The role of sleep and psychological factors in painful temporomandibular disorders and the use of non-invasive brain stimulation for its management

Alberto Herrero Babiloni, DDS, MS

Division of Experimental Medicine

McGill University

Montreal, Quebec, Canada,

March 2024

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of PhD in Experimental Medicine

TABLE OF CONTENTS

Abstract…… Page 6

Résumé..…….. Page 8

Acknowledgements……..…….. Page 12

Contribution of knowledge…….……..…….....Page 13

Contribution of authors…….……..…….. Page 14

List of Tables…….……..……..Page 15

List of Figures…….……...……Page 16

General Introduction...…….……...……. Page 17

1.1 Pain …… Page 17

1.2. Not all pains are alike……...Page 18

1.3. Temporomandibular disorders…….Page 19

1.4 The evolution of pain models…….. Page 21

1.4.1. Classic theories of pain……. Page 21

1.4.2. Recent theories: gate control and Neuromatrix……Page 22

1.4.3 Biopsychosocial model of pain…….…….. Page 24

1.4.3.1. Sleep and its place in the biopsychosocial model of pain…….. Page 25

1.4.3.2. Chronic pain treatment modalities based on the biopsychosocial model of pain…… Page 26

1.5.1. Therapeutic use of repetitive transcranial neuromodulation and repetitive transcranial magnetic stimulation (rTMS) for chronic pain……Page 27

1.5.2. Therapeutic use of repetitive transcranial magnetic stimulation (rTMS) for sleep problems…….. Page 28

1.6. Gaps in knowledge…….. Page 31

1.7. Thesis objectives…… Page 33

CHAPTER 1. REVIEW PAPER 1……..……..……... Page 35

Abstract……. Page 36

Introduction……..... Page 36

The Relationship Between Sleep and Pain: What Direction?..... Page 40

Possible Mechanisms Underlying the Sleep And Pain Relationship……. Page 43

Future directions……..Page 60

References……... Page 61

Transition to Chapter 2……..……..……... Page 83

CHAPTER 2. REVIEW PAPER 2………..Page 84

Abstract……. Page 85

Introduction……...Page 86

What is pain…….. .. Page 86

What is sleep…….. Page 88

Subjective Sleep Quality in TMD…….. Page 92

Objective Sleep Quality in TMD…….Page 94

Insomnia and TMD…… Page 97

Sleep Breathing Disorders and TMD…….. Page 99

Screening of Sleep Disorders in TMD……Page 100

Management of Sleep Disorders in TMD…….. Page 101

Conclusions……... Page 106

References……..Page 107

Transition to Chapter 3…….……. Page 125

CHAPTER 3. EXPERIMENTAL PAPER 1..……. Page 126

Abstract……Page 127

Introduction……..Page 129

Methods…….. Page 131

Results…….Page 138

Discussion……...Page 147

References……..Page 155

Transition to Chapter 4…….……...Page 169

CHAPTER 4. EXPERIMENTAL PAPER 2……..……..Page 170

Abstract……Page 171

Introduction……..Page 174

Methods……...Page 176

Results…… Page 187

Discussion……...Page 194

References……..Page 200

CHAPTER 5. DISCUSSION……..……..Page 218

5.1. “Sleep and pain” association underlying mechanisms…….Page 218

5.2. Factors contributing to daily TMD pain fluctuations……..Page 220

5.3. The potential utility of TMS for improving TMD pain…….Page 224

5.4. Clinical implications……Page 229

5.5. Thesis limitations…….Page 231

5.6. Future directions…….Page 232

CHAPTER 6. CONCLUSIONS……..…… Page 235

7.REFERENCES..……..……..…… Page 237

Abstract

Temporomandibular disorders (TMD) are common conditions characterized by pain and dysfunction in the temporomandibular joint and associated structures. Sleep disturbances frequently coexist with TMD, can exacerbate pain, and lead to a decreased quality of life. The objectives of the present thesis were to provide an overview of the relationship between sleep and chronic pain (Chapters 1 & 2), to explore the contribution of sleep and psychological factors to daily fluctuations in TMD pain (Chapter 3), and to assess the potential effects of non-invasive brain stimulation for reducing TMD intensity and other TMD-related outcomes (Chapter 4), including sleep problems.

In the present thesis, two narrative reviews were conducted. The first one is a review of studies that have examined the association between sleep and various types of chronic pain conditions, including TMD. The review offered a wider scope by highlighting some of the biological and psychological factors that might underlie the association between sleep and pain as a way to offer mechanistic insights. Results showed that multiple factors, including endogenous pain modulation, inflammation, cyclic alternating pattern (CAP), affect, mood, and pain catastrophizing, contribute to the complex interplay between sleep and TMD-related pain. The second review was focused specifically on TMD and had primarily a clinical scope by identifying potential areas of study and avenues for interventions. The review offered a thorough description of various objective and subjective sleep measures that can be used, and the potential clinical utility of these measures for the screening and management of TMD patients.. This review showed that micro-longitudinal studies focused on sleep, pain and other possible related factors such as pain catastrophizing are currently lacking.

In Chapter 3 of this thesis, we conducted a micro-longitudinal study assessing if day-to-day variations in sleep quality and pain catastrophizing contribute significantly to within-day pain fluctuations, an underexplored outcome in the TMD literature. We found that poorer sleep quality and higher pain catastrophizing increased the likelihood of experiencing clinically meaningful increases in pain over the course of the day. These results highlight the need of targeted interventions that address sleep disturbances and pain catastrophizing in this population, such as hybrid cognitive behavioral therapy or alternative treatment options. Non-invasive brain stimulation techniques, specifically repetitive transcranial magnetic stimulation (rTMS), have also shown promise as a potential treatment for chronic pain, but to date little research has explored the effects of rTMS on painful TMD. In Chapter 4, we conducted a randomized, double-blind, sham-controlled study to explore the effects of TMS among TMD individuals. We found that a single session of active rTMS can provide immediate analgesic (i.e., pain reduction) effects in a safely manner. However, longer-term benefits may require multiple sessions.

In conclusion, this thesis provides several insights into the complex interplay between sleep and pain problems among patients with painful TMD. Findings from the present thesis could also inform the assessment and management of pain, sleep, and other comorbidities among patients with TMD.

Résumé

Les troubles temporo-mandibulaires (TTM) sont des affections courantes caractérisées par une douleur ainsi que par un dysfonctionnement de l'articulation temporo-mandibulaire et des structures associées. Les troubles du sommeil, coexistant fréquemment avec les TTM, peuvent exacerber la douleur et entraîner une diminution de la qualité de vie. Les objectifs de la présente thèse étaient de fournir une vue d'ensemble de la relation entre le sommeil et la douleur chronique (chapitres 1 et 2), d'explorer l'impact du sommeil et des facteurs psychologiques sur les fluctuations quotidiennes de la douleur liée aux TTM (chapitre 3) et d'évaluer les effets potentiels de la stimulation cérébrale non invasive dans la réduction de l'intensité des TTM et d'autres conséquences associées aux TTM, y compris les difficultés de sommeil (chapitre 4).

Dans la présente thèse, deux revues narratives ont été réalisées. La première contenait une revue des études ayant examiné l'association entre le sommeil et différentes conditions de douleur chronique, y compris les TTM. L'objectif était de mettre en évidence certains facteurs biologiques et psychologiques pouvant sous-tendre l'association entre le sommeil et la douleur, afin d'offrir des perspectives sur les mécanismes et les facteurs potentiellement impliqués. Les résultats ont montré que de multiples facteurs, dont la modulation endogène de la douleur, l'inflammation, l'alternance cyclique, l'affect, l'humeur et la pensée catastrophique liée à la douleur, contribuent à l'interaction complexe entre le sommeil et la douleur liée aux TTM. La seconde revue narrative portait spécifiquement sur les TTM et avait une visée clinique dont l'objectif était d'identifier des domaines d'étude et des pistes d'intervention potentielles à considérer. Ce travail a offert une description approfondie de diverses mesures objectives et

subjectives du sommeil pouvant être utilisées, et de l'utilité clinique potentielle de ces mesures pour le dépistage et la prise en charge des patients souffrant TTM. Cette revue a démontré que les études micro-longitudinales axées sur le sommeil, la douleur et d'autres facteurs connexes, dont la pensée catastrophique liée à la douleur, sont limitées, voire inexistantes à l'heure actuelle dans la littérature.

Dans le chapitre 3 de cette thèse, nous avons mené une étude micro-longitudinale pour évaluer si les variations quotidiennes de la qualité du sommeil et de la pensée catastrophique liée à la douleur contribuent de manière significative aux fluctuations de la douleur au cours d'une journée, ce qui a été peu exploré dans la littérature sur les TTM. Nous avons constaté qu'un sommeil de moins bonne qualité et un plus grand niveau de pensée catastrophique liée à la douleur augmentent la probabilité d'une intensification d'une douleur cliniquement significative au cours de la journée. Ces résultats soulignent la nécessité d'élaborer des interventions ciblant les troubles du sommeil et la pensée catastrophique liée à la douleur au sein de cette population, notamment la thérapie cognitive et comportementale hybride ou d'autres options thérapeutiques alternatives. À cet effet, les techniques non invasives de stimulation cérébrale, en particulier la stimulation magnétique transcrânienne répétitive (SMTr), ont montré des résultats prometteurs en tant que traitement potentiel de la douleur chronique. Par ailleurs, à ce jour, peu de recherches ont exploré les effets de la SMTr sur la douleur associée aux TTM. Au chapitre 4, nous avons mené une étude randomisée, en double aveugle et contrôlée par placebo pour explorer les effets de la SMTr chez les personnes avec de TTD. Nous avons constaté qu'une seule séance de SMTr active peut avoir des effets analgésiques immédiats (c.-à-d. réduction de la douleur), et ce, sans effet secondaire.

Cependant, plusieurs séances peuvent s’avérer nécessaires afin d’obtenir un maintien des effets bénéfiques à plus long terme.

En conclusion, cette thèse fournit plusieurs informations sur l'interaction complexe entre les problèmes de sommeil et de douleur chez les patients avec de TTM. Les résultats de cette thèse pourraient permettre d’améliorer l'évaluation ainsi que la gestion de la douleur, du sommeil et d'autres comorbidités observées chez les patients avec de TTM.

This thesis is dedicated to Dr. Marc O Martel and Dr. Gilles J Lavigne, my supervisors, and to Dr. Louis De Beaumont, my other great mentor, who provided their unwavering support and invaluable guidance during the keenest moments but, extraordinarily, during the most challenging ones, demonstrating their exceptional human quality throughout this beautiful academic journey.

“We are hardwired for kindness” Rutger Bregman.

ACKNOWLEDGEMENTS

I would also like to extend my appreciation to the members of my thesis committee, Hugo Theoret, Carolina Meloto, Luke McCaffrey, and Barry Sessle for their insightful feedback and constructive critiques, which significantly enriched the quality of this work. Additionally, I am grateful to the Vanier Scholarship, the Fonds de Recherche du Québec - Santé (FRQS), the Canadian Pain Society (CPS), the International Association for Dental Research (IADR), Le Réseau de recherche en santé buccodentaire et osseuse (RSBO), the Quebec Network of Junior Pain Investigators (QNJPI) and the Department of Experimental Medicine and for their support.

Undoubtably, this work would have not been possible without my team at Sacre-Coeur Hospital, including, Bea, Amelie, the two Camille's, Marianne, Catherine, Léa, Daphne, Sam, Ian, Edith, Audrey, Sophie, Caroline, and Marie-Pier.

Of course, I would like to thank the members of the Martel Lab, Alice (i.e., guiding light), Amanda, Masha, Robina, and Connie, who brought innumerable positive things to my life, and who I consider my friends.

Finally, I want to appreciate the unconditional help of my family. I am deeply thankful for them, who have always been my pillars of strength, when in the same location or 6000 miles away. Through the ups and downs, they have stood by my side, constantly offering support and encouragement. Their love and devotion have been a constant source of inspiration, and I am truly blessed to have in my life my mother Maribel, my father Jose Antonio, and Isabel (yes, you are family too).

And to Gabrielle, who once was everything, and always will be something.

CONTRIBUTION TO ORIGINAL KNOWLEDGE

- Sleep quality and pain catastrophizing are significant factors in TMD, as they are linked to an increased likelihood of within-day clinically meaningful pain exacerbations in TMD patients.
- Daily decreases in pain catastrophizing are also associated with a higher probability of experiencing meaningful pain reductions over the course of the day.
- Repetitive transcranial magnetic stimulation (rTMS) shows promise in providing analgesic effects for TMD-related pain, resulting in significant but mild reductions in pain intensity and unpleasantness after a single session.
- Long-term sustainability of the analgesic effects from a single session are questionable, suggesting that repeated or multiple sessions of rTMS may be necessary for achieving more lasting pain relief.
- Minor and transient side effects reported support the safety and tolerability of rTMS as a therapeutic intervention for TMD-related pain.

CONTRIBUTION OF AUTHORS

Alberto Herrero Babiloni participated in the conception of the original idea, study design, data collection, data analyses, and manuscript writing and revision.

Dr. Marc O Martel participated in the conception of the original idea, study design, data analyses, and manuscript revision. Additionally, he supervised all the processes performed by the student and provided financial funding.

Dr. Gilles Lavigne participated in the conception of the original idea, study design, and manuscript revision. Additionally, he supervised all the processes performed by the student and provided financial funding.

Dr. Louis De Beaumont participated in the conception of the original idea, study design, and manuscript revision. Additionally, he provided the necessary equipment to perform the study.

Catherine Provost, Beatrice De Koninck, Camille Charlebois-Plante, and Dr. Amelie Apinis-Deshaies participated in data collection and manuscript revision.

Gabrielle Beetz participated in data visualization and figures development, as well as in manuscript revision.

LIST OF TABLES

Table 2.1. Studies evaluating objective sleep parameters in TMD patients…… Page 95

Table 3.1. Descriptive characteristics at baseline…….. Page 138

Table 3.2. Average daily reports on measures of pain, sleep and psychological variables…….. Page 141

Table 3.3. Frequency (%) and number of participants experiencing pain fluctuation events. ……..... Page 142

Table 3.4. Multilevel logistic regressions examining the factors contributing to within-day pain exacerbations and pain decreases..... Page 144

Table 3.5 Supplementary Table: Multilevel linear regression analysis examining the contribution of sleep and psychological variables on the magnitude of within-day pain increases…….…….. Page 147

Table 4.1. Descriptive characteristics at baseline……..... Page 188

Table 4.2. Multilevel modeling results assessing the effects of active rTMS and sham rTMS on primary and secondary outcomes over a 7-day period, expressed as means and standard errors of mean. ……..…….. Page 191

LIST OF FIGURES

Figure 1.1. Consequences of chronic sleep-pain interaction. …….. Page 38

Figure 1.2. Possible mechanisms underlaying the sleep-pain relationship in sleep and awake models. ……..……..... Page 45

Figure 2.1. Sleep disorders/issues that can be associated with temporomandibular disorders (TMD) ……..……..... Page 88

Figure 2.2. Management avenues for primary insomnia and obstructive sleep apnea (OSA) concomitant to temporomandibular disorders (TMD)……...Page 102

Figure 4.0. Graphical abstract ……..Page 173

Figure 4.1. Study timeline……..…….. Page 178

Figure 4.2. Immediate effects of active and sham rTMS on pain intensity (A) and pain unpleasantness (B).……..…….... Page 190

1. General introduction

1.1. Pain

Pain has been recently redefined as "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,*" by the International Association for the Study of Pain (IASP) (1). Based on the duration of pain symptoms, pain has been classically categorized as "acute" if symptoms last less than 3 or 6 months, or "chronic" if symptoms last more than 3 or 6 months (2, 3). While acute pain is usually provoked by a disease or injury and can serve as a useful biologic purpose, chronic pain outlasts the normal time of healing, serves no biologic purpose, and it is considered a disease in itself (3). Indeed, the World Health Organization (WHO) currently includes chronic pain as a diagnosis in its own (4), and access to pain management has been considered has a basic human right (5).

Pain is considered a major health problem. In Canada, it has been reported that 7.6 million people (1 in 5) live with chronic pain, and the total direct and indirect cost of chronic pain in 2019 has been calculated to be around $38.2 billion to $40.3 billion (6). Globally, an epidemiological study assessing estimates of chronic pain prevalence across 56 countries reported that the prevalence of chronic pain standardized by age and sex reported was 27.5%, and that women, older persons, and rural residents were significantly more likely to report pain (7). In addition, chronic pain can lead to poorer health outcomes, as it is frequently comorbid to, and in some cases a risk factor for several physical and mental health conditions (8, 9). Therefore, it is clear that pain has become a societal burden, affecting not only individuals' physical and emotional well-being but also straining healthcare systems and economies worldwide.

