7
PPT (kg/cm²)	341	0,4	10,4	2,3	0,9	1,7	2,2	2,8

5.3 Chronic pain and sex

The statistical analysis (chi-square test) associated women with a greater tendency towards chronic pain (p = 0.05). Table 2 presents the relationship between Chronic Pain and sex. A significant association was found between these two variables.

Table 2: Distribution of each sex between healthy and chronic pain patients.

Sex		Pain		Total
		Healthy	Chronic Pain	Total
Men	n	137	22	159
	% (Line)	86,2%	13,8%	100,0%
	% (Colum)	44,1%	32,4%	42,0%
Women	n	174	46	220
	% (Line)	79,1%	20,9%	100,0%
	% (Colum)	55,9%	67,6%	58,0%
Total	n	311	68	379
	% (Line)	82,1%	17,9%	100,0%
	% (Colum)	100,0%	100,0%	100,0%

Chi-Square Tests (X^2= 3,136; p= 0,050)

Each variable was individually analyzed in relation to sex to search for differences within the healthy and chronic pain patients. Within the group of healthy individuals, significant differences were found between men and woman for anxiety traits, mechanical pain thresholds, pressure pain thresholds and endogenous pain modulation (table 3).

Table 3: Values for healthy individuals for each independent variable for men and women.

VARIABLE	Men				Women				Mann-Whitney Test	
	N	Percentiles			N	Percentiles				
		25th	50th (Median)	75th		25th	50th (Median)	75th	Mann-Whitney U	Asymp. Sig. (2-tailed)
Trait-Anxiety	87	28,0	34,0	41,0	30	37,75	41	50	3993,5	0,001*
State-Anxiety	87	29,0	35,0	42,0	30	32	37,5	44,8	4717	0,121
Pain Catastrophizing	45	8,0	14,0	23,0	68	21	25	34	921	0,460
Pittsburgh	45	4,5	6,0	8,0	68	5,2	6,5	8	899	0,354
Fantastic Lifestyle	45	70,5	75,0	82,0	30	48,8	53,7	58,9	867	0,240
MPT (g)	95	39,3	85,0	126,5	30	8,5	36,0	98,1	3595,5	0,016*
CPM (%)	137	-31,9	-18,8	-4,0	68	-28,7	-13,7	-3,3	10396	0,053
WUR (series/single VAS)	95	1,5	2,0	2,6	68	1,5	2,3	3,0	4460	0,890
PPT (kg/cm²)	137	2,0	2,6	3,2	30	1,4	1,8	2,0	8057,5	> 0,01*

* represents statistical significance (p<0,05)

When considered only the chronic pain group, differences found between genders on healthy patients were not observed on this group. Men and women presented similar values for anxiety traits, somatosensory tests and endogenous modulation. The only difference found between them was that men presented significant higher scores on the Pittsburgh questionnaire, inferring a worse reported sleep quality among men (table 4).

Table 4: Values for chronic TMD pain patients for each independent variable for men and women.

Variable	Men				Women				Mann-Whitney Test	
	N	Percentiles			N	Percentiles				
		25th	50th (Median)	75th		25th	50th (Median)	75th	Mann-Whitney U	Asymp. Sig. (2-tailed)
Trait-Anxiety	15	37,0	40,0	46,0	15	38,0	41,0	53,0	93	0,416
State-Anxiety	15	32,0	39,0	44,0	15	31,0	37,0	47,0	98,5	0,56
Pain Catastrophizing	22	20,3	24,5	34,0	46	22,0	25,5	34,5	458,5	0,533

Pittsburgh	22	5,8	7,8	9,0	46	5,0	6,0	8,0	354	0,045*
Fantastic Lifestyle	15	49,8	55,4	58,8	15	47,8	49,8	56,1	86,5	0,28
MPT (g)	15	9,2	38,4	101,0	15	8,0	11,0	65,9	94	0,443
CPM (%)	22	-25,0	-12,5	0,0	46	-36,4	-15,0	-5,6	427	0,3
WUR (series/single VAS)	22	1,2	1,6	3,0	46	1,8	2,3	3,0	391	0,131
PPT (kg/cm²)	15	1,5	1,9	2,0	15	1,2	1,5	2,0	86	0,272