1.2. Not all pains are alike

As noted by Okeson, *"Pain is an experience that cannot be shared. It is wholly personal, belonging to the sufferer alone"* (10). This sentence, written by one of the most recognized orofacial pain specialists, captures the essence of this unique and personal concept, which has different meaning and connotation across different individuals. The subjective nature of pain poses a significant challenge in healthcare, as clinicians must rely on patients' personal descriptions and self-assessments to diagnose and treat pain effectively. Consequently, the quest for better pain management strategies and treatments becomes all the more critical, as it aims to alleviate this deeply personal suffering and improve the lives of those affected by it. One crucial step in addressing chronic pain is the classification of pain types, as it allows for a more precise understanding of its underlying causes and potential treatment approaches.

Besides the abovementioned pragmatic classification based on pain duration (acute vs chronic), different classification systems have been proposed and used over the years. One is based on neurobiological mechanisms, such as the one proposed by Woolf (11), who states that pain can be broadly divided into three main categories. (A) Nociceptive pain, representing the sensation related to the detection of potentially tissue-damaging noxious stimuli, being protective in nature. (B) Inflammatory pain, associated with tissue damage and the involvement of the immune system, promoting repair by producing pain hypersensitivity until healing begins. (C) Pathological pain, considered as a disease state caused by damage to the nervous system (neuropathic) or by its abnormal function (dysfunctional).

Another classification system is the one from the International Classification of Diseases (ICD-11) developed by the IASP Task Force (2). The ICD-11 classification system is a comprehensive system that is more readily applicable in clinical settings. This classification is multilayered and gives priority to pain etiology, followed by underlying pathophysiological mechanisms, and finally the body site (12). The ICD-11 classification includes "chronic primary pain syndromes" in which pain is conceived as a disease in its own. Diagnostic entities within this category are subdivided into chronic widespread pain (e.g., fibromyalgia), complex regional pain syndromes, chronic primary headache and orofacial pain (e.g., chronic migraine or temporomandibular disorder), chronic primary visceral pain (e.g., irritable bowel syndrome), and chronic primary musculoskeletal pain (e.g., non-specific low-back pain). Chronic "secondary pain syndromes" are linked to other diseases as the underlying cause, for which pain may initially be regarded as a symptom (e.g., chronic cancer pain, chronic posttraumatic and postsurgical pain, chronic neuropathic pain, chronic headache and orofacial pain, chronic visceral pain, and chronic musculoskeletal pain).

1.3. Temporomandibular disorders (TMD)

TMD is an umbrella term referring to different disorders that affect the temporomandibular joint (TMJ) and/or muscles of mastication (13), and it has its own subsection in the ICD-11, under the category “chronic headache and orofacial pain” (2). Signs or symptoms of TMD include pain and tenderness in or around the ear, the jaw joint, or the muscles of the jaw, face or temples. Other symptoms include mechanical problems and difficulty when opening or closing the mouth, clicking, popping, crunching or grinding noise when chewing, yawning or moving the jaw. Painful TMD can be broadly

divided in articular, when the pain is originated in the TMJ, and muscular, when the origin of pain is in the muscles of mastication. However, a combination of both is quite frequent. TMD is the most common chronic orofacial pain condition after odontogenic pain, and the second most commonly occurring musculoskeletal condition, affecting around 12% of the general population and up to 36% of adults aged 20–49 years (14, 15). Females are usually more affected than males, and although it can present at any age, it is most common in young and middle-aged adults (15, 16). Chronic painful TMD is considered a burdensome condition, as it can significantly impact patients' function, quality of life, and psychological well-being (17, 18).

The exact pathophysiological mechanisms of painful TMD are currently unclear, although it is thought to be a combination of peripheral and central mechanisms (19-22). These include non-mutually exclusive mechanisms related to neurological, endocrine, and inflammatory pathways. Reduced activity of Catecholamine-O-methyltransferase (COMT) has also been linked to both pain and TMD, suggesting a role in their manifestation. Additionally, weaker associations have been observed between chronic painful TMD and autonomic function, inflammatory markers, and endogenous pain modulation. The development and persistence of painful temporomandibular disorder (TMD) are influenced by various predisposing, initiating, and perpetuating factors (19-22). Predisposing factors include baseline health status, social context, psychological distress, and orofacial clinical features. Specifically, comorbid conditions, nonspecific orofacial symptoms such as fatigue, and pain interference with normal work have emerged as significant predictors. Moreover, factors like oral parafunctions, limited mouth opening, painful muscle sites on palpation, somatic awareness, and older age can

contribute to TMD onset. Incident jaw injuries, baseline migraine symptoms, and headache frequency are among the initiating factors strongly associated with subsequent TMD incidence.

TMD frequently coexist with other painful trigeminal conditions such as migraine and tension type headache and with other extra-trigeminal ones such as fibromyalgia, being often categorized as one of the “chronic overlapping pain conditions”(23-26). TMD patients also present several sleep related complains (27), including sleep disorders (e.g., insomnia or sleep apnea) (28) and other sleep quality issues leading to reports of non-restorative/recuperative sleep, wake time tiredness, fatigue, and lack of energy (29-31).

1.4 The evolution of pain models

Another important aspect in the understanding and eventually management of pain has been the development of theoretical models that can help explain mechanisms involved in the perception of pain. The most widely acknowledged are: the Intensity Theory, the Cartesian Dualism Theory, the Specificity Theory, the Pattern Theory, the Gate Control Theory, the Neuromatrix Model, and the Biopsychosocial Model (32). The sections below will offer a brief overview of these models, with a particular focus on the Gate Control Theory and the Biopsychosocial Model, as these models are now widely acknowledged and have had a direct impact on the way chronic pain is assessed and managed.

1.4.1. Classic theories of pain

One of the first theories of pain was the Intensity Theory attributed to the ancient philosopher Plato, which posits that pain is not a unique experience but rather an emotion

that arises in response to intense and lasting stimuli. Later on, in the 19th century, experiments, including tactile and electrical stimulations, were conducted to investigate pain thresholds and the role of dorsal horn neurons, providing valuable insights into pain processing (32).

Subsequently, Rene Descartes introduced the Cartesian Dualistic Theory, which proposed that pain could result from physical or psychological injury independently, without interaction between the two (33), hence making physical and psychological pain mutually exclusive entities (34). Descartes also suggested a connection between pain and the soul, locating it in the pineal gland. However, this theory fell short in explaining the various factors contributing to pain and the variability in pain experiences among individuals.

Another theory is the Specificity Theory, proposed by Charles Bell. This theory outlined that different sensations were processed through distinct pathways, and recognized the intricate structure of the brain and the presence of separate somatosensory modalities (35). Nonetheless, it could not account for factors beyond physical nature or explain why pain sometimes persists after the initial injury has healed. The Pattern Theory was introduced by John Paul Nafe, suggesting that sensations were encoded in the brain as patterns or sequences of signals. While initially popular, this theory was later debunked with the discovery of specific receptors for each sensation (32).

1.4.2. Recent theories: Gate Control and Neuromatrix

In 1965, Patrick Wall and Ronald Melzack, proposed a new theory for the explanation and visualization of pain modulation, coined “The Gate Control” theory (36), which marked a significant departure from earlier views of pain. In essence, it introduced the idea that pain perception is not solely a result of physical injury but is influenced by complex interactions within the nervous system. According to this theory, when a painful stimulus occurs, such as touching a hot surface, sensory information must pass through a metaphorical "gate" within the spinal cord before reaching the brain. This gate can either allow or block the pain signal from reaching the brain. The state of this gate is not fixed and can be influenced by various factors. These include the intensity of the stimulus, cognitive factors like attention or distraction, and emotional factors such as anxiety or fear. Importantly, the Gate Control Theory highlights the profound role of psychological factors in pain perception. For instance, a distracted or relaxed individual might partially or completely close the gate, reducing the perception of pain. Conversely, negative emotional states like stress or anxiety can open the gate wider, allowing more pain signals to reach the brain and making pain feel more intense. Additionally, this theory has implications for chronic pain specifically. When the gate becomes dysfunctional, it can allow pain signals to persist even after the initial injury has healed. This may be due to changes in the spinal cord's neural pathways or alterations in the brain's processing of pain signals. Therefore, the Gate Control Theory revolutionized pain understanding by highlighting the intricate interplay between sensory, emotional, and cognitive factors (37).

Ronald Melzack's Neuromatrix Model, introduced almost three decades after the Gate Control Theory, further advanced the understanding of pain perception (38). This model shifted the focus from peripheral injury as the primary source of pain to the central

nervous system itself. In this model, specific components within the central nervous system are responsible for creating the unique "neurosignature" of pain. These components include the spinal cord, brainstem, thalamus, limbic system, insular cortex, somatosensory cortex, motor cortex, and prefrontal cortex. It suggests that input from the periphery can initiate or influence the neurosignature but cannot create one on its own. The Neuromatrix Model also introduces the concept of pain memory. It postulates that the central nervous system stores memories of pain experiences, which can influence an individual's response to subsequent painful stimuli. When similar circumstances occur in the future, these stored memories allow for the re-experience of the same sensation. Like the Gate Control Theory, the Neuromatrix Model acknowledges the impact of cognitive and emotional factors on pain perception. For instance, hyperactivity of the stress response can heighten pain perception. However, it primarily focuses on the biological and neurological aspects of pain, leaving out sociological factors that can also significantly influence pain experiences.

1.4.3 Biopsychosocial model of pain

The Biopsychosocial Model represents the most comprehensive approach to understand the etiology of pain. It recognizes that pain is not solely a biological phenomenon resulting from physical injury but is instead the product of intricate interactions between biological, psychological, and sociological factors (39, 40). Each individual experiences pain and is influenced by these factors uniquely, to modulate a patient’s report of symptoms and subsequent disability. Within this model, biological factors influence nociception, the body's ability to sense and signal tissue damage, including genetic predispositions and physiological processes related to pain.

Psychological factors are equally influential, including an individual's emotional state, cognition, beliefs, and coping strategies. For instance, negative affect (i.e., feelings of emotional distress, encompassing anxiety, sadness, fear, anger, guilt and shame, irritability, and other unpleasant emotions) (41), positive affect (i.e., experiences of positive moods such as joy, interest, and alertness) (41), or pain catastrophizing (i.e., exaggerated negative orientation toward actual or anticipated pain experiences) (42) can play a critical role in pain perception and modulation. Social factors are integral to the Biopsychosocial Model as well. These include societal and cultural beliefs about pain and suffering, social support networks, socioeconomic status, and environmental factors. Additionally, the model acknowledges the large inter-individual differences in pain behavior, such as facial pain expressions, seeking medical help, or avoiding certain activities.

1.4.3.1. Sleep and its place in the Biopsychosocial Model of pain

Sleep is defined as a behavioral and physiological quiescence accompanied by closed eyes, recumbent posture, limited muscular activity and a reduced response to sensory stimuli, which can be easily reversed (43)**.** Sleep is essential for many vital functions including development, energy conservation, brain waste clearance, modulation of immune responses, cognition, performance, vigilance, disease, and psychological state (44)**.** Therefore, disturbed sleep can significantly affect health and well-being of a given individual.

Sleep disturbances and chronic pain often coexist, with insomnia and obstructive sleep apnea (OSA) being the most commonly diagnosed sleep conditions (45, 46). Individuals with chronic pain present poorer and more disturbed sleep than healthy

controls, with reduced sleep quality and efficiency, longer sleep onset latency, and increased wake after sleep onset (46). Previous hypotheses have emphasized a bidirectional relationship between sleep and pain, with poor sleep increasing pain and pain disturbing sleep. However, the influence of poor sleep on chronic pain has received more robust empirical support lately (47). Although this link is widely reported, different pathways have been proposed, and the mechanisms underlying this relationship have yet to be fully elucidated. Given the biological, psychological and social implications of sleep, it can be stated that sleep holds a pivotal place in the Biopsychosocial Model of pain as it intersects with multiple aspects of an individual's pain experience (40).

1.4.3.2 Chronic pain treatment modalities based on the Biopsychosocial Model

Given the complexity of chronic pain and its etiology, a multidisciplinary approach guided by the biopsychosocial model is commonly used for the assessment and management of patients with chronic pain conditions (40). This frequently includes education and a combination of disciplines such as physical and occupational therapy, pharmacotherapy, and psychology, which should be adapted in a tailored manner according to patients' specific chronic pain disorders, characteristics, and preferences. For example, The Patients Experience Evidence Research (PEER) Simplified Guideline developed by the Canadian Pain Taskforce recommends physical activity as the foundation of a treatment plan for patients with chronic low back pain and osteoarthritis, with psychological therapy (e.g., cognitive behavioural therapy and mindfulness) and medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) or certain antidepressants with analgesic properties as add-on options (48). Nevertheless, it is

recognized that in many cases these treatment options provide limited pain relief, and other pharmacological options such as opioids and cannabinoids, which has been vastly promoted, have not led to the expected benefits. Importantly, some of the harms associated with opioids have been found to exceed their benefits (48-52). Additionally, the presence of opioid misuse behaviors associated with prescribed opioids has been widely acknowledged in the literature (49, 53), potentially leading to serious adverse health-related consequences, including overdose and death (54, 55). Therefore, given that pain management remains elusive in a substantial proportion of patients, and that some pharmacological options are associated with considerable side effects, the development of new treatment avenues for patients with chronic pain is highly needed.

1.5.1 Therapeutic use of repetitive transcranial neuromodulation and repetitive transcranial magnetic stimulation (rTMS) for chronic pain

Neuromodulation techniques including non-invasive brain stimulation, are interventions based on external physical agents (e.g., images, sounds or ultrasounds, electric currents) that are delivered to the nervous system for therapeutic purposes in a safe manner (56). One of such techniques is repetitive transcranial magnetic stimulation (rTMS), which can increase or decrease neuronal activity through electric changes produced indirectly via magnetic fields (57). rTMS is delivered through a magnetic coil placed over the head that can be focalized to different areas of the brain, and in broad terms, different effects can be obtained depending on what area is stimulated and what frequency is used (58). For example, low frequencies (≤ 1Hz) can induce neuronal inhibitory function, whereas high frequencies (≥ 5Hz) are typically associated with

increased cortical excitability. Repeated stimulation to the left prefrontal cortex is usually associated with antidepressant and mood stabilizer effects, while repeated stimulation of the primary motor cortex (M1) can produce analgesic effects (59). The mechanisms behind the analgesic effects of rTMS are not fully elucidated, but it is thought that rTMS can enhance pain inhibition by stimulating brain areas involved in pain modulation, such as the periaqueductal grey, insula, anterior, cingulate cortex, or basal ganglia, among others (60, 61). Different preclinical and clinical studies have also reported the involvement of opioidergic, GABAergic, serotonergic, and glutamatergic pathways, and it seems that rTMS can also modify N-Methyl-D-aspartic acid (NMDA) receptors and induce long-term potentiation and depression-like mechanisms (60, 61).

Therefore, rTMS has emerged as an alternative option to manage chronic pain disorders, including neuropathic pain, fibromyalgia, and some orofacial pain and headache disorders (62, 63). In previous years, evidence-based guidelines have been developed for its therapeutic use among clinical populations (59).

1.5.2. Therapeutic use of repetitive transcranial magnetic stimulation (rTMS) for sleep problems

rTMS is gaining a lot of attention as an alternative management option for sleep disorders, as it can affect cortical and subcortical pathways by reducing cortical arousal levels and by balancing autonomic function via downregulation of hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–thyroid (HPT) axes. rTMS has also been found to promote the release of melatonin, BDNF, and GABA, which are critical for the sleep–

wake cycle. In a 2021 systematic review encompassing 28 studies across various neuropsychological conditions, the impact of repetitive Transcranial Magnetic Stimulation (rTMS) on sleep quality and disturbances was investigated(64). Among these studies, five focused on insomnia, involving a total of 303 participants. The collective findings indicated a global enhancement in both objective and subjective measures of sleep quality. Notably, improvements were observed in sleep efficiency, non-rapid eye movement (NREM) stage 3, rapid eye movement (REM) sleep cycles, and indirect sleep markers related to the HPA and HPT axes. While lacking a sham control, one study suggested a correlation between improved subjective sleep quality and increased expression of brain-derived neurotrophic factor (BDNF) and gamma-aminobutyric acid (GABA) levels [6].

Most studies in this review targeted the dorsolateral prefrontal cortex, predominantly the left hemisphere, employing stimulation frequencies, such as 1 Hz. Reports indicated significantly reduced recurrence rates of sleep disturbances at 3 months in the active rTMS group compared to sleep medication and psychotherapy groups [7]. The reported side effects were either minor, such as mild headaches and neck pain, or not reported.

A subsequent systematic review, incorporating an additional 5 studies on rTMS for primary insomnia, recently published, included data from 211 more patients (65). Overall, these studies stimulated the same cortical areas at similar frequencies as those in the previous review, but with a higher number of sessions (e.g., 10 or 12), resulting in more lasting effects—improvements persisted up to 1-month post-treatment. Additionally, one study reported that improved sleep variables correlated with reduced functional

connectivity between the right insula and the left medial frontal gyrus (66). Another study found a significant increase in GABA and creatine concentration in the left dorsolateral prefrontal cortex, measured with 1H-magnetic resonance spectroscopy, associated with sleep improvements (67). Noteworthy findings from both reviews included the positive impact of dorsolateral prefrontal cortex (DLPFC) and motor cortex (M1) stimulation at higher frequencies on sleep quality in neuropsychiatric conditions like depression, chronic pain, anxiety, or Parkinson's disease. Moreover, in healthy subjects with sleep deprivation, stimulation over various cortical areas at higher frequencies (5 Hz and 10 Hz) and over the DLPFC promoted concentration, beneficial cognitive effects, and improved task performance.

In summary, potential mechanisms contributing to the improvement of insomnia involve reducing the hyperarousal state, regulating the HPA and HPT axis to induce dopamine and pineal melatonin release, increasing concentrations of brain serotonin and noradrenaline, and elevating serum levels of GABA and BDNF—key neurotransmitters in the sleep–wake cycle (64, 68).

TMS has also explored in other prevalent sleep disorders such as sleep apnea, restless leg syndrome (RLS), and sleep bruxism(68, 69). In sleep apnea, research is more inconsistent compared to insomnia, partly due to the complexity and differences in underlying mechanisms. TMS has been explored as a method to recruit upper airway dilator muscles in patients with obstructive sleep apnea (OSA), aiming to improve inspiratory inflow during sleep without causing awakenings. While some studies observed cortical motor facilitation over the genioglossus and increased inspiratory patterns with

single TMS pulses, the mechanical properties of the upper airways did not significantly change with rTMS. High-frequency rTMS during sleep did not show improvements in upper airway mechanical properties, raising questions about the therapeutic potential of rTMS in sleep apnea. As OSA can be categorized into four different endotypes, TMS might be more effective in addressing specific endotypes related to muscle tone and hyperarousal compared to other OSA subtypes. Regarding RLS, both high-frequency and low-frequency rTMS applied over specific cortical areas have shown transient beneficial effects in RLS patients, improving subjective motor and sensory symptoms.(65) Emerging data also suggest that rTMS may contribute to restoring imbalances in neural circuitry, as measured by functional magnetic resonance imaging (fMRI) or motor-evoked potentials (MEP).(65, 70). Finally, evidence regarding rTMS and sleep bruxism (SB) is anecdotal with only one open-label study showing a decrease in muscle soreness and night jaw-closing muscle electromyographic (EMG) activity during sleep recorded with a portable EMG when M1 of the masseter muscles was stimulated (71).

1.6. Gaps in knowledge

Although advances have been made in our understanding of the basic (i.e., biological) mechanisms underlying chronic pain, including TMD pain, many questions remain unaddressed regarding the factors that contribute to the day-to-day experience of pain. A considerable amount of work has focused on exploring how biological (72-74) and psychological (75, 76) factors contribute to inter-individual differences in pain, but less is known on the role of sleep. As noted earlier, sleep is intricately woven into the Biopsychosocial Model of pain, influencing various facets of an individual's pain experience. Yet, the directionality of the association between sleep and pain problems is

complex and unclear, and the mechanisms underpinning such association remain not fully elucidated (77). A further understanding of the association between sleep and pain, as well as their underlying mechanisms, can help to gain a deeper insight of its diagnosis and guide the development of targeted interventions and treatments in order to reduce the societal burden of chronic pain and sleep disorders. Additionally, in spite of the current evidence highlighting the importance of sleep in TMD (29-31), the association and possible interplay between sleep problems and pain among these patients is not well-understood. A comprehensive literature review is helpful to identify gaps in knowledge regarding the factors that might underlie the association between sleep and TMD pain. Such a review can allow the assessment of the existing body of research, pinpoint areas where information is limited or conflicting, and recognize the specific aspects of the sleep-TMD relationship that require further investigation. Thus, research can be directed toward designing new studies and targeted interventions for patients with TMD pain.

There is also a need to better understand the factors that contribute specifically to TMD pain, and how targeting these factors could be relevant for the diagnosis, prognosis, and management of patients with TMD. In this population (i.e., TMD), the bulk of studies has revolved around exploring factors contributing to the overall intensity of TMD-related pain in a cross-sectional manner (i.e., singe time point assessment), or in macro-longitudinal designs. Given that TMD pain might fluctuate on a daily basis, these studies are limited and provide little insights into the within-day or day-to-day contributors to TMD pain. Little is also known on other important characteristics of TMD pain, such as abrupt day-to-day pain fluctuations, often termed "pain flares", which can be debilitating, and result in a sense of lack of control in patients' lives (78, 79). As noted previously, within

the biopsychosocial model, psychological variables such as affect (i.e., positive or negative affect), pain catastrophizing, and other factors such as sleep are critical in shaping the pain experience, but it remains unclear whether these factors play a role in the within-day or day-to-day fluctuations in pain that may be potentially experienced by TMD patients. There is empirical evidence linking poor sleep and heightened pain catastrophizing with an increased likelihood of experiencing pain fluctuations in conditions such as hip osteoarthritis and fibromyalgia (80, 81), but the contribution of these factors to daily TMD pain fluctuations has yet to be explored. There is reason to believe that sleep quality and other psychological variables such as pain catastrophizing and affect (positive and/or negative) could similarly be associated with within-day pain fluctuations among TMD patients.

Finally, despite the use of all the standard care treatment options, the difficulty in managing TMD makes clinical care very challenging in a high proportion of patients. In this context, the development and investigation of other treatment avenues becomes highly significant. In that context, the exploration of rTMS in TMD patients emerges as alluring due to its promising analgesic potential and limited side effects (82, 83). Although preliminary evidence supports the analgesic benefits of rTMS among patients with neuropathic pain and fibromyalgia (62, 63), it remains unclear whether rTMS could lead to immediate or longer-term analgesic benefits among patients with chronic TMD pain.

1.7. Thesis objectives

The overarching goal of this thesis was to further understand the association between sleep and pain among patients with TMD, and to explore the potential effects of rTMS for reducing TMD pain and other TMD-related outcomes in this population. In the

context of the present thesis, two chapters were based on a review of the literature in this area, and other two chapters relied on experimental study designs. The specific objectives of the present thesis were:

I) To review the association between sleep and chronic pain, with a specific focus on describing the directionality of the "sleep-pain" association and putative underlying mechanisms (Chapter 1).

II) To review the association between sleep and TMD pain, with a specific focus on describing objective and subjective sleep measures and identifying potential areas of study and intervention (Chapter 2).

III) To examine the contribution of sleep quality and psychological factors to within-day pain fluctuations in patients with TMD (Chapter 3).

IV) To assess the potential effects of rTMS on pain and other TMD-related outcomes (i.e., sleep) in patients with TMD (Chapter 4).

CHAPTER 1. REVIEW ARTICLE 1.

Herrero Babiloni A, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. J Neural Transm (Vienna). 2020 Apr;127(4):647-660. doi: 10.1007/s00702-019-02067-z. Epub 2019 Aug 26. PMID: 31452048. Citations: 143.

Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship

Alberto HERRERO BABILONI[1,2], Beatrice P DE KONINCK[1], Gabrielle BEETZ[1], Louis DE BEAUMONT[1], Marc O MARTEL[3,4], Gilles J LAVIGNE[1,2,3]

[1] Research Center, Hôpital du Sacré-Coeur de Montréal, CIUSSS du Nord-de-l'Île-de-Montréal, Université De Montréal, Québec, Canada

[2] Faculté de Médecine Dentaire, Université de Montréal, Québec, Canada

[3] Faculty of Dentistry, McGill University

[4] Department of Anesthesia, McGill University

Email: herre220@umn.edu

Phone: 514-338-2222 Extension 3790

Fax: 514-238-2531

Conflicts of interest: none

Keywords: “sleep disturbance”, “chronic pain”, “insomnia”, “obstructive sleep apnea”, “pain modulation”

Abstract: Sleep disturbances and chronic pain are considered public health concerns. They are frequently associated, and the direction of its relationship and possible mechanisms underlying it are frequently debated. The exploration of the sleep-pain association is of great clinical interest to explore in order to steer potential therapeutic avenues, accommodate the patient’s experience, and adapt the common practice of health professionals. In this review, the direction between sleep-pain in adult and pediatric populations will be discussed. Moreover, possible mechanisms contributing to this relationship as endogenous pain modulation, inflammation, affect, mood and other states, the role of different endogenous substances (dopamine, orexin, melatonin, vitamin D) as well as other lesser-known such as cyclic alternating pattern (CAP) among others, will be explored. Finally, directions for future studies on this area will be discussed, opening up to the addition of tools such as brain imaging (e.g., fMRI), electrophysiology and non-invasive brain stimulation techniques. Such resources paired with artificial intelligence are key to personalized medicine management for patients facing pain and sleep interacting conditions.

INTRODUCTION

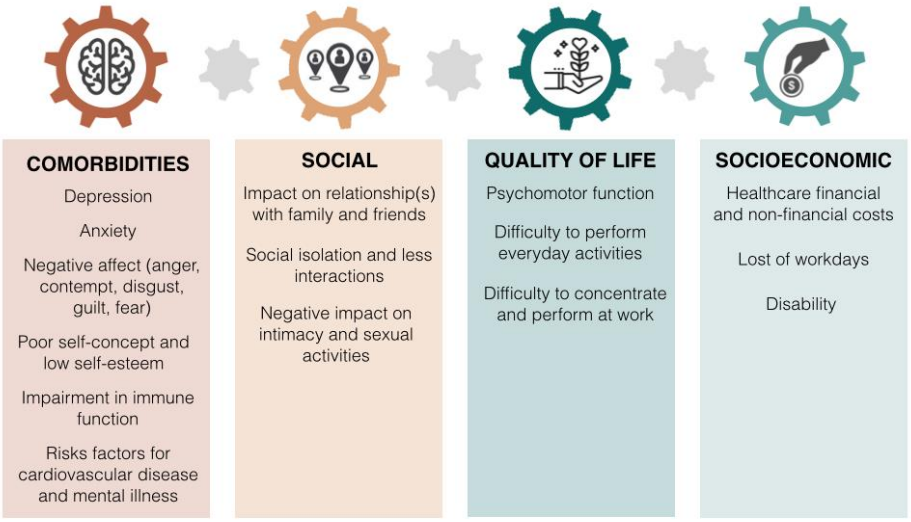
Sleep is a complex physiological and behavioral process that partially allows the individual to isolate from the external environment, which is thought to be essential for the psychological and physical recuperation, memory consolidation, emotional modulation,

performance, and learning [1,2]. Sleep can be broadly separated into two main phases: non-rapid eye movement (NREM) and rapid eye movement (REM). Each of these phases is categorized by different physiological, behavioral, neurochemical and electrophysical attributes. According to electroencephalogram (EEG) parameters, NREM sleep can be further subdivided into 3 different stages: N 1 and N 2, characterized by lower arousal thresholds and often referred to as “light sleep”; and N 3 (formerly 3 and 4, now merged into a single stage) or “deep sleep”, characterized by higher arousal thresholds and dominance of slow-wave brain activity. While NREM sleep is associated with stable decrease of mental and physical activity, heart rate, blood pressure, and breathing [1,3], REM or “paradoxical” sleep, which follows the NREM phase in the sleep cycle, is characterized by an increase of mental activity while muscles remain paralyzed or inactive. During REM phase, EEG patterns are more variable and physiological parameters such as heart rate, blood pressure or breathing frequency are unstable. Dreams occur in all sleep stages but REM is characterized by more vivid or creative dreams [4]. In healthy adults, sleep onset usually occurs within 20-30 minutes of going to bed. A typical night of sleep encompasses 3 to 5 NREM to REM ultradian cycles (90 minutes on average, except for the first cycle which lasts about 120 minutes), where lighter sleep turns into deep sleep, which is then followed by a REM phase. As the night advances, duration and frequency of stage N 3 decreases, stage 2 becomes more predominant, and REM phases become longer [5].

It has been reported that sleep difficulties (initiating and maintaining sleep, and experiencing inadequate sleep) can affect approximately 20-30% of the Western population on a daily to weekly basis[6], and as much as 45% according to a survey

performed in Australia[7]. Sleep loss impairs cognition, decision-making, psychomotor function, mood, and immune function [8,9]. In addition, poor sleep quality is considered a risk factor for cardiovascular disease, dementia, obesity, diabetes, depression, pain and mortality, among others[10-15]. These physical and psychological changes can significantly affect health, well-being, and quality of life, sometimes leading to suicidal ideation[16-19]. Moreover, inadequate sleep leads to a significant decrease in productivity and a substantial financial and nonfinancial costs, becoming an important social and economic burden [20](Figure 1.1).

Figure 1.1. Consequences of chronic sleep-pain interaction.



Pain was defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [21]. Although this definition is

probably the most frequently used, there is not a clear consensus about its utilization, and recent efforts have been made in updating and reaching a more comprehensive definition of pain. Lately, the following definition was proposed: “Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components”[22]. In fact, pain is recognized as a very complex process generated by neural activity in a network composed of several different structures in the brain, called neuromatrix, where its different components may be associated with the anticipation of pain, the discrimination of pain, or with the unpleasant affective manifestations of pain [23,24]. Broadly speaking, pain can be classified into three main categories: Nociceptive; Inflammatory; and Pathological. I) Nociceptive, considered a normal physiological response and an early-warning protective system in order to minimize contact with damaging or noxious stimuli. II) Inflammatory, when the immune system gets activated by tissue injury or infection, and pain assists in the healing of the injury by discouraging physical contact and movement, thereby promoting recovery. As they are adaptive and protective in nature, these two types of pain are considered functional. The third pain category is III) Pathological, which is maladaptive as opposed to protective. It can be further subdivided in a) Neuropathic, resulting from a lesion in the peripheral or central nervous systems; or b) Dysfunctional, when there is no such damage or inflammation (fibromyalgia, temporomandibular disorders, or irritable bowel syndrome).

Pain is considered as “acute” when lasting for a duration that does not exceed the expected healing period (usually nociceptive or inflammatory), or as “chronic” when pain outlast or recur beyond the expected 3-to-6 month healing period (often pathological) [25,26]. It is reported that chronic pain affects nearly 20% of people worldwide, and that 15%

to 20% of all physician visits are intended to address pain-related issues [27]. Annual estimates of the direct and indirect costs linked to chronic pain reach 635 billions dollars strictly in the US[28], which represents a staggering economic and social burden. Beyond costs, chronic pain has a significant impact on patients' well-being and quality of life, affecting their mood, coping resources, expectations, sleep quality, physical function, and daily activities, being highly related with disability and suicidal risk[29-31] (Figure 1.1). Given the considerable suffering associated with pain, access to pain treatment is considered a basic human right by the World Health Organization [32,33].

In this review, an overview of studies that have examined the relationship between sleep and pain will be provided. The direction of this relationship will be discussed and the potential mechanisms underlying this relationship will be addressed. Finally, directions for future studies in the area of sleep and pain will be discussed. Given the broad nature of our objectives, and in order to capture a higher number of study types including preliminary evidence, a narrative review was conducted.

THE RELATIONSHIP BETWEEN SLEEP AND PAIN: WHAT DIRECTION?