* represents statistical significance (p<0,05)

5.3 Healthy individuals vs chronic TMD pain

The Mann-Whitney Test was applied to compare differences between healthy individuals and patients with orofacial chronic pain across all variables. There were found significant differences between the healthy and chronic pain groups (p <0.05). The group that presents chronic TMD pain tends to present greater values for age (p=0,001), anxiety traits (p=0,008), catastrophizing (p<0,001) and Pittsburgh scores (0,002) than healthy individuals. As for the healthy individuals, greater values of fantastic lifestyle score (p<0,001), mechanical pain threshold (p=0,012), pressure pain threshold (p<0,001), were found. This indicates a greater perceived healthy lifestyle, and higher overall pain thresholds for the healthy group (Table 5).

Table 5: Values for Healthy and Chronic TMD patients for each independent variable.

Variable	Healthy				Chronic TMD Pain				Mann-Whitney Test	
	N	Percentiles			N	Percentiles				
		25th	50th (Median)	75th		25th	50th (Median)	75th	Mann-Whitney U	Asymp. Sig. (2-tailed)
Trait-Anxiety	211	31,0	37,0	45,0	30	37,8	41,0	50,0	2212,5	0,008*
State-Anxiety	211	30,0	35,0	43,0	30	32,0	37,5	44,8	2865	0,401
Pain Catastrophizing	90	9,0	16,0	23,3	68	21,0	25,0	34,0	1386,5	0,000*
Pittsburgh	90	4,0	5,0	7,0	68	5,2	6,5	8,0	2195	0,002*
Fantastic Lifestyle	90	69,0	74,0	81,3	30	48,8	53,7	58,8	66	0,000*
MPT (g)	190	36,5	73,3	110,6	30	8,5	36,0	98,1	2040	0,012*
CPM (%)	311	-35,3	-21,7	-5,6	68	-28,7	-13,7	-3,3	9219	0,098
WUR (series/single VAS)	190	1,4	2,0	2,7	68	1,5	2,3	3,0	5760,5	0,185
PPT (kg/cm²)	311	1,7	2,3	2,9	30	1,4	1,8	2,0	2477	0,000*

* represents statistical significance (p<0,05)

A logistical regression associated with the variable “chronic orofacial pain” found an inverse association with the variables “fantastic lifestyle checklist” (B= -0,594; p=0,007), pressure pain threshold (B= -16,538, p=0,049) and the level of physical activity (B=-4,381; p=0,002). Indicating that chronic TMD pain patients consistently reported lower scores of lifestyle quality and lower pressure pain thresholds. The regression also indicates a greater presence of chronic pain patients on the sedentary and moderate activity groups.

5.4 CPM response levels with 3 different stimuli

The Kruskal-Wallis Test was applied to analyze and compare the capacity to invoke an endogenous pain modulation response among the three different protocols (Warm water, Cold water, and Q-Sense). When the percentage of pain modulation among the 3 groups was compared, no statistical differences could be observed (X^2 = 3,888; p=0,143). The three protocols were able to invoke the endogenous pain modulation system on susceptible individuals.

5.5 CPM respondents vs non-respondents

Healthy and chronic pain patients were divided into CPM respondents and non-respondents, classified by a -10% cutoff between the initial evaluation (control test stimulus) and the same measured test value after the conditioning stimulus was applied. Negative percentages indicated a “loss of funcion” of the tested pain mechanism between the first test stimulus and second test stimulus (after the conditioning stimulus). Lower values inferred a greater capacity for pain modulation.