Numerous cross-sectional studies have shown a high comorbidity between chronic pain and sleep impairments. A recent meta-analysis estimated a pooled prevalence of sleep disorders in 44% of adult chronic pain patients; insomnia (72%), restless leg syndrome (32%) and obstructive sleep apnea (32%) being the most common diagnoses [34]. The latter investigation also established that adult patients with chronic pain had worse measures for sleep onset latency and efficiency, time awake after onset and recurrent awakenings (large effects) when compared to controls. Moreover, chronic pain patients also exhibit worse scores on sleep-related measures such as total sleep time,

light sleep duration (NREM 1), number of stage shifts, respiratory-related events and periodic limb movements, even though the effect sizes were small to medium [34]. Although the association between poor quality and chronic pain seems obvious, its directionality has been debated for several years. Earlier, it was thought to be bidirectional, where sleep impairments were thought to exacerbate pain and pain was thought to contribute to sleep instability or disturbances. However, recent qualitative analyses of longitudinal (less time points, usually far apart in time) and micro-longitudinal (more time points, close in time) studies point towards a stronger and more consistent unidirectional effect of sleep causing pain exacerbation in adult populations, especially in experimental and acute pain models[35-39]. For instance, it has been shown that sleep deprivation protocols can induce hyperalgesic responses (i.e., abnormally increased sensitivity to pain) that correlate with electrophysiological measures (e.g., decrease in laser evoked potentials) in healthy individuals[39,40], and that some of those responses can be reversed by napping or short sleep, regardless of vigilance status [41]. Recent comprehensive literature reviews and a commentary have been published lately on the bidirectionality of sleep-pain in adults[35,42,43]. For more information on this topic, the reader may refer to them.

Among pediatric populations, the bidirectionality of this relationship is also unclear. A systematic review of 56 studies that included different pain conditions supported a bidirectional relationship between sleep and pain intensity, where besides sleep problems predisposing to pain, studies based on behavioral assessments and PSG generally detected a relationship between intense pain and disrupted sleep [44]. In addition, the majority of these studies indicated that even after controlling for confounding variables, intense pain was found to be predictive of disrupted sleep patterns, and more frequent

headaches predicted sleep disorders symptoms such as parasomnias, sleep walking, and bruxism[44]. Nevertheless, findings from recent studies are more contradictory. On one hand, in keeping with evidence from the adult population, a more linear relationship between pain intensity and sleep disturbances was observed in several investigations. In a study, 67 children between the ages of 10 and 17 diagnosed with acute musculoskeletal pain (<1 month duration) underwent 8 nights of sleep monitoring actigraphy and completed pain diaries twice a day. Generalized linear models were used in order to test nighttime sleep as a predictor of morning pain, and evening pain as a predictor of nighttime sleep. The authors found that shorter sleep duration and poorer sleep quality predicted higher morning pain intensity. In contrast, evening pain did not predict nighttime sleep, suggesting that sleep deficiency, as opposed to late-night pain, is more related to next-day pain [45]. Furthermore, another study conducted in 60 children (10-18-year-olds) who underwent a major surgery used a multi-methods sleep assessment (electronic diaries, subjective ratings, validated questionnaire measures, and ambulatory actigraphy monitoring; therefore, objective and subjective assessments). Findings indicated that at an individual level, sleep quality and efficiency were significantly reduced at 2 weeks after the surgery, and that poorer sleep quality was associated with greater next-day pain intensity [46]. In contrast, two studies conducted with sickle cell disease children (n=88 aged 8–17 years; n=30 African American 8–18 years) showed a bidirectional relationship, where poor subjective sleep quality and efficiency during the night were related to worse pain intensity the next day, and intense pain was related to poor sleep subjective sleep quality and efficiency that night [47,48].

The sections above highlight the complexity of the sleep-pain relationship as well as the potential factors that might underlie the direction and magnitude of this relationship. Caution in the interpretation of these studies is necessary as many of them did not control for confounding variables such as pain comorbidities or mood disorders, which are known to account for some of the sleep quality variability[49]. Another factor that should receive attention is the role of expectation and placebo/nocebo effects during sleep, as studies have shown that: i) analgesic expectations induced before sleep produced a reduction in cortical arousals evoked by noxious stimuli during REM sleep[50]; ii) induction of analgesic expectations before sleep leaded to a reduced nocturnal pain perception, subjective sleep disturbances, and activated brain processes that modulate incoming nociceptive signals differentially according to sleep stage [51]; iii) REM sleep appears to moderate the relationship between pain relief expectations and placebo analgesia[52]; and iv) although nocebo effects (expectations of higher pain levels) can increase sensitivity to electrically induced pain, they do not explain sleep restriction-related hyperalgesia, as they appear to be mediated by different cortical mechanisms than sleep restriction[53].

The possible variation between subjective or objective sleep measures needs to be considered as well, as it has been suggested that each of them may measure different aspects of sleep [54,55], and finally, more refined methodological modelling approaches to capture directionality are warranted for future investigations.

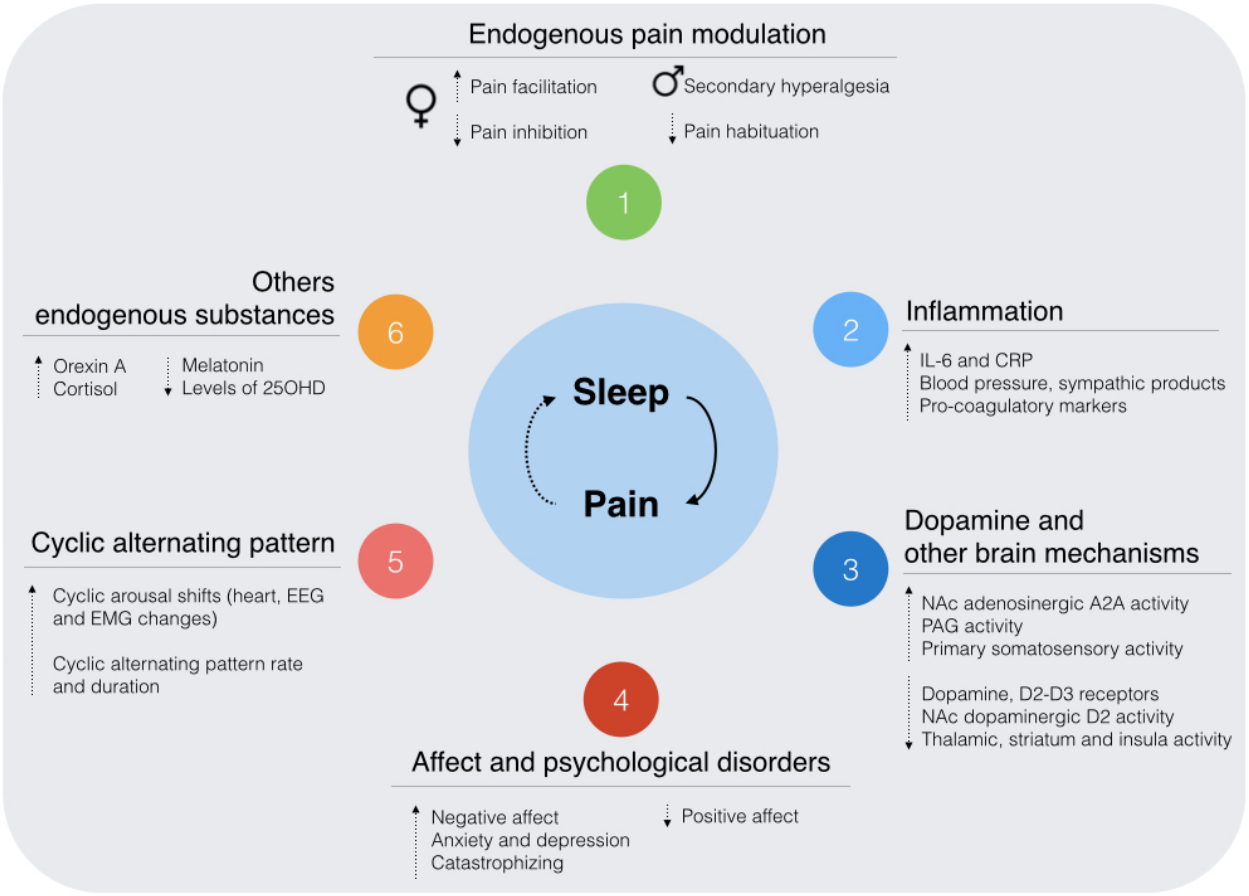
POSSIBLE MECHANISMS UNDERLYING THE SLEEP AND PAIN RELATIONSHIP

Sleep is an active process; it is not coma neither anesthesia. In fact, processing of sensory inputs could be preserved under particular circumstances[56]. Brain-evoked

potentials to painful laser stimuli, which reflect cortical activity, have been recorded during all sleep stages [57]. Research has shown that nociceptive stimuli can interrupt sleep (more easily in stage 1 or 2 when compared to deep sleep or REM), and produce significantly more arousals than non-nociceptive ones [56,58,59]. Moreover, electroencephalographic (EEG) thalamic signals seem to vary according to the nature of the awakenings (i.e., "spontaneous" vs “nociceptive-induced”)[60].

Although the link between sleep and pain is widely established, the mechanisms underlying this relationship have yet to be fully elucidated. Different reports have pointed towards the potential role of endogenous pain modulation, inflammatory markers, affect, mood and other states such as emotional distress or catastrophizing as possible mediators. Moreover, we will also discuss the potential importance of different endogenous substances, and the role of other mechanisms brain such as brain anatomical areas or cyclic alternating pattern (Figure 1.2).

Figure 1.2. Possible mechanisms underlaying the sleep-pain relationship in sleep and awake models.



Abbreviations. IL-6: interleukin 6; CRP: C reactive protein. NAc: nucleus accumbens; A2A: Adenosine 2 receptor; PAG: periaqueductal grey; EEG: electroencephalogram; EMG: electromyogram; 25OHD: 25-hydroxyvitamin D. Legend: Putative mechanisms include 1) increased pain facilitation and decreased pain inhibition in females, secondary hyperalgesia in males, and decreased pain habituation in both sexes; 2) Increased specific pro-inflammatory markers and non-specific related to blood pressure, sympathetic arousal, and coagulation; 3) Increased brain region specific activity and decreased dopamine subtype receptor and brain region specific activity; 4) Increased

negative affect, anxiety, depression and catastrophizing and decreased positive affect; 5) Increased sleep instability as measured by cyclic alternating markers, frequency and duration; 6) Increased release of endogenous substances such as orexin A and cortisol, and decreased release of melatonin and Vitamin D.

Endogenous pain modulation (EPM). EPM can be defined as the array of actions of several central nervous system (CNS) mechanisms that affect nociceptive signal processing. Deficient EPM, can be represented by increased pain facilitation or impaired pain inhibition. Pain facilitation can be measured through temporal summation paradigms, by delivering suprathreshold noxious stimuli repeatedly in frequencies ≥ 0.33 Hz that lead to increased pain perception[61], and it is considered a clinical correlate of the wind-up phenomenon[62]. Pain inhibition can be assessed through conditioned pain modulation (CPM), offset analgesia, or a combination of both. CPM paradigms are the clinical equivalent of “pain inhibits pain” testing in animal models, which triggers diffuse noxious inhibitory controls, and it is usually induced by presenting two noxious stimuli in distant body sites simultaneously or sequentially [63]. Alternatively, offset analgesia is another paradigm that represents a temporal filtering of nociceptive information, where a disproportionately large decrease of pain perception after a brief, temporary increment of thermal pain stimulus occurs [64,65]. The presence of increased pain facilitation and impaired pain inhibition has been implicated in the development and maintenance of various chronic pain conditions, including musculoskeletal, visceral, and neuropathic pain [66-71]. In addition, it has been suggested that EPM testing can be used to predict pain onset and also pain treatment outcomes[72-74].

The effects of sleep on EPM mechanisms have been investigated in different studies. Although both pain facilitation and inhibition mechanisms have been found to be altered in in an insomnia population (n=17) when compared to controls[75], it has been suggested that pain inhibition could be more affected by sleep disruption than pain facilitation. Females were also found to be more susceptible to sleep deprivations effects in EPM than males [37,76,77]. A cross-over balanced study (i.e., one night of total sleep deprivation was contrasted with one night of habitual sleep) showed that the endogenous capacity to inhibit pain was only reduced in sleep-deprived females, further pointing towards a sex-dependent effect of total sleep deprivation on descending pain pathways[77]. In another study conducted among healthy females in which partial sleep deprivation was induced by forced awakenings, a significant loss of pain inhibition and an increase in spontaneous pain was observed, suggesting that sleep continuity disturbance can impair EPM inhibitory function[78]. On the contrary, other studies have shown absent-to-mild effects of partial sleep restriction and sleep alterations in CPM and temporal summation measures, the latter findings being at odds with previous findings. However, no sex-specific effect was assessed [79,80].

Although conjectural, a recent study conducted among 79 healthy adults showed that the association between sleep disruption and central sensitization (pain amplification by central nervous system [CNS] mechanisms) involved distinct action mechanisms according to sex. In males, sleep disruption induced secondary hyperalgesia, whereas sleep disruption increased temporal summation in females [81]. Another study followed 14 healthy individuals undergoing both a 3-week protocol involving restricted sleep with limited recovery (5 nights of 4 hours sleep per night followed by 2 nights of 8 hours sleep

per night) and a control protocol involving 3 consecutive weeks of normal sleep (8 hours sleep per night). Spontaneous pain, heat-pain thresholds, cold-pain tolerance and habituation, and temporal summation were measured at multiple points during each protocol. Compared to participants exposed to the control protocol, participants in the sleep-restriction protocol experienced mild increases in spontaneous pain, decrease in time of heat-pain thresholds, decreased pain habituation, and increased temporal summation in the last 2 weeks of sleep restriction. These results suggest that exposure to chronic insufficient sleep may increase vulnerability to chronic pain by altering processes of pain habituation and sensitization [82]. Interestingly, other study showed that one night of sleep deprivation resulted in an attention-dependent enhancement of habituation to noxious laser stimuli, which could be interpreted as a homeostatic self-protective mechanism produced by sleep deprivation [40,83].

Subjective sleep quality has been related to CPM efficacy in both fibromyalgia and acute low back pain patient populations [84,85]. Moreover, in a PSG study of patients experiencing chronic TMD pain, decreased sleep efficiency was significantly associated with diminished pain inhibition or CPM efficacy [86]. Likewise, self-reported sleep disturbances in chronic rheumatoid arthritis patients were related to reduced CPM efficacy [87]. In sum, alterations in EPM appears to be a potent mechanism underlying the sleep and pain relationship. However, longitudinal studies are needed to ascertain the importance of EPM in new onset and chronification of pain. Moreover, the effects of sleep in other EPM testing such as offset analgesia could provide different lines of valuable research [88,89].

Inflammation. Inflammation itself, as in many other chronic pain conditions, has been an essential constituent in the relationship between sleep and pain [90]. Pro-inflammatory cytokines (i.e., IL-1β, IL-6 and TNF-α) are known to be part of the development of inflammatory and neuropathic pain [91] and are primarily involved in the regulation of sleep through the central nervous system [92]. The immune system is also characterized by variations modulated by the sleep-wake cycle. For example, some immune cells are at their lowest point in the morning, while others reach their peak level at night [93-95]. An increase of cytokines secretion has been observed in a context of sleep deprivation [93,96], and morning IL-6 concentrations were negatively associated with impaired sleep quality among healthy adults [97]. Interestingly, a meta-analysis of cohort studies and experimental sleep deprivation models indicated that sleep disturbance and long sleep duration, excluding short sleep duration, were associated with increases in markers of systemic inflammation (CRP and IL-6)[98]. It has been reported that sleep deprivation can also exert important effects on the host defense including immune memory (i.e., the ability of the immune system to respond more rapidly and effectively to pathogens that have been encountered previously), thus increasing the risk for infections[99]. Chronic sleep deficiencies, as seen in insomnia, could increase low-grade inflammation (i.e., the chronic production, but in a low-grade state, of inflammatory factors) through different mechanisms, such as intestinal dysbiosis, impairment of HPA axes, circadian sleep disruption, obesity, or physical inactivity among others. On the other hand, inflammation/immune response can affect sleep as well, through cytokines, prostaglandins, or other sleep regulatory substances, such as components and/or decomposition products of pathogens[65,72.]

Autonomic activation and resistance to insulin are other theorized mechanisms involved in the sleep inflammation pathway[92,100]. It has been shown that blood pressure, sympathetic products and pro-coagulatory markers were increased in healthy participants after sleep deprivation[100], and that the experience of acute and physical stress force along with the increase of blood pressure trigger inflammatory mediators [101,102]. Alternatively, resistance to insulin and reduction of glucose metabolism have been linked to impaired vascular function and increased inflammation [103,104]. Thus, parameters such as sympathetic activation, stress, metabolism and sex, need to be accounted when making assumptions about this relationship.

In sum, the sections above highlight the importance of inflammation in the sleep and pain relationship, as sleep alterations may lead to an alteration of the immune response that could worsen chronic pain disorders, and inflammation products could dysregulate sleep mechanisms.

Affect, mood, and other states. Negative affect (NA) is a personality variable that involves the experience of negative emotions such as anger, contempt, disgust, guilt, fear and also poor self-concept, while positive affect (PA) is characterized by emotions such as enthusiasm, energy, confidence, activeness, and alertness. Although NA and PA are negatively correlated, they are not completely opposite constructs[105], being actually psychometrically different[106]. The relationship of these affective states and sleep has been firmly demonstrated, with some studies showing the effect of sleep disruption on PA/NA and vice-versa[107,108]. The same concept has also been observed with chronic pain[109]. Higher NA is thought to increase arousal and hypervigilance to pain, causing sensitization to pain, avoidance, and functional disability[110]. On the contrary, it is believed

that higher PA attenuates both the perception of pain and the negative affective response to pain, increasing the resilience of the individual, whereas the absence of PA exposes vulnerable patients to poor pain-related outcomes[111,112].

NA/PA are considered some of the most important mediators in the sleep and pain relationship in non-clinically depressed samples. A cross-sectional study conducted in 213 children and adolescents presenting with chronic pain indicated that 74% of children reported altered sleep and that poor sleep quality was significantly associated with increased pain, disability, higher NA, and decreased PA. NA (but not PA) was considered as a mediator of the relationship between poor sleep and increased pain, and both NA and PA mediated the relationship between poor sleep and increased functional disability [113]. In the latter study affect did not modulate the relationship between poor sleep and increased pain. Another cross-sectional study was conducted in 948 mid-to late-life individuals with chronic pain. Mediation analyses revealed that sleep disturbance indirectly predicted pain interference via NA and PA, and that both of these neurotransmitters mediated the total sleep time and pain interference relationship[114]. A longitudinal study conducted in 220 patients with fibromyalgia involved completion of electronic diary records for 21 consecutive days assessing both pain levels and subsequent activity interference and levels of PA and NA. Multilevel structural equation modeling showed that pain and PA mediated the relation between sleep quality and activity interference, that early-morning reports of poor sleep quality the previous night predicted elevated levels of pain and lower levels of PA at late-morning. In turn, PA levels measured at the late-morning time point also predicted elevated end-of-day activity interference. PA levels were also found to be a stronger mediator than pain between sleep

quality and subsequent activity interference, while NA was not a significant mediator in this study[115].

These reports highlight NA and PA as essential contributing factors to consider if we are to understand the relationship between sleep and pain. Further longitudinal research on this matter, incorporating objective sleep measures and perhaps also neuroimaging, may help to further clarify the exact role of NA and PA in this relationship. The pivotal role played by affect as a mediator of the sleep and pain association also has important clinical implications. More specifically, there is reason to believe that treatment interventions designed to improve sleep quality might improve patients' affective states (i.e., by lowering negative affect and/or enhancing positive affect), which in turn could lead to reductions in pain. Treatment studies involving cognitive-behavioral treatment approaches designed to improve sleep quality, chronic pain, or both, have proven effective in improving sleep symptoms, patients' affective states and pain-related outcomes [116-118].

Other comorbidities frequently associated with deteriorated sleep and chronic pain are mood disorders such as anxiety and depression. Studies have shown that depressive symptoms partially mediate the relationship between insomnia/short sleep and chronic pain development, and that anxiety symptoms partially mediated the relationship between insomnia symptoms and incidence of pain[119,120]. Additionally, elevated emotional distress and greater catastrophizing have also been considered mediators of the association between sleep disturbance and chronic pain intensity [121]. When referred to pain, catastrophizing has been defined as the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, and by a relative inability to inhibit

pain-related thoughts in anticipation of, during or following a painful encounter[122]. A cross-sectional study conducted in 214 participants with TMD showed that pain catastrophizing was associated with greater sleep disturbance, and that a significant portion of the variance of clinical pain severity and pain-related interference attributed to pain catastrophizing, especially through rumination, was mediated by sleep disturbances[123]. However, another longitudinal study conducted in 50 consecutive chronic non-malignant pain patients, concluded that pain was the mediator in the relationship between sleep and pain catastrophizing [124]. Nevertheless, one should note that the tested models did not include pain as an antecedent to poor sleep quality or catastrophizing as a moderator.

Endogenous substances (dopamine, orexin, melatonin, vitamin D). Dopamine (DA) is a neurotransmitter and also a hormone involved in several functions of the body. In the brain, DA is well known for playing a major role in the sleep-wake cycle, in the reward motivation system, and for its involvement in movement control. In the sleep-wake cycle, more DA is associated with more time awake, and less DA with a sleep inductor state. It is currently thought that dopamine neurons are a heterogeneous population of neurons that respond to both appetitive and aversive stimuli to mediate motivated behavior[125].

Release of dopamine after an acute painful stimulus acts as a salience cue and is critical for approach or avoidance behavior. It has been theorized that chronic pain may lead to significant impairment of the mesolimbic dopaminergic system (i.e., reward pathways), which in turn could interfere with motivation[125]. Moreover, animal models showed that acute sleep deprivation is associated with downregulated D2/3 receptors activity, which could at least partially explained reduced alertness after sleep

deprivation[126]. Downregulation of D2/3 receptors activity may also affect other systems where DA is involved, including the reward motivation and pain modulation systems [127]. DA has also been related with antinociceptive effects and with motivated behavior despite chronic pain [127-129], and some authors have hypothesized that this “lack” of DA may lead to a decreased protection towards pain, which then facilitates nociception [127]. For instance, in fibromyalgia patients, one of the most common chronic pain conditions, a dysfunction of the dopaminergic system has been observed[130]. Moreover, patients with Parkinson's disease, a neurodegenerative disease where DA projections are progressively abolished, also present frequent pain and sleep complaints[131].

Orexin, also known as hypocretine, is a neuropeptide involved in the regulation of arousal, wake-sleep cycle, and appetite among others, which has become very popular in recent years for its involvement in multiple central nervous system processes. Two types of orexin peptides (Orexin 1 and 2) and two types of receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R) have been identified. The orexinergic system has different projections to various areas in the CNS, and the latter system is thought to be involved in different physiological functions and conditions such as feeding and metabolism, cardiovascular homeostasis, hormone secretion, reproduction, sleep/wake cycle, reward and addiction, anxiety and stress, seizures, and recently pain modulation [132-134]. To date, the bulk of evidence on the various roles of orexin in pain comes from animal models and suggests a contribution of the orexin system to neuropathic and visceral nociception, headaches, orofacial pain, rheumatoid arthritis, and stress-induced analgesia among others. It appears that that the effects of orexin-A on pain is more potent than orexin-B, and that these orexin subtypes can regulate thermal, mechanical and

chemical antinociceptive effects at spinal and supraspinal levels[135]. Despite having their main cell bodies located in the hypothalamus, regions such as the cerebral cortex, basal ganglia, NAc, hippocampus, hypothalamic and thalamic nuclei, dorsal and medial raphe, locus coeruleus (LC) and regions involved in pain modulation, such as periaqueductal gray (PAG) and reticular formation, also receive projections from the orexin system. However, the exact action mechanism of this system in nociception and pain modulation is not fully understood.

Other important substance is melatonin (5-methoxy-N-acetyltryptamine), a neurohormone secreted in the pineal gland and regulated by the suprachiasmatic nucleus. It is synchronized to the light/dark cycle of the environment and is involved in circadian rhythms, which control its timing, quantity, and quality. Melatonin acts through melatonin 1 (MT1) and MT2 receptors in mammals, located in the hypothalamus, thalamus, anterior pituitary, dorsal horn of the spinal cord, spinal trigeminal tract, and trigeminal nucleus[136,137]. Besides participating in circadian rhythms, melatonin is also involved in other physiological functions, such as mood states and pain regulation. Additionally, melatonin has been related to the pathogenesis of a number of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease [136,137]. It appears that melatonin also has free-radical activity and interacts with different pathways involved in pain, including N-methyl-D-aspartate (NMDA) and GABA, opioid, extracellular signal-regulated kinase (ERK/MAPK), and nitric oxide systems. Thus, melatonin could decrease pain improving sleep through circadian rhythms normalization, but also in an independent manner through its action on melatonin receptors and several neurotransmitter systems [138]. Animal models have also

demonstrated that the suppression of melatonin secretion due to sleep deprivation can increase glial activation and aggravate neuropathic pain [139]. Moreover, disrupted melatonin secretion has been related to clinical symptoms in major depression and fibromyalgia patients [140].

Vitamin D is another essential substance that can be obtained through sunlight exposure or diet, available in different types. Vitamin D plays a major role in calcium metabolism and bone mineralization among others [141]. Its status is based on the serum levels of 25-hydroxyvitamin D (25OHD), the metabolite found in the human body in higher concentration. Vitamin D is also related to the sleep-wake cycle and with the nociceptive process, mainly due to its role on inflammation[142-144]. Different studies have speculated about the importance of vitamin D in sleep disorders, as it appears that vitamin D receptors have been found in different sleep-awake cycle areas such as the hypothalamus, and that lower levels of 25OHD have been correlated with shorter sleep duration, less sleep efficiency, and with the presence of sleep disorders such as obstructive sleep apnea (OSA) in adults and pediatric patients, restless leg syndrome or narcolepsy[143]. In an OSA study, along with clinical symptoms, 25OHD levels increased with continuous positive airways pressure (CPAP) treatment, mainly in an obese group[145]. Vitamin D and its modulating role on the immune system and the inflammatory cascade has been emphasized, suggesting possible neuro-immunomodulatory properties[143]. As with sleep conditions, lower levels of 25OHD (frequently defined as lower than 20ng/mL) have been found in fibromyalgia, rheumatoid arthritis, osteoarthritis, or sickle cell disease among others [143,144]. Decreased 25OHD has also been associated with a higher

consumption of opioids in a cancer pain population, and with exacerbated central sensitivity in a chronic musculoskeletal pain sample [146,147].

Finally, attention should also be directed towards the role of other neurotransmitters such as serotonin, noradrenaline or oxytocin, which are commonly implicated in sleep and chronic pain pathways[148,149].

Anatomical brain areas. A recent study, using a controlled laboratory sleep deprivation model in 21 healthy subjects, evaluated the acute effects of experimental sleep disruption on pain-related activation of the nucleus accumbens (NAc) with functional MRI (fMRI). The NAc is a brain area involved in pain modulation and reward motivation, receiving multiple dopaminergic inputs from different brain structures also involved with pain and cognition. The results of this study demonstrated that sleep disruption can attenuate NAc function and increase reward-related connectivity with the anterior midcingulate cortex (aMCC), a region commonly associated with the use of cognitive resources to regulate pain [150]. Furthermore, there is evidence showing that sleep deprivation increases pain by increasing NAc adenosinergic A2A activity and by decreasing NAc dopaminergic D2 activity, and that chronic sleep restriction increases pain sensitivity over time in the PAG area (primary control center for descending pain modulation) and NAc in a dependent manner [151,152].

Other recent fMRI study investigated thermal pain thresholds in 25 healthy participants undergoing one night of sleep and one night of sleep deprivation [153]. After a PSG night of normal sleep or sleep deprivation (enforced wakening period with non-stressful activities), thermal pain thresholds were assessed outside the fMRI scanner, which was followed by an in-scanner thermal pain sensitivity task. The latter involved a

pseudo-randomly ordered sequence of painful hot, and non-painful warm stimuli. The authors observed that sleep deprivation significantly increased pain reactivity within the right primary somatosensory cortex (the pain was induced over the left side of the body) and that the extent of sleep deprivation amplified somatosensory pain reactivity positively, which significantly predicted the lowering of pain thresholds. Moreover, following sleep deprivation, significant decreases in activity were observed in the thalamus and other brain areas involved in decision-making such as the striatum, insula, and NAc. The reduction of thalamic activity also significantly and negatively predicted lowering of pain thresholds across individuals. Authors concluded that sleep loss triggering hyperalgesia involves complex brain processes, as the impact of insufficient sleep on pain likely involves both an amplification of primary cortical pain processing, potentially due to thalamic disinhibition, and a shift in affective valuation and decision-making involving the insula and NAc[153].

Cyclic Alternating Pattern (CAP). As mentioned above, sleep is an active process, where the individual is not completely isolated from external and internal stimuli. During NREM sleep, a process called CAP is present[154]. CAP is considered a visualization method and a physiological phenomenon that represent the balance between sleep quietness and sleep arousal. Thus, there are frequent brief brain, heart, and muscle reactivations or microarousals called “windows” that last 3 to 15 seconds. These windows occur approximately 5 to 15 times per hour, allowing the individual to reposition or to recognize any harmful situation[155]. The sleep arousal is part of a protective “flight or fight mechanism” that remains present during NREM sleep to preserve body integrity (sleep positioning, adjustments in heart rate, etc.) and to react to

threatening event. This process does not occur in an “abrupt binary way”, as it appears that it may represent to some extent a transition between wakefulness and sleep, in order to preserve the continuity of sleep over the possibility to react in life-threatening situations [60]. CAP is divided into two phases: an active and a quiet phase. The active A phase is further subdivided in A1 (high dominance of slow-wave sleep/ promotor of sleep restoration), in A2 (a transition phase) and A3 (an arousal-dominant phase that is essential for our survival). The high rate of A2 and A3 phase represents sleep fragmentation, which is associated with higher number of arousals and decreased sleep efficiency[154,155]. During the quiet phase, corresponding to the B phase, sleep is very stable and quiet [156]. CAP phases are in the minute’s domains and their rate rise with age or in presence of disease. Therefore, it seems that CAP represents a possible “window” for arousal, and in fact, CAP is considered by many as a marker of sleep instability[155].

Despite the fact that CAP has not been widely investigated in chronic pain populations, some studies have been conducted among patients with fibromyalgia. These patients have been found to present 50% more cyclic arousal shifts (heart, EEG and EMG changes) during their sleep, and that CAP rate and duration were significantly increased in these patients when compared to controls. This activity pattern suggests a possible autonomic dysfunction and an alteration in sleep microstructure. It is to note that these results have yet to be reproduced in other studies. CAP was also associated with less sleep efficiency and more clinical symptoms such as pain intensity, and recent speculations suggested that sleep may cause the same effect as a stressing test in chronic pain patients [157,158]. Moreover, CAP has also been strongly associated with the onset of sleep bruxism[159]. More investigations about this marker in pain populations could

better illustrate its role in the sleep and pain relationship, perhaps clarifying the relative weight of this possible mechanism.

Other sleep-pain mediators. Other identified mediators for the relationship between impaired sleep and higher pain intensity are fatigue, activation of HPA axis measured through cortisol[160,161], and although inconclusive, several authors have identified the need to further investigate the role of physical activity, frequently associated with sleep disturbances and chronic pain[162,163]. Caffeine, alcohol or nicotine intake, other comorbidities, and the use of medications such as opioids can also have direct influence on sleep quality and pain instability[164,165].

FUTURE DIRECTIONS

Although more longitudinal, micro-longitudinal and mediation studies using subjective and objective outcomes have emerged in the past few years, additional studies using brain imaging (e.g., fMRI), electrophysiology, or human adaptation of other techniques (e.g., optogenetics, chemogenetics) will be needed to shed light on the neural underpinnings underlying the sleep and pain association[166,167]. The use of non-invasive techniques, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) may also be of great value to further investigate the mechanisms underlying the sleep-pain association. Research will be needed to determine whether non-invasive techniques such as TMS or tDCS could represent an effective therapeutic alternative for patients with pain with comorbid sleep problems. For instance, both

techniques have been used to treat different chronic pain and sleep conditions [168-172], and TMS was also used to assess cortical excitability of OSA, restless leg syndrome (RLS), and chronic insomnia patients [173,174]. Finally, novel modeling techniques will be needed to thoroughly assess potential relationships between sleep and pain phenotypes. Machine learning, for instance, is a mathematical approach that can help to identify patterns or clusters in variables in order to characterize phenotypes and observe more precise characteristics of vulnerability among patients. For example, it could be used to evaluate: a) the influence of pain and use of management strategies (medication, CBT, etc.) on sleep, which is not solidly confirmed with usual statistical method; and b) to further assess the impact of poor sleep or sleep disturbances on next-day functioning, pain, or quality of life [175,176]. Such tools could reveal to be a major addition to personalized medicine diagnosis and treatment for patients facing pain and sleep conditions.