Modulation showed no significant association with chronic pain (X2 = 0.250; p=0.357). Internal analysis (Mann-Whitney Test) of both the healthy individuals’ group and chronic pain patients’ group, observed significant lower scores of catastrophizing (U= 663,00; p=0,13) and PPT values (U=9090,00; p=0,049) on healthy individuals that were able to modulate pain. On the chronic orofacial pain group, there were not found any significant differences (U=553; p>0,05) between patients that were able to modulate pain and non-CPM respondents for any of the variables.

The Logistical

5.6 Level of physical activity analysis

The 158 individuals were divided into 5 groups depending on their level of physical activity level and chronic pain status. The Kruskal Wallis Test was applied to evaluate statistical differences among these groups. Significance values have been adjusted by the Bonferroni correction for multiple tests.

5.6.1 Questionnaires

At the Anxiety Index (STAI), significant differences were found between sedentary patients with chronic pain when compared to both healthy active (X^2 = 28,087; p^1=0,032) and healthy highly active individuals (X^2 = 34,954; p^1=0,002) where sedentary chronic pain patients showed higher levels of reported anxiety traits. In our sample, healthy sedentary individuals presented moderate levels of anxiety traits (IDATE-T). The catastrophizing scale showed significant differences (X^2 = 51,401; p^1<0,001) only between chronic patients and healthy subjects, independent of the levels of physical activity practiced by each group. The Pittsburg questionnaire presented what it considered higher scores (5+) for all groups, except for group 2. Significant differences were found between group 2 (heathy moderate activity) and group 4 (sedentary chronic pain) (X^2 = 38,768; p^1=0,002). The scores of reported lifestyle quality showed significant differences between healthy individuals and chronic pain patients (X^2 = 70,655; p<0,001). All healthy groups (g1,g2,g3) presented significant higher scores (71-76) in comparison to those in the chronic pain groups (g4, g5) that presented lower scores (41-53), which is considered as “regular” by the metrics established by the test protocol (SPIELBERGER; SCHISTEK; KOMPATSCHER, 1983).

5.6.2 Somatosensory testing

Statistical analysis (Kruskal Wallis) did not show significant differences (X^2 = 3,387; p=0,495) on the percentage of pain modulation, MPT (X^2 =2,282; p=0,684), PPT (X^2 =2,192; p=0,701), and temporal summation (X^2 =8,554; p=0,073) among groups divided by the frequency of physical activity that its members reportedly practiced. This suggests that in our sample, the frequency physical activity did not play a role on aiding or suppressing the individual’s endogenous pain modulation system.

6 Discussion

6 DISCUSSION

6.1 Chronic pain and gender

The statistical analysis (chi-square test) associated women with a greater tendency towards chronic pain (p = 0.05). This disproportionate distribution described in the literature has been explained by several authors due to the greater concern and willingness in women to seek care as soon as some more persistent pain is perceived. This gender difference also occurs in other areas, where women tend to seek more help for the treatment of illnesses such as depression, drug abuse and physical disabilities (GALDAS; CHEATER; MARSHALL, 2005) (THOM, 1986). However, there are studies that describe physiological factors such as hormonal and psychological variations that are more present in women and can lead to greater awareness of pain (PIERETTI; DI GIANNUARIO; DI GIOVANNANDREA; MARZOLI *et al.*, 2016); (BARTLEY; FILLINGIM, 2013). Another possible reason for this finding in our sample was the location of recruitment of these patients with chronic pain, all were prevenient from an orofacial pain study and treatment center, in which the demand for treatment was spontaneous and predominantly female.

Analysis of gender differences within each group (healthy/chronic pain) also generated interesting results. After the application of the Mann-Whitney test in the group of healthy individuals, it was observed that men had higher pain thresholds of PPT ($p<0.001$), MPT ($p=0.16$), and a tendency to better modulate pain ($p=0.053$). In contrast, female individuals had higher scores for general anxiety ($p=0.001$). Most studies have indicated that men have a higher threshold for mechanical nociceptive stimuli and greater pain tolerance (ELLERMEIER; WESTPHAL, 1995) (CHESTERTON; BARLAS; FOSTER; BAXTER *et al.*, 2003) (AYESH; JENSEN; SVENSSON, 2007). Regarding the modulation found during CPM, there is no agreement between the authors, where some studies suggest that men have greater inhibition, (GE; MADELEINE; ARENDT-NIELSEN, 2004) (GRANOT; WEISSMAN-FOGEL; CRISPEL; PUD *et al.*, 2008) while others attribute a greater modulation effect to females. (FRANCE; SUCHOWIECKI, 1999) (EDWARDS; FILLINGIM; NESS, 2003) Sexual differences in anxiety have also been reported, so that women tend to report higher levels of anxiety and are at greater risk for many disorders arising from this

condition (BEKKER; VAN MENS-VERHULST, 2007) (TOUFEXIS; MYERS; DAVIS, 2006).

Interestingly, the same statistical analysis (Mann-Whitney test) when applied to patients with chronic pain, did not reveal significant differences between genders, both in psychophysical tests and in psychosocial questionnaires (except for sleep quality). This result may demonstrate that chronic pain has a similar sensory pattern in both sexes, which ends up mitigating differences in values between men and women.

6.2 Healthy individuals vs. Chronic pain patients

The sample for chronic orofacial pain was significantly composed of older people when compared to healthy patients, even considering that all individuals were within the spectrum between 18 and 50 years old. This was relatively expected due to the nature of the chronic pains that usually takes time to develop and tend to appear in the later stages of adulthood. These data corroborate studies that suggest the prevalence of chronic pain in older patients, compared to young adults (FAYAZ; CROFT; LANGFORD; DONALDSON *et al.*, 2016). The relationship between chronic pain and older ages has multifactorial characteristics. For example, older adults are more likely to have comorbidities. Likewise, their longer active life may increase the possibilities of exposure to harmful stimuli and tissue injuries that can justify the appearance of chronic pain (JOHNSON; MCELHANEY, 2009). The focus of the present study was not a detailed assessment on the influence of age in the presence of chronic pain, that is why participants over 50 years old were excluded from our sample. However, even without the presence of the elderly, it was possible to observe the effect of age on the diagnosis of chronic pain from our subjects between 18 and 50 years old.

The statistical difference in the reported general anxiety scores was also an interesting factor in this analysis. There was a discrepancy between the anxiety trait scores (Trait-anxiety) and the momentary anxiety questionnaire (State-Anxiety). General reported anxiety of patients with chronic pain was significantly higher ($p = 0.008$) than in healthy ones, however, both healthy patients and the group with chronic pain had similar State-Anxiety values ($p = 0.401$). This difference can be interpreted as a momentary increase in the report of anxiety by healthy individuals due to the nature of the complete battery of tests applied during the study. The whole protocol

took 35 minutes to complete and involved several psychophysical tests including painful stimuli (CPM, PPT, MPT, WUR), which could have raised the level of momentaneous anxiety in individuals, eliminating this difference in relation to patients with chronic pain. According to the scores of the instrument developed by Spielberger et al (SPIELBERGER; VAGG, 1984), both groups had similar momentary anxiety profiles.

6.2.1 Pain Catastrophizing and Sleep Quality

Individuals with chronic pain tend to have significantly higher scores on the Pain Catastrophizing ($p<0.001$) and Pittsburg ($p=0.02$) questionnaires, which represents a higher frequency of catastrophic thoughts about pain and a worse quality of sleep (CALL-SCHMIDT; RICHARDSON, 2003) (KHAN; AHMED; BLAKEWAY; SKAPINAKIS *et al.*, 2011). Forsythe et al. (2008) (FORSYTHE; DUNBAR; HENNIGAR; SULLIVAN *et al.*, 2008), followed a group of arthritis patients and their study observed that individuals who obtained high scores on a measure of catastrophizing had a higher probability of experiencing persistent knee pain and disability two years following their surgery. Prior assessment of pain catastrophizing has also been investigated as a predictor factor for the development of chronic pain and disability following occupational injury and surgical procedures (PICAVET; VLAEYEN; SCHOUTEN, 2002) (WADDELL; CEFALU; BRICKER, 2003).