REFERENCES

1. Siegel JM. Clues to the functions of mammalian sleep. *Nature.* 2005;437(7063):1264-1271.
2. Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annual review of psychology.* 2006;57:139-166.
3. Ogilvie RD. The process of falling asleep. *Sleep medicine reviews.* 2001;5(3):247-270.
4. Siegel JM. REM sleep: a biological and psychological paradox. *Sleep medicine reviews.* 2011;15(3):139-142.

5. Chokroverty S. Overview of sleep & sleep disorders. *The Indian journal of medical research.* 2010;131:126-140.

6. Hillman DR, Lack LC. Public health implications of sleep loss: the community burden. *The Medical journal of Australia.* 2013;199(8):S7-10.

7. Adams RJ, Appleton SL, Taylor AW, et al. Sleep health of Australian adults in 2016: results of the 2016 Sleep Health Foundation national survey. *Sleep health.* 2017;3(1):35-42.

8. Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep.* 1997;20(4):267-277.

9. Killgore WD, Balkin TJ, Wesensten NJ. Impaired decision making following 49 h of sleep deprivation. *Journal of sleep research.* 2006;15(1):7-13.

10. Yin J, Jin X, Shan Z, et al. Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association.* 2017;6(9).

11. Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep medicine reviews.* 2018;40:4-16.

12. Fatima Y, Doi SA, Mamun AA. Sleep quality and obesity in young subjects: a meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2016;17(11):1154-1166.

13. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep.* 2008;31(5):619-626.

14. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Sleep.* 2007;30(12):1667-1673.

15. Zhai L, Zhang H, Zhang D. Sleep Duration and Depression among Adults: A Meta-Analysis of Prospective Studies. *Depression and anxiety.* 2015;32(9):664-670.

16. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *The Journal of clinical psychiatry.* 2012;73(9):e1160-1167.

17. Bishop TM, Ashrafioun L, Pigeon WR. The Association Between Sleep Apnea and Suicidal Thought and Behavior: An Analysis of National Survey Data. *The Journal of clinical psychiatry.* 2018;79(1).

18. Liu JW, Tu YK, Lai YF, et al. Associations between sleep disturbances and suicidal ideation, plans, and attempts in Adolescents: A Systematic Review and Meta-Analysis. *Sleep.* 2019.

19. Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. *Sleep Med Rev.* 2018;39:82-97.

20. Hillman D, Mitchell S, Streatfeild J, Burns C, Bruck D, Pezzullo L. The economic cost of inadequate sleep. *Sleep.* 2018;41(8).

21. Treede RD. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain reports.* 2018;3(2):e643.

22. Williams AC, Craig KD. Updating the definition of pain. *Pain.* 2016;157(11):2420-2423.

23. Melzack R. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci.* 1990;13(3):88-92.

24. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science.* 2000;288(5472):1769-1772.

25. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain.* 2019;160(1):19-27.

26. Woolf CJ. What is this thing called pain? *J Clin Invest.* 2010;120(11):3742-3744.

27. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain.* 2015;156(6):1003-1007.

28. Gaskin DJ, Richard P. The economic costs of pain in the United States. *The journal of pain : official journal of the American Pain Society.* 2012;13(8):715-724.

29. Racine M. Chronic pain and suicide risk: A comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;87(Pt B):269-280.

30. Duenas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. *J Pain Res.* 2016;9:457-467.

31. Turk DC, Fillingim RB, Ohrbach R, Patel KV. Assessment of Psychosocial and Functional Impact of Chronic Pain. *J Pain.* 2016;17(9 Suppl):T21-49.

32. International Pain Summit Of The International Association For The Study Of P. Declaration of Montreal: declaration that access to pain management is a fundamental human right. *J Pain Palliat Care Pharmacother.* 2011;25(1):29-31.

33. https://www.who.int/medicines/areas/quality_safety/guide_on_pain/en/. Web statement on pain management guidance. 2019.

34. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. *Sleep medicine.* 2018.

35. Andersen ML, Araujo P, Frange C, Tufik S. Sleep Disturbance and Pain: A Tale of Two Common Problems. *Chest.* 2018;154(5):1249-1259.

36. Lavigne GJ, Sessle BJ. The Neurobiology of Orofacial Pain and Sleep and Their Interactions. *Journal of dental research.* 2016.

37. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain.* 2013;14(12):1539-1552.

38. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev.* 2006;10(5):357-369.

39. Schuh-Hofer S, Wodarski R, Pfau DB, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain.* 2013;154(9):1613-1621.

40. Schuh-Hofer S, Baumgartner U, Treede RD. Effect of sleep deprivation on the electrophysiological signature of habituation to noxious laser stimuli. *Eur J Pain.* 2015;19(8):1197-1209.

41. Faraut B, Leger D, Medkour T, et al. Napping reverses increased pain sensitivity due to sleep restriction. *PLoS ONE [Electronic Resource].* 2015;10(2):e0117425.

42. Haack M, Simpson N, Sethna N, Kaur S, Mullington J. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology.* 2019.

43. Lautenbacher S. Sleep and pain are definitely coupled-but how tight is this coupling? *Pain.* 2018;159(1):3-4.

44. Valrie CR, Bromberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. *Journal of developmental and behavioral pediatrics : JDBP.* 2013;34(2):120-128.

45. Lewandowski Holley A, Rabbitts J, Zhou C, Durkin L, Palermo TM. Temporal daily associations among sleep and pain in treatment-seeking youth with acute musculoskeletal pain. *Journal of behavioral medicine.* 2017;40(4):675-681.

46. Rabbitts JA, Zhou C, Narayanan A, Palermo TM. Longitudinal and Temporal Associations Between Daily Pain and Sleep Patterns After Major Pediatric Surgery. *J Pain.* 2017;18(6):656-663.

47. Valrie CR, Kilpatrick RL, Alston K, et al. Investigating the Sleep-Pain Relationship in Youth with Sickle Cell Utilizing mHealth Technology. *J Pediatr Psychol.* 2019;44(3):323-332.

48. Fisher K, Laikin AM, Sharp KMH, Criddle CA, Palermo TM, Karlson CW. Temporal relationship between daily pain and actigraphy sleep patterns in pediatric sickle cell disease. *J Behav Med.* 2018;41(3):416-422.

49. Dubrovsky B, Janal MN, Lavigne GJ, et al. Depressive symptoms account for differences between self-reported versus polysomnographic assessment of sleep quality in women with myofascial TMD. *J Oral Rehabil.* 2017;44(12):925-933.

50. Laverdure-Dupont D, Rainville P, Renancio C, Montplaisir J, Lavigne G. Placebo analgesia persists during sleep: An experimental study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;85:33-38.

51. Chouchou F, Dang-Vu TT, Rainville P, Lavigne G. The Role of Sleep in Learning Placebo Effects. *International Review of Neurobiology.* 2018;139:321-355.

52. Chouchou F, Chauny JM, Rainville P, Lavigne GJ. Selective REM Sleep Deprivation Improves Expectation-Related Placebo Analgesia. *PLoS ONE [Electronic Resource].* 2015;10(12):e0144992.

53. Ree A, Nilsen KB, Knardahl S, Sand T, Matre D. Sleep restriction does not potentiate nocebo-induced changes in pain and cortical potentials. *Eur J Pain.* 2019.

54. Landry GJ, Best JR, Liu-Ambrose T. Measuring sleep quality in older adults: a comparison using subjective and objective methods. *Front Aging Neurosci.* 2015;7:166.

55. Wu YL, Chang LY, Lee HC, Fang SC, Tsai PS. Sleep disturbances in fibromyalgia: A meta-analysis of case-control studies. *J Psychosom Res.* 2017;96:89-97.

56. Mazza S, Magnin M, Bastuji H. Pain and sleep: from reaction to action. *Neurophysiologie Clinique.* 2012;42(5):337-344.

57. Bastuji H, Perchet C, Legrain V, Montes C, Garcia-Larrea L. Laser evoked responses to painful stimulation persist during sleep and predict subsequent arousals. *Pain.* 2008;137(3):589-599.

58. Bentley AJ, Newton S, Zio CD. Sensitivity of sleep stages to painful thermal stimuli. *J Sleep Res.* 2003;12(2):143-147.

59. Lavigne G, Zucconi M, Castronovo C, Manzini C, Marchettini P, Smirne S. Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems. *Pain.* 2000;84(2-3):283-290.

60. Peter-Derex L, Magnin M, Bastuji H. Heterogeneity of arousals in human sleep: A stereo-electroencephalographic study. *Neuroimage.* 2015;123:229-244.

61. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain.* 1977;3(1):57-68.

62. Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Progress in neurobiology.* 2000;61(2):169-203.

63. Nir RR, Yarnitsky D. Conditioned pain modulation. *Current opinion in supportive and palliative care.* 2015;9(2):131-137.

64. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *Journal of neurophysiology.* 2002;87(4):2205-2208.

65. Moana-Filho EJ, Herrero Babiloni A, Nisley A. Endogenous pain modulation assessed with offset analgesia is not impaired in chronic temporomandibular disorder pain patients. *J Oral Rehabil.* 2019.

66. Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. *Neurology.* 2005;65(3):437-443.

67. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. *Expert review of neurotherapeutics.* 2012;12(5):577-585.

68. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain.* 2012;13(10):936-944.

69. O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, Carrillo-de-la-Pena MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal

Summation and Conditioned Pain Modulation Paradigms. *J Pain.* 2018;19(8):819-836.

70. Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: a systematic review and meta-analysis. *Pain.* 2018;159(8):1441-1455.

71. Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. *Pain.* 2008;140(3):465-471.

72. Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: between pro- and antinociception. *Pain.* 2014;155(4):663-665.

73. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain.* 2015;156 Suppl 1:S24-31.

74. Moana-Filho EJ, Herrero Babiloni A. Endogenous Pain Modulation in Chronic TMD: Derivation of Pain Modulation Profiles and Assessment of Its Relationship with Clinical Characteristics. *J Oral Rehabil.* 2018.

75. Haack M, Scott-Sutherland J, Santangelo G, Simpson NS, Sethna N, Mullington JM. Pain sensitivity and modulation in primary insomnia. *European journal of pain.* 2012;16(4):522-533.

76. Tiede W, Magerl W, Baumgartner U, Durrer B, Ehlert U, Treede RD. Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. *Pain.* 2010;148(1):36-42.

77. Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. *Neuroscience.* 2018;387:191-200.

78. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep.* 2007;30(4):494-505.

79. Matre D, Andersen MR, Knardahl S, Nilsen KB. Conditioned pain modulation is not decreased after partial sleep restriction. *European journal of pain.* 2016;20(3):408-416.

80. Karmann AJ, Lauer C, Ziegler E, Killian L, Horn-Hofmann C, Lautenbacher S. Associations of nocturnal sleep with experimental pain and pain catastrophizing in healthy volunteers. *Biol Psychol.* 2018;135:1-7.

81. Smith MT, Jr., Remeniuk B, Finan PH, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: implications for sex differences in chronic pain. *Sleep.* 2019;42(2).

82. Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. *Pain.* 2018;159(1):33-40.

83. Valeriani M. Increased habituation to painful stimuli: a self-protective mechanism during prolonged wakefulness? *Eur J Pain.* 2015;19(8):1055-1056.

84. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect

of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *J Pain.* 2018;19(8):942 e941-942 e918.

85. Paul-Savoie E, Marchand S, Morin M, et al. Is the deficit in pain inhibition in fibromyalgia influenced by sleep impairments? *The open rheumatology journal.* 2012;6:296-302.

86. Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *European journal of pain.* 2009;13(10):1043-1047.

87. Lee YC, Lu B, Edwards RR, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. *Arthritis and rheumatism.* 2013;65(1):59-68.

88. Ligato D, Petersen KK, Morch CD, Arendt-Nielsen L. Offset analgesia: The role of peripheral and central mechanisms. *Eur J Pain.* 2018;22(1):142-149.

89. Niesters M, Hoitsma E, Sarton E, Aarts L, Dahan A. Offset analgesia in neuropathic pain patients and effect of treatment with morphine and ketamine. *Anesthesiology.* 2011;115(5):1063-1071.

90. Watkins LR, Milligan ED, Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. *Advances in experimental medicine and biology.* 2003;521:1-21.

91. Zhang JM, An J. Cytokines, inflammation, and pain. *International anesthesiology clinics.* 2007;45(2):27-37.

92. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best practice & research Clinical endocrinology & metabolism.* 2010;24(5):775-784.

93. Simpson N, Dinges DF. Sleep and inflammation. *Nutrition reviews.* 2007;65(12 Pt 2):S244-252.

94. Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *The Journal of clinical endocrinology and metabolism.* 2000;85(10):3597-3603.

95. Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. *Journal of immunology.* 1997;158(9):4454-4464.

96. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *The Journal of clinical endocrinology and metabolism.* 1999;84(8):2603-2607.

97. Hong S, Mills PJ, Loredo JS, Adler KA, Dimsdale JE. The association between interleukin-6, sleep, and demographic characteristics. *Brain, behavior, and immunity.* 2005;19(2):165-172.

98. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biological psychiatry.* 2016;80(1):40-52.

99. Everson CA. Sustained sleep deprivation impairs host defense. *The American journal of physiology.* 1993;265(5 Pt 2):R1148-1154.

100. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. *Physiological reviews.* 2019;99(3):1325-1380.

101. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension.* 2001;38(3):399-403.

102. Sauvet F, Leftheriotis G, Gomez-Merino D, et al. Effect of acute sleep deprivation on vascular function in healthy subjects. *Journal of applied physiology.* 2010;108(1):68-75.

103. Gonzalez-Ortiz M, Martinez-Abundis E, Balcazar-Munoz BR, Pascoe-Gonzalez S. Effect of sleep deprivation on insulin sensitivity and cortisol concentration in healthy subjects. *Diabetes, nutrition & metabolism.* 2000;13(2):80-83.

104. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep medicine reviews.* 2007;11(3):163-178.

105. Larsen JT, Hershfield HE, Stastny BJ, Hester N. On the relationship between positive and negative affect: Their correlation and their co-occurrence. *Emotion.* 2017;17(2):323-336.

106. Smith BW, Zautra AJ. Vulnerability and resilience in women with arthritis: test of a two-factor model. *Journal of consulting and clinical psychology.* 2008;76(5):799-810.

107. Finan PH, Quartana PJ, Remeniuk B, et al. Partial Sleep Deprivation Attenuates the Positive Affective System: Effects Across Multiple Measurement Modalities. *Sleep.* 2017;40(1).

108. Konjarski M, Murray G, Lee VV, Jackson ML. Reciprocal relationships between daily sleep and mood: A systematic review of naturalistic prospective studies. *Sleep medicine reviews.* 2018;42:47-58.

109. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage.* 2009;47(3):987-994.

110. Janssen SA. Negative affect and sensitization to pain. *Scandinavian journal of psychology.* 2002;43(2):131-137.

111. Finan PH, Garland EL. The role of positive affect in pain and its treatment. *Clin J Pain.* 2015;31(2):177-187.

112. Arewasikporn A, Ehde DM, Alschuler KN, Turner AP, Jensen MP. Positive factors, pain, and function in adults with multiple sclerosis. *Rehabilitation psychology.* 2018;63(4):612-620.

113. Evans S, Djilas V, Seidman LC, Zeltzer LK, Tsao JCI. Sleep Quality, Affect, Pain, and Disability in Children With Chronic Pain: Is Affect a Mediator or Moderator? *J Pain.* 2017;18(9):1087-1095.

114. Ravyts SG, Dzierzewski JM, Raldiris T, Perez E. Sleep and pain interference in individuals with chronic pain in mid- to late-life: The influence of negative and positive affect. *Journal of sleep research.* 2018:e12807.

115. Kothari DJ, Davis MC, Yeung EW, Tennen HA. Positive affect and pain: mediators of the within-day relation linking sleep quality to activity interference in fibromyalgia. *Pain.* 2015;156(3):540-546.

116. Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. *Sleep medicine clinics.* 2014;9(2):261-274.

117. Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep medicine reviews.* 2015;19:6-16.

118. McCrae CS, Williams J, Roditi D, et al. Cognitive behavioral treatments for insomnia (CBT-I) and pain (CBT-P) in adults with comorbid chronic insomnia and fibromyalgia: Clinical outcomes from the SPIN randomized controlled trial. *Sleep.* 2018.

119. Generaal E, Vogelzangs N, Penninx BW, Dekker J. Insomnia, Sleep Duration, Depressive Symptoms, and the Onset of Chronic Multisite Musculoskeletal Pain. *Sleep.* 2017;40(1).