This greater catastrophizing in patients with chronic pain was already expected due to the presence of more frequent and constant pain in the patients examined, when compared to healthy individuals, who only experience pain sporadically. Higher values of catastrophizing related to chronic pain are consistent with several studies in the literature that point to high levels of catastrophizing as an important factor in the emergence and chronicity of pain (KHAN; AHMED; BLAKEWAY; SKAPINAKIS *et al.*, 2011) (PICAVET; VLAEYEN; SCHOUTEN, 2002) (FORSYTHE; DUNBAR; HENNIGAR; SULLIVAN *et al.*, 2008).

Poor sleep quality has been associated with chronic pain, both as a possible amplifier and as a consequence of persistent pain. A review by Kelly (2011), found consistent evidence that chronic back pain was associated with various sleep disorders, such as sleep disturbance; reduced sleep duration; poor day-time function; and greater sleep dissatisfaction (KELLY; BLAKE; POWER; O'KEEFFE *et al.*, 2011).

Differences were found in pressure pain thresholds (p = 0.001) and pinprick pain (p=0.012) between patients with chronic pain and healthy patients. Patients with chronic pain had lower thresholds for these two psychophysical tests and some factors can explain this phenomenon as it is described in several articles that patients with chronic pain generally have lower pain thresholds than healthy people. (IMAMURA; CHEN; MATSUBAYASHI; TARGINO *et al.*, 2013) (STAUD; WEYL; PRICE; ROBINSON, 2012) Another factor that may have influenced the test results is the proximity of the painful source (joint and facial musculature) with the region where the psychophysical tests were performed, in some patients the stimulus was applied to the affected region itself, which decreased the pain threshold due to a previous local awareness. (LAMOTTE; THALHAMMER; TOREBJORK; ROBINSON, 1982; MARTINEZ; FLETCHER; BOUHASSIRA; SESSLER *et al.*, 2007).

In the logistic regression model, the variables most strongly related to the presence of chronic pain were low pressure pain thresholds (p <0.001), low scores reported in the lifestyle questionnaire (p = 0.01), and the lack of practice of physical activity (p <0.001). Low pressure pain thresholds are associated with patients with temporomandibular pain. Our sample presented a local sensitivity factor that resulted in lower thresholds for the pressure pain test. Also, central sensitization occurs especially in patients with chronic pain and consequently can also lower their thresholds (CURATOLO; ARENDT-NIELSEN; PETERSEN-FELIX, 2006).

There is consistent evidence that patients with chronic pain after whiplash injury have decreased pain thresholds compared to healthy participants. (SHEATHER-REID; COHEN, 1998) (KOELBAEK JOHANSEN; GRAVEN-NIELSEN; SCHOU OLESEN; ARENDT-NIELSEN, 1999) (MOOG; QUINTNER; HALL; ZUSMAN, 2002) This increase in the sensitivity of chronic pain patients occurs not only in affected areas, but also in regions where there is no tissue damage. For example, patients with chronic cervical pain have decreased pain threshold when areas of the leg are tested suggesting a central sensitization of the nociceptive pathways. Likewise, whiplash patients or those with other chronic pain syndromes have spread of pain sensation to wider areas after hypertonic saline intramuscular injection compared to healthy subjects, which may indicate central sensitization (KOELBAEK JOHANSEN; GRAVEN-NIELSEN; SCHOU OLESEN; ARENDT-NIELSEN, 1999) (SORENSEN; GRAVEN-NIELSEN; HENRIKSSON; BENGTSSON *et al.*, 1998).

The group of patients with chronic pain had a median score of 53 points in the lifestyle questionnaire, which the scale determined by the author considers as “regular”. This relationship found with the presence of chronic pain is possibly due to the clear limitation that persistent pain causes in the life of any individual, leading to a worse perception of their quality of life (WITTKOPF; CARDOSO; DE CARVALHO; CARDOSO, 2018) (BURCKHARDT; CLARK; BENNETT, 1993) (WOLFE; ANDERSON; HARKNESS; BENNETT *et al.*, 1997). Less physical activity was also associated with the group of patients with chronic pain. The beneficial effects of physical activity on general pain relief are widely described (MALFLIET; ICKMANS; HUYSMANS; COPPIETERS *et al.*, 2019) (MONTEIRO-JUNIOR; DE SOUZA; LATTARI; ROCHA *et al.*, 2015), and this pattern was also found in the logical regression model performed in our sample. However, a factor that may have influenced this result was the study's own limitation in finding patients with chronic pain who practiced more vigorous physical activities and with a higher frequency, which clearly limited the performed analysis.

6.3 Conditioning pain modulation analysis

One of the caveats of our study is that data collection was carried out in 4 different studies over a period of 3 years. Although most tests were performed using the same methodology defined by the Bauru Orofacial Pain research group, using the same equipment and questionnaires, no simultaneous calibration could be done between examiners. Data collection regarding pain modulation was performed using 3 different stimuli (cold or hot water bath, and the medoc system). All 3 methods are validated and have been used safely in several studies to provoke a response from the modulatory system and provide a percentage of modulation in each individual (KOTHARI; BAAD-HANSEN; OONO; SVENSSON, 2015). When performing the Kruskal-Wallis test to compare the modulation generated by each test modality, no differences were observed in the percentage of modulation produced ($p = 0.143$). This analysis indicates that this may not have been a limiting factor in the study.

The type of conditioning stimulus was the objective of a study where water temperature variation was evaluated. Participants' non-dominant hand was immersed, which included levels of cold perception (12, 16 and 18ºC), neutral (33ºC) and of heat (44 and 46.5ºC). Healthy participants had to assess pain induced by a thermal

nociceptive test stimulus (heat) applied to the forearm contralateral to the conditioning stimulus. It was observed that only extreme temperatures (12 and 46ºC) induced analgesia during the test stimulus. Even more, there was a correlation between the levels of modulation found in the conditioning stimuli (12 and 46ºC), which indicates that subjects who presented greater inhibition of painful perception in the cold (12ºC), also showed the same tendency when the conditioning stimulus was heat (46ºC). These data suggest that the level of inhibition induced by MPC is more related to the intensity of the pain of the conditioning stimulus than its nature (heat vs. cold) (GRANOT; WEISSMAN-FOGEL; CRISPEL; PUD *et al.*, 2008).

When performing the Mann-Whitney test to compare the healthy and chronic pain groups, no statistically significant differences (p=0.098) were found between these two groups. Patients with chronic pain, such as fibromyalgia, osteoarthritis, chronic tension-type headache have been linked to low levels of pain modulation by several studies (KING; WONG; CURRIE; MAUDERLI *et al.*, 2009; ARENDT-NIELSEN; NIE; LAURSEN; LAURSEN *et al.*, 2010; KING; WONG; CURRIE; MAUDERLI *et al.*, 2009; OONO; WANG; BAAD-HANSEN; FUTARMAL *et al.*, 2014), which was not possible to observe in the analyzed sample. There are several factors that can lead to the chronification of temporomandibular pain and changes in the modulation system. It is possible that in our analysis of endogenous pain modulation was not the main factor involved in the chronicity of pain in these patients, and other psychosocial variables (anxiety, catastrophizing, and poor sleep quality) and psychophysical variables (low pain thresholds) were the predominant factors. Another important point to note is that the criteria for the study group were patients with persistent temporomandibular pain for more than 3 months, regardless of whether these pains were continuous or intermittent, with greater or lesser frequency.