120. Dunietz GL, Swanson LM, Jansen EC, et al. Key insomnia symptoms and incident pain in older adults: direct and mediated pathways through depression and anxiety. *Sleep.* 2018;41(9).

121. Burgess HJ, Burns JW, Buvanendran A, et al. Associations Between Sleep Disturbance and Chronic Pain Intensity and Function: A Test of Direct and Indirect Pathways. *Clin J Pain.* 2019.

122. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother.* 2009;9(5):745-758.

123. Buenaver LF, Quartana PJ, Grace EG, et al. Evidence for indirect effects of pain catastrophizing on clinical pain among myofascial temporomandibular disorder participants: the mediating role of sleep disturbance. *Pain.* 2012;153(6):1159-1166.

124. Wilt JA, Davin S, Scheman J. A multilevel path model analysis of the relations between sleep, pain, and pain catastrophizing in chronic pain rehabilitation patients. *Scandinavian journal of pain.* 2016;10:122-129.

125. Taylor AM, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction. *Pain.* 2016;157(6):1194-1198.

126. Volkow ND, Tomasi D, Wang GJ, et al. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2012;32(19):6711-6717.

127. Finan PH, Remeniuk B. Is the brain reward system a mechanism of the association of sleep and pain? *Pain management.* 2016;6(1):5-8.

128. Moradi M, Yazdanian M, Haghparast A. Role of dopamine D2-like receptors within the ventral tegmental area and nucleus accumbens in antinociception induced by lateral hypothalamus stimulation. *Behavioural brain research.* 2015;292:508-514.

129. Schwartz N, Temkin P, Jurado S, et al. Chronic pain. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. *Science.* 2014;345(6196):535-542.

130. Wood PB, Patterson JC, 2nd, Sunderland JJ, Tainter KH, Glabus MF, Lilien DL. Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study. *J Pain.* 2007;8(1):51-58.

131. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A survey of pain in idiopathic Parkinson's disease. *Journal of pain and symptom management.* 2006;32(5):462-469.

132. Gotter AL, Webber AL, Coleman PJ, Renger JJ, Winrow CJ. International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. *Pharmacological reviews.* 2012;64(3):389-420.

133. Razavi BM, Hosseinzadeh H. A review of the role of orexin system in pain modulation. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie.* 2017;90:187-193.

134. Roohbakhsh A, Alavi MS, Azhdari-Zarmehri H. The Orexinergic (Hypocretin) System and Nociception: An Update to Supraspinal Mechanisms. *Current medicinal chemistry.* 2018;25(32):3917-3929.

135. Cady RJ, Denson JE, Sullivan LQ, Durham PL. Dual orexin receptor antagonist 12 inhibits expression of proteins in neurons and glia implicated in peripheral and central sensitization. *Neuroscience.* 2014;269:79-92.

136. Ng KY, Leong MK, Liang H, Paxinos G. Melatonin receptors: distribution in mammalian brain and their respective putative functions. *Brain structure & function.* 2017;222(7):2921-2939.

137. Kaur T, Shyu BC. Melatonin: A New-Generation Therapy for Reducing Chronic Pain and Improving Sleep Disorder-Related Pain. *Advances in experimental medicine and biology.* 2018;1099:229-251.

138. Danilov A, Kurganova J. Melatonin in Chronic Pain Syndromes. *Pain and therapy.* 2016;5(1):1-17.

139. Huang CT, Chiang RP, Chen CL, Tsai YJ. Sleep deprivation aggravates median nerve injury-induced neuropathic pain and enhances microglial activation by suppressing melatonin secretion. *Sleep.* 2014;37(9):1513-1523.

140. Caumo W, Hidalgo MP, Souza A, Torres ILS, Antunes LC. Melatonin is a biomarker of circadian dysregulation and is correlated with major depression and fibromyalgia symptom severity. *Journal of pain research.* 2019;12:545-556.

141. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American journal of clinical nutrition.* 2004;80(6 Suppl):1678S-1688S.

142. Shipton EA, Shipton EE. Vitamin D and Pain: Vitamin D and Its Role in the Aetiology and Maintenance of Chronic Pain States and Associated Comorbidities. *Pain research and treatment.* 2015;2015:904967.

143. de Oliveira DL, Hirotsu C, Tufik S, Andersen ML. The interfaces between vitamin D, sleep and pain. *The Journal of endocrinology.* 2017;234(1):R23-R36.

144. Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R. The association between vitamin D concentration and pain: a systematic review and meta-analysis. *Public health nutrition.* 2018;21(11):2022-2037.

145. Liguori C, Izzi F, Mercuri NB, et al. Vitamin D status of male OSAS patients improved after long-term CPAP treatment mainly in obese subjects. *Sleep medicine.* 2017;29:81-85.

146. Bergman P, Sperneder S, Hoijer J, Bergqvist J, Bjorkhem-Bergman L. Low vitamin D levels are associated with higher opioid dose in palliative cancer patients--results from an observational study in Sweden. *PloS one.* 2015;10(5):e0128223.

147. von Kanel R, Muller-Hartmannsgruber V, Kokinogenis G, Egloff N. Vitamin D and central hypersensitivity in patients with chronic pain. *Pain medicine.* 2014;15(9):1609-1618.

148. Boakye PA, Olechowski C, Rashiq S, et al. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. *Clin J Pain.* 2016;32(4):327-336.

149. Schuh-Hofer S, Eichhorn N, Grinevich V, Treede RD. Sleep Deprivation Related Changes of Plasma Oxytocin in Males and Female Contraceptive Users Depend on Sex and Correlate Differentially With Anxiety and Pain Hypersensitivity. *Front Behav Neurosci.* 2018;12:161.

150. Seminowicz DA, Remeniuk B, Krimmel SR, et al. Pain-related nucleus accumbens function: modulation by reward and sleep disruption. *Pain.* 2019;160(5):1196-1207.

151. Sardi NF, Lazzarim MK, Guilhen VA, et al. Chronic sleep restriction increases pain sensitivity over time in a periaqueductal gray and nucleus accumbens dependent manner. *Neuropharmacology.* 2018;139:52-60.

152. Sardi NF, Tobaldini G, Morais RN, Fischer L. Nucleus accumbens mediates the pronociceptive effect of sleep deprivation: the role of adenosine A2A and dopamine D2 receptors. *Pain.* 2018;159(1):75-84.

153. Krause AJ, Prather AA, Wager TD, Lindquist MA, Walker MP. The Pain of Sleep Loss: A Brain Characterization in Humans. *J Neurosci.* 2019;39(12):2291-2300.

154. Parrino L, Grassi A, Milioli G. Cyclic alternating pattern in polysomnography: what is it and what does it mean? *Curr Opin Pulm Med.* 2014;20(6):533-541.

155. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep Med Rev.* 2012;16(1):27-45.

156. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. *Electroencephalography and clinical neurophysiology.* 1998;107(6):439-450.

157. Rizzi M, Radovanovic D, Santus P, et al. Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients. *Clin Exp Rheumatol.* 2017;35 Suppl 105(3):74-80.

158. Rizzi M, Sarzi-Puttini P, Atzeni F, et al. Cyclic alternating pattern: a new marker of sleep alteration in patients with fibromyalgia? *J Rheumatol.* 2004;31(6):1193-1199.

159. Carra MC, Rompre PH, Kato T, et al. Sleep bruxism and sleep arousal: an experimental challenge to assess the role of cyclic alternating pattern. *J Oral Rehabil.* 2011;38(9):635-642.

160. Bonvanie IJ, Oldehinkel AJ, Rosmalen JG, Janssens KA. Sleep problems and pain: a longitudinal cohort study in emerging adults. *Pain.* 2016;157(4):957-963.

161. Goodin BR, Smith MT, Quinn NB, King CD, McGuire L. Poor sleep quality and exaggerated salivary cortisol reactivity to the cold pressor task predict greater acute pain severity in a non-clinical sample. *Biological psychology.* 2012;91(1):36-41.

162. Banno M, Harada Y, Taniguchi M, et al. Exercise can improve sleep quality: a systematic review and meta-analysis. *PeerJ.* 2018;6:e5172.

163. Kichline T, Cushing CC, Ortega A, Friesen C, Schurman JV. Associations between Physical Activity and Chronic Pain Severity in Youth With Chronic Abdominal Pain. *Clin J Pain.* 2019.

164. Marshansky S, Mayer P, Rizzo D, Baltzan M, Denis R, Lavigne GJ. Sleep, chronic pain, and opioid risk for apnea. *Progress in neuro-psychopharmacology & biological psychiatry.* 2018;87(Pt B):234-244.

165. Whibley D, AlKandari N, Kristensen K, et al. Sleep and Pain: A Systematic Review of Studies of Mediation. *Clin J Pain.* 2019.

166. Dinh ST, Nickel MM, Tiemann L, et al. Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. *Pain.* 2019.

167. Venner A, Todd WD, Fraigne J, et al. Newly identified sleep-wake and circadian circuits as potential therapeutic targets. *Sleep.* 2019;42(5).

168. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev.* 2018;3:CD008208.

169. Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. *J Pain Res.* 2018;11:1445-1457.

170. Huang Z, Li Y, Bianchi MT, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: A randomized, double-blind, sham-controlled pilot study. *Brain stimulation.* 2018;11(5):1103-1109.

171. Frase L, Selhausen P, Krone L, et al. Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls. *Brain stimulation.* 2019;12(3):674-683.

172. Jodoin M, Rouleau D, Larson-Dupuis C, Gosselin N, De Beaumont L. The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2017.

173. Salas RE, Galea JM, Gamaldo AA, et al. Increased use-dependent plasticity in chronic insomnia. *Sleep.* 2014;37(3):535-544.

174. Herrero Babiloni A, De Beaumont L, Lavigne GJ. Transcranial Magnetic Stimulation: Potential Use in Obstructive Sleep Apnea and Sleep Bruxism. *Sleep Med Clin.* 2018;13(4):571-582.

175. Lotsch J, Ultsch A. Machine learning in pain research. *Pain.* 2018;159(4):623-630.

176. Shahin M, Ahmed B, Hamida ST, Mulaffer FL, Glos M, Penzel T. Deep Learning and Insomnia: Assisting Clinicians With Their Diagnosis. *IEEE journal of biomedical and health informatics.* 2017;21(6):1546-1553.

Transition to Chapter 2

Chapter 1 provides a comprehensive review of the bidirectional relationship between sleep and pain, including its mechanisms and multifaceted nature. Our review found consistent evidence indicating that poor sleep quality can subsequently lead to increased pain intensity and decreased pain tolerance. However, evidence indicating that chronic pain leads to altered sleep patterns and/or sleep problems is less consistent. The mechanisms contributing to the sleep-pain relationship are complex and include alterations in endogenous pain modulation, increased inflammation, and endogenous substances such as dopamine, orexin, melatonin, and vitamin D. Mechanisms that have received less attention, such as the cyclic alternating pattern (CAP), also appear to play a role in the sleep and pain association. Finally, psychological factors such as affect/mood and pain catastrophizing also play an important role in the co-occurrence of sleep and pain problems.

Given that the sleep and pain association might not unfold equally across all pain conditions, Chapter 2 of the present thesis reviewed the literature on sleep and temporomandibular disorders (TMD), the most common orofacial pain condition after odontogenic pain. Specifically, we will examine how TMD affects sleep quality and patterns, as well as how sleep disturbances can exacerbate TMD symptoms. The review also offered a thorough description of objective and subjective sleep measures that could be used in future studies. Finally, the potential clinical utility of our review findings for the screening and management of TMD patients was discussed.

CHAPTER 2. REVIEW ARTICLE 2.

Herrero Babiloni A, Martel MO, Lavigne GJ. ”Sleep disturbances in temporomandibular disorders: a narrative review”. Oral Surg, 2020. 13: 335-348. doi:10.1111/ors.12451.. Citations: 4.

Sleep disturbances in temporomandibular disorders: a narrative review

Alberto HERRERO BABILONI[1,2], DDS, MS; Marc O MARTEL[2,3,4], PhD; Gilles J LAVIGNE[1], DMD, PhD

[1] Research Center, Hôpital du Sacré-Coeur de Montréal, CIUSSS du Nord-de-l'Île-de-Montréal, Université De Montréal, Québec, Canada

[2] Division of Experimental Medicine, McGill University, Montreal, Canada

[3] Faculty of Dentistry, McGill University, Montreal, Canada

[4] Department of Anesthesia, McGill University, Montreal, Canada

Email: herre220@umn.edu

Phone: 514-338-2222

Fax: 514-238-2531

Conflicts of interest: none

Acknowledgements: We would like to acknowledge Gabrielle Beetz (Université De Montréal) for her contribution and assistance in the development of this manuscript.

ABSTRACT: Sleep complaints are frequently reported by patients with temporomandibular disorders (TMD). This review aims to offer dental practitioners and allied specialties a basic understanding of sleep quality, measured it subjectively and objectively, and common sleep disturbances that are present in TMD patients. Guidance in identifying and managing patients with TMD and comorbid sleep related complaints will be provided as well. Dentists should be able to screen sleep disorders such as insomnia, sleep disordered breathing (apnea, snoring), or sleep bruxism, and to refer patients to the appropriate specialist when necessary Individualized management and a multidisciplinary approach must be pursued when managing patients with TMD and comorbid sleep disturbances and/or sleep disorders, such as insomnia or obstructive sleep apnea.

Keywords: “polysomnography” “pain” “temporomandibular joint disorders” “sleep apnea syndromes” “surveys and questionnaires” “comorbidity”.

INTRODUCTION

Patients with painful temporomandibular disorders (TMD) also present several sleep related complains [1]. They may feel that their sleep is not restorative/recuperative as expressed by wake time tiredness, fatigue, and lack of energy with an important impact on mood. Poor sleep in vulnerable subjects can contribute to the presence and maintenance of pain, while pain also may interfere with sleep onset or maintenance. Although the directionality of the sleep-pain relationship is still debated, both sleep and pain (including TMD) have important consequences in the individual's well-being and in the socioeconomic system [2].

The objective of this narrative review is to guide dentists identifying and managing TMD patients with sleep related complaints. Given the clinical nature of our objectives and in order to enhance clinical accessibility and explore emerging areas, a narrative review was conducted. Dentists need to screen sleep disorders such as insomnia, sleep disordered breathing (apnea, snoring), and sleep bruxism. In some cases, dentists may also check for the impact of other conditions such as periodic limb movement syndrome. Possible management options in situations where sleep disturbances and TMD co-exist will be described as well. Sleep bruxism will not be covered in this review, as it will be addressed in another article from this journal issue.

For more information about the impact of sleep on other orofacial pain disorders, a series of recent comprehensive reviews may also be consulted [3-5].

WHAT IS PAIN

Pain has been defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [6]. When pain lasts beyond what is considered a normal expected healing period, it is categorized as chronic (often delimited as more than 3 or 6 months). To be noted that a consensus is not yet reached on the very accurate definition of pain, and other definitions such as the following: “Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components” have also been proposed [7].

Orofacial pain is a type of pain present in the face or in the oral cavity thus comprehending different painful disorders affecting teeth, nerves, and musculoskeletal structures. TMD is an umbrella term referring to different disorders that affect the temporomandibular joint (TMJ) and/or muscles of mastication[8]. Signs or symptoms of TMD include pain and tenderness in or around the ear, the jaw joint, or the muscles of the jaw, face or temples. Other symptoms include mechanical problems when opening or closing the mouth, such as difficulty to open the mouth, and clicking, popping, crunching or grinding noise when chewing, yawning or moving the jaw. Painful TMD can be broadly divided in articular, when the pain is originated in the TMJ, and muscular, when the origin of pain is in the muscles of mastication. However, a combination of both is quite frequent. After pain of dental origin, TMD are the most frequent orofacial pain disorders, affecting up to 12% of the general population[9].

The exact pathophysiological mechanisms of painful TMD are currently unclear, although it is thought to be a combination of peripheral and central mechanisms[10-13]. TMD frequently coexist with other painful trigeminal conditions such as migraine and tension

type headache and with other extra-trigeminal ones such as fibromyalgia, being often categorized as one of the “chronic overlapping pain conditions”[14-17]. Patients with chronic TMD usually present psychosocial issues, which include mood disorders or different sleep disturbances (Figure 2.1) [18,19].