Continuous pain can lead to changes in pain receptors that can lead to states of hyperexcitability and chronic pain. Another alteration that can occur, in the presence of prolonged stimuli, is the activation of NMDA receptors, which are normally inactive during short-term stimuli due to their binding to the magnesium ion (Mg). In the presence of prolonged stimuli, displacement of Mg occurs, allowing glutamate to bind to the NMDA receptor and, calcium to enter the intracellular environment, which can be harmful to the neuron. An example of the activation of NMDA receptors occurs during the phenomenon of Wind-up / temporal summation (A FERIZERFAN, 2015). This mechanism potentiates the responses of second order neurons, known as Wide

Dynamic Range Neurons (WDR). This increase in sensitization may induce a previous innocuous stimulus (eg mechanical touch), to now anomalously stimulate the WDR, increasing the sensation of pain (known as Allodynia) (POZEK; BEAUSANG; BARATTA; VISCUSI, 2016). These neuroplasticity changes are favored when there are constant stimuli (or with a high frequency of neuronal firing), and they hardly occur in intermittent stages of pain.

When evaluated, temporal summation induced by the wind up ratio QST, did not show any association with other studied variables ($p>0.05$). This is a common finding in several studies (ROLKE; MAGERL; CAMPBELL; SCHALBER *et al.*, 2006) (PIGG; BAAD-HANSEN; SVENSSON; DRANGSHOLT *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; PRICE; ROBINSON; MAUDERLI *et al.*, 2004). Pigg (2010) (PIGG; BAAD-HANSEN; SVENSSON; DRANGSHOLT *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 CPM respondents vs non-respondents

When the sample was divided between those who modulated above 10% and who did not respond to CPM, regardless of their painful state, and we applied the individual logistic regression model in each group. A positive relationship was observed in higher reported quality of lifestyle scores ($p = 0.031$) and most individuals who practiced moderate to vigorous physical activity belonged to the CPM respondent group ($p = 0.014$).

Some studies suggest a link relationship between physical activity and pain sensitivity. However, few reports had approached the link between physical activity and functionality of pain modulatory processes. Regular exercises have beneficial effects on increasing biological mediators such as serotonin and endorphins of pain modulation. (AAN HET ROT; COLLINS; FITTERLING, 2009) (ANSHEL; RUSSELL, 1994) (STAGG; MATA; IBRAHIM; HENRIKSEN *et al.*, 2011) Endogenous pain inhibition has been investigated using different models. For example, CPM, which

might be summarized as "pain inhibits pain," is a central inhibition of pain driven by a second noxious stimulus delivered in remote areas of the body. (WILLER; ROBY; LE BARS, 1984) Another inhibitory phenomenon known as Offset Analgesia is characterized by an inhibitory temporal sharpening mechanism that induces a reduction in pain perception when there is a slight decrease in noxious temperatures. (MARTUCCI; EISENACH; TONG; COGHILL, 2012) When the physical activity was assessed to predict pain modulation by CPM or Offset Analgesia, self-reported physical activity predicted CPM pain modulation. However, there was no relationship between physical activity and Offset Analgesia or temporal summation of pain. (NAUGLE; RILEY, 2014)

6.5 Effects of physical activity

6.5.1 Anxiety traits

Significant differences were found between sedentary patients with chronic pain when compared to both healthy active (p=0,32) and healthy highly active individuals (p=0,002) where sedentary chronic pain patients showed higher levels of reported anxiety traits. In our sample, healthy sedentary individuals presented moderate levels of anxiety traits (IDATE-T), it took moderate or vigorous levels of physical activity to observe significant lower anxiety scores when compared to sedentary chronic pain patients. individual These findings agree with similar studies that found lower levels of anxiety when healthy individuals practiced moderate or high intensity physical activity.

6.5.2 Pain catastrophizing

Significant differences (p<0,001) were found only between chronic patients and healthy subjects, independent of the levels of physical activity practiced by each group. It can be concluded that physical activity may not directly play a role in pain catastrophizing thoughts, and the presence of persistent pain is the main factor for higher scores on this evaluation. A study by Severeijns et. al (2001) examined the relation between catastrophizing and pain intensity, pain-related disability, and psychological distress in a group of patients with chronic pain. Overall, the study found that chronic pain patients who catastrophize reported more pain intensity, felt more disabled by their pain problem, and experienced more psychological distress.

6.5.3 Quality of sleep (Pittsburg questionnaire)

All groups, except for group 2, presented what it considered higher scores (6+) at the pittsburg questionnaire, inferring a poor quality of sleep. Significant differences were found between group 2 and group 4, indicating better quality of sleep for healthy patients that practiced a moderate frequency of physical activity. These higher Pittsburg scores, even on healthy individuals, can be explained by the profession of most healthy individuals that were recruited at the Bauru School of Dentistry – USP. Several studies have shown poor sleep quality among higher education students due to the high levels stress and unpredictable schedules associated with the profession. It can be inferred by our data that a moderate frequency of activity can be helpful to improve sleep quality and that environmental factor can probably play a role in improving or lowering the quality of sleep, even on healthy individuals.

6.5.4 Reported lifestyle quality

The scores of reported lifestyle showed significant differences between healthy individuals and chronic pain patients ($p<0,001$). All healthy groups (g1,g2,g3) presented significant ($p<0,001$) higher scores (71-76) in comparison to those in the chronic pain groups (g4, g5) that presented lower scores (41-53), which is considered as “regular” by the metrics established by the test protocol (Anez et al, 2008). Interestingly, there were significant differences ($p=0,042$) found between group 1 and 3, which can indicate that a higher frequency of weekly exercise can improve the perceived quality of life by the individual.

6.5.5 Pain Modulation (CPM protocol)

One of the objectives of this study, was to evaluate a possible influence of physical exercise on endogenous pain modulation levels. This association has been rather controversial, with some studies observing a positive correlation (GEVA; Defrin, 2013; UMEDA, 2016), others a negative correlation (FLOOD 2017; TESARZ, 2013), and some found did not found any association between the two variables (UMEDA et al, 2017). Another study by Kothari et al (KOTHARI; BAAD-HANSEN; OONO;

SVENSSON, 2015) (2015), assessed whether conditioned pain modulation (CPM) differed between TMD pain patients and healthy controls. Conditioned pain modulation was tested by comparing pressure pain thresholds (PPTs) before, during, and after the application of painful and nonpainful cold stimuli, and no significant difference in the relative CPM effect was found between groups (P = 0.227). The study concluded that CPM effects were similar in TMD pain patients and healthy controls. On our study, statistical analysis (Kruskal Wallis) did not show significant differences (p=0,495) on the percentage of pain modulation among groups divided by the frequency of physical activity that its members reportedly practiced. This suggests that in our sample, the frequency physical activity did not play a role on aiding or suppressing the individual's endogenous pain modulation system.

7 Conclusions

7 CONCLUSIONS

Based on the study described in this thesis, and according to our data, we conclude:

Chronic TMD pain patients have similar patterns of endogenous pain modulation as heathy individuals.

Higher frequency of reported physical exercise does not have an association with higher values of endogenous pain modulation.

Frequent excercise seems to have a positive effect on anxiety levels, sleep quality, and lifestyle quality.

Higher levels of anxiety, catastrophizing, and worse sleep and lifestyle quality were associated with the chronic pain group.

The 3 different CPM methods (hot water, cold water, Q-Sense) were capable of inducing the endogenous pain modulation similarly across all tested groups.

Chronic TMD pain patients have lower thresholds for pain inducing somatosensory testing (MPT, PPT)

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