Figure 2.1. Sleep disorders/issues that can be associated with temporomandibular disorders (TMD)

WHAT IS SLEEP

Behaviorally, sleep is defined as the quiescence accompanied by closed eyes, recumbent posture, limited muscular activity and a reduced response to sensory stimuli, which can be easily reversed. Sleep can be divided into two main phases: non-rapid eye movement (NREM) and rapid eye movement (REM). Each of those is categorized by different behavioral, physiological, neurochemical and electrophysical attributes[20,21].

NREM sleep can be further subdivided into 3 different stages according to electroencephalogram (EEG) parameters, being stage N1 and N2 considered as “light sleep” (lower arousal thresholds), and N3 (formerly 3 and 4, now merged in one stage) as “deep sleep” (higher arousal thresholds and dominance of slow wave sleep). NREM sleep is associated with decreased mental and physical activity, heart rate, blood pressure, and breathing frequency among others, which is stable across the stages [20,21]. On the other hand, REM or “paradoxical” sleep, which follows the NREM phase in the sleep cycle, is characterized by an increase of mental activity while muscles maintained paralyzed or inactive. During REM phase, EEG patterns are more variable and physiological parameters such as heart rate, blood pressure or breathing frequency are more instable. It is in this phase where dreams more frequently occur [22].

In healthy adults, sleep onset usually occurs after 20-30 minutes of going to bed. A typical night of sleep encompasses 3 to 5 NREM to REM ultradian cycles (90 minutes on average, being 120 minutes the first one), where lighter sleep turns into deep sleep, which is then followed by a REM phase, for a total of 6-9 average hours of sleep. As the night advances, stage N 3 decreases, stage 2 becomes more predominant, and REM phases become longer [23]. During these cycles, there are frequent brief brain, heart, and muscle reactivations or microarousals called “windows” that last 3 to 15 seconds. Those occur approximately 5 to 15 times per hour, allowing the individual to reposition or to recognize any harmful situation[24].

Sleep is an active process, it is not coma neither anesthesia. During sleep, a cyclic alternating pattern (CAP) is present. CAP is a visualization method and a physiological phenomenon that represents the balance between sleep quietness and sleep arousal.

The sleep arousal is part of a protective “fight or flight” mechanism that remains present during NREM sleep to preserve body integrity (sleep positioning, adjustments in heart rate, etc.) and to react to threatening events. CAP is divided in 2 phases: active and quiet. The active (A) phase is further subdivided in A1 (high dominance of slow wave sleep, promotor of sleep restoration), in A2 (a transition phase) and A3 (an arousal dominant phase, essential for survival). The high rate of A2 and A3 phase represents sleep fragmentation. The quiet phase (B), is the one during which sleep is very stable and quiet [25]. CAP phases are in the minute’s domains and their rate rise with age or in presence of different conditions. For example, more active phases are observed in fibromyalgia [26], and CAP has been associated to the onset of sleep bruxism[27].

Sleep deprivation

Sleep deprivation, which can be briefly defined as lack of sleep or too short sleep, can occur due to bad habit, poor sleep hygiene, age, or disorder/disease. It can be also induced experimentally by total prevention or partial restriction of sleep, done by retarding sleep onset or waking a subject in the night for a given period.

Sleep deprivation is present in around 20% of the general population and it may be associated to sleep disorders such as insomnia or sleep apnea [28]. Studies have shown that sleep deprivation can affect memory, mood, physical activity, immune system, metabolism, and increase the risk of motor vehicle accidents, cardiovascular diseases, or dementia among others[29-31], and sleep disturbances are frequently associated with pain[32].

Importantly, the intake of alcohol and tobacco, two of the most commonly used psychoactive substances in the community, can disrupt sleep through different mechanisms. For example, it is thought that alcohol disrupts sleep architecture, triggers insomnia, contributes to abnormalities of circadian rhythms, and also increases breathing-related sleep events such as snoring and oxygen desaturation[33]. Additionally, tobacco smoking, probably due to nicotine, has been also associated with disrupted sleep architecture, and it is considered a risk factor for sleep disordered breathing [34,35]. Stimulant medications such as methylphenidate or amphetamine can led to longer sleep latency, worse sleep efficiency, and shorter sleep duration[36], and opioids, which can be used to treat pain, may exacerbate sleep disturbances and increase sleep apnea episodes [37].

Sleep and pain interaction

In healthy individuals, sleep restriction has been shown to be associated with the development of clinical somatic pain-related complaints [38], and to produce hyperalgesic effects such as decreased pressure pain tolerance [39] [40], heat pain thresholds [41], and withdrawal latency [42]. Sleep disturbances have also been associated with alterations in endogenous pain modulation, with sex specificity to be confirmed [43-45]. In fact, a recent study showed increased secondary hyperalgesia in males and significantly increased temporal summation in females, suggesting that different pain mechanism and pathways may be associated to sex [43].

The interaction between sleep and pain has been frequently reported, following a linear model in acute pain states and a bidirectional model in chronic ones. In that way, pain episodes can disrupt or alter sleep, and sleep disturbances can increase, predispose or perpetuate pain sensation. Although this bidirectional or circular interaction can be dominant in chronic pain cases [4], its directionality remains debated, as there is more evidence pointing towards poor sleep increasing pain and not the other way around[2].

Sleep complains are present in around 80% of chronic pain disorders [46], and reports of insomnia can be as high as 30-40% in patients with chronic pain [47]. Polysomnography (PSG) studies have reported the important coexistence of sleep disorders/disturbances in chronic pain populations [48], and sleep continuity parameters have also been identified as risk factors for clinical pain [49-51]. A recent systematic review and meta-analysis revealed that deterioration in sleep was associated with worse self-reported physical functioning (medium effect size) while improvement in sleep was associated with better physical functioning (small effect size) [52].

SUBJECTIVE SLEEP QUALITY IN TMD

Subjective sleep quality has been defined as tiredness on waking and throughout the day, feeling rested and restored on waking, and as the number of awakenings experienced in the night [53]. This component is usually measured through questionnaires, which are easily administered and cost-effective, thus facilitating the feasibility of this measurement. In TMD and orofacial pain patients, up to 8 questionnaires have been used to report subjective sleep quality. Some of the most commonly used ones include the

Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Insomnia Severity Index (ISI), and the Sleep Assessment Questionnaire [54].

The PSQI, a questionnaire formed by 18 items measuring general sleep quality in the last month, is the most commonly used tool to measure sleep quality[55]. The PSQI is a valid and reliable instrument that has been employed in different clinical and non-clinical populations[56]. It has 7 different components, which measure different aspects of sleep such as overall sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and physical dysfunction. A cut-off of >5 is used to differentiate poor sleepers, with sensitivity of 89.6% and specificity of 86.5%.

When compared to pain-free controls, TMD patients exhibited poorer sleep quality and were mainly categorized as poor sleepers, with mean scores ranging from 6.69 to 13.7 in different TMD populations [57-65]. These scores and findings are similar than the ones obtained in other painful conditions such as fibromyalgia or rheumatoid arthritis [66,67]. In addition, poorer sleep quality has been positively correlated with clinical pain intensity and psychological distress in TMD patients [57]. In the Orofacial Pain Prospective Risk Assessment (OPPERA) study, which is the largest study designed to identify risk factors for TMD in pain-free participants (n=2453 filled PSQI), TMD incidence was twice as high in participants whose baseline subjective sleep quality was poor (demographically adjusted Hazard Ratio = 2.04; 95% Confidence Interval, 1.55–2.70) [68]. In addition, tertiary analysis of OPPERA data showed that subtle sleep quality impairments were noted on PSQI beforehand in participants developing TMD (n=220) [69,70].

Additionally, it is important to highlight fatigue, which is an important marker of poor sleep or non-recuperative process, in patients with sleep disturbances. Fatigue is a

frequent complaint in chronic pain and in TMD patients that deserve attention in its diagnosis and management [71,72]. Only a few tools are currently available to assess the presence of fatigue, and it is important that clinicians differentiate fatigue as a general somatic and behavioral complaint from chronic fatigue syndrome in TMD patients [73,74].

OBJECTIVE SLEEP QUALITY IN TMD

Objectively, sleep quality can be defined as sufficient duration, high efficiency, and low fragmentation (i.e., not too many stage shifts, body movements, breathing disturbances, drop in oxygen), as well as proper staging of sleep, which are measured through polysomnographic evaluation (PSG) [75].

PSG evaluation comprehends a series of biophysiological changes, including EEG, eye movements, muscle activity, heart rhythm, and respiratory function [75]. PSG, which is the gold standard to diagnose sleep disorders such as sleep disordered breathing or periodic limb movement, involves costlier equipment and resources, including overnight stay of the person being studied when it is done in the sleep laboratory (type 1 recording), therefore limiting its research applicability. PSG is not an ideal perfect method since the sleep laboratory is not a “natural milieu” and the electrode montage may disrupt sleep. Additionally, it should be considered that the obtained information represents a “snapshot” or a one-night picture. An alternative method is the use of portable monitor devices or home recording, (multi channels down to one channel; type 2 to 4 respectively). The major gain of this modality is that patients sleep in their natural environment, allowing as well to record multiple nights in order to improve the precision of the test. Importantly, subjective sleep quality usually correlates poorly with objective

sleep quality parameters, suggesting that each of them could measure different dimension of sleep [76].

There are different studies investigating objective parameters of sleep quality in different populations of TMD patients (Table 2.1).

Table 2.1. Studies evaluating objective sleep parameters in TMD patients.

Study	Sample	Objective	Method	Main findings
Camparis et al. 2006 [77]	20 with SB and MFP 20 with SB without MFP	Compare bruxism and sleep parameters	PSG, 1 night	No differences in bruxism episodes and sleep variables
Rossetti et al. 2008 [78]	30 MFP 30 matched controls	Evaluate association between RMMA-SB and MFP	PSG, 1 night	Significant associations were observed between RMMA-SB and MFP, as well as between daily clenching (self-report) and MFP
Smith et al. 2009 [80]	53 MFP	Characterize sleep disorder rates in TMD and evaluate possible associations between sleep disorders and laboratory measures of pain sensitivity	PSG, 2 consecutive nights	17% presented sleep bruxism, 36% insomnia disorder and 28.4% sleep apnea
Edwards et al. 2009 [79]	53 MFP (same sample as above)	Assess whether individual differences in sleep continuity and/or architecture were related to diffuse noxious inhibitory controls (DNIC)	PSG, 2 consecutive nights	Higher sleep efficiency and longer total sleep time were positively associated with higher conditioned pain modulation
Dubrovsky et al. 2014 [84]	124 MFP cases and 46 controls	Evaluate measures of sleep and respiratory distur bance in a large representative sample of TMD cases in comparison with matched controls	PSG, 2 consecutive nights	TMD cases presented significant increase in stage N1 sleep, mild but significant elevations in arousals associated with all types of respiratory events and in RERAs when compared to controls. MFP predicted a lower sleep efficiency, more frequent awakenings, and higher RERA index among TMD cases.
De Siqueira et al. 2017 [81]	10 SB/MFP patients with widespread pain	Investigate whether the presence of concomitant widespread pain	PSG, 1 night	Group with widespread pain presented lower sleep efficiency

10	SB/MFP patients without widespread pain	could	influence sleep characteristics of patients with SB and MFP

TMD: temporomandibular disorders; MFP: myofascial pain; SB: sleep bruxism; RMMA: rhythmic masticatory muscle activity; RERA: respiratory effort related arousal.

Some of them did not find any difference in sleep parameters between TMD patients and pain-free controls, although the relatively small sample and the somewhat restrictive inclusion criteria calls for caution in the interpretation of their results [77,78]. Other studies using uncontrolled samples also found sleep characteristics within normal range [79-81], yet one of them reported a positive significant correlation between sleep efficiency and endogenous pain inhibitory function measured by a conditioned pain modulation paradigm[79].

The largest study using PSG in TMD patients until the present date, revealed interesting differences between 124 females with myofascial TMD and 64 matched pain-free controls who underwent two nights of PSG recording[82-84]. In a series of reports, the authors pointed three main findings. In regards sleep parameters, the authors found that respiratory effort related arousals (RERA), which are arousals from sleep without concomitant oxygen desaturations that do not technically meet the definitions of apneas or hypopneas but do disrupt sleep, were significantly increased in TMD patients and also statistically independent from sleep fragmentation measures. These findings leaded the authors to speculate about the possible existence of an upper airway resistance in their sample, which have also been proposed in other pain conditions such as fibromyalgia [85,86]. Other findings include the presence of higher N1 sleep stage, a

tendency towards a great number of awakenings, and greater number of stage N1 shifts in TMD patients when compared to controls, thus showing more sleep instability[84]. They also found that more awakenings and less sleep efficiency was associated with more pain intensity during the following day, and that poor sleep quality reports were better attributed to depressive symptoms rather than pain intensity or objective sleep quality measures obtained through PSG [87].

Additionally, the authors also reported that sleep background electromyography (EMG), defined as masseter muscle EMG activity occurring outside of sleep bruxism or other defined motor event periods, was significantly higher in TMD cases when compared to controls and also positively associated with higher levels of clinical pain intensity[83]. They hypothesize that elevated sleep background EMG may lead to fatigue and pain, suggesting it as a possible risk factor for pain maintenance in TMD. Relatively similar findings were also observed in other study using portable EMG devices during several nights [62].

Although this study can be considered as a reference in sleep and TMD, caution in the representability of these results is warranted, as the selected sample is very specific, and the primary objective of the study was different [82-84].

In summary, although interpretation of the results needs to consider smaller and/or very restrictive samples, PSG studies highlight the presence of sleep disorders and the importance of sleep fragmentation, disruptions, RERAs, and also background muscular activity in TMD patients.

INSOMNIA AND TMD

Insomnia is a disorder defined as difficulty to initiate or maintain sleep, when sleep onset does not occur after 30 min for at least 3 times per week for 3 or more months, or if spontaneous awakenings occur during the night without the ability to resume sleep [88]. The presence of insomnia can cause fatigue, lack of attention, mood alterations, and gastrointestinal symptoms among others, being also considered a risk factor for coronary heart disease and depression [89,90].

Insomnia occurs in approximately 10% of the general population [91] and up to 72% of people with chronic pain [48]. It has been shown that pain can increase the risk of insomnia and vice versa [92,93], and that insomnia is associated with a reduction in pain tolerance in patients with chronic pain [40]. A recent study showed that 1/3 of patients seeking care at an orofacial pain unit (mixed orofacial pain conditions, including TMD) presented sleep disturbances, where 37% of the studied patients (352 out of 952) responded positively to a screening question for insomnia and/or hypersomnia, being the majority of them categorized as moderate to severe insomnia [1]. This is in line with findings from a prior PSG study performed in TMD patients (n=53), which revealed that 36% of them suffered from insomnia, being 26% of those cases primary insomnia (not attributable to a medical, psychiatric, or environmental cause) [80]. Moreover, it was also shown that primary insomnia diagnosis was associated with reduced mechanical and thermal thresholds in the masseter muscles and in the forearm in TMD patients [80], and that increases in the severity of symptoms of insomnia are prospectively associated with next month daily increases of pain [94]. These findings suggest that insomnia, which is a common disorder in chronic pain and orofacial pain populations, is an important and

prevalent comorbidity in TMD and can have an influence in pain and affect importantly patient's quality of life. Therefore, insomnia should be suspected and screened in patients suffering from TMD.

SLEEP BREATHING DISORDERS AND TMD

Sleep-related breathing disorders is another term used to describe several chronic conditions in which partial or complete cessation of breathing occurs many times throughout the night, mainly resulting in fatigue or daytime sleepiness, which interferes with a person's ability to function. Symptoms may include snoring, pauses in breathing described by bed partners, and disturbed sleep [95]. The most common sleep breathing disorder is obstructive sleep apnea (OSA), which is defined clinically by the presence of at last 5 respiratory events per hour of sleep (including apneas, hypopneas, and respiratory effort related arousals) accompanied by daytime sleepiness, loud snoring, witnessed breathing pauses, or awakenings due to gasping, or by the presence of at least 15 respiratory events without the presence of signs and symptoms [88,96]. Although the respiratory disturbance index (RDI) may be more comprehensive, the main metric for the diagnosis of OSA is still the apnea hypopnea index (AHI). OSA prevalence ranges from 9% to 38% when an AHI of ≥5 is used as a threshold, being more frequent in men and in obese people, and increasing considerably with age [95,97]. The presence of untreated OSA has been related with higher risk of cardiovascular diseases, metabolic syndrome, or diabetes among others [98].

OSA is estimated to be a common comorbidity in general chronic pain populations, with a pooled prevalence of up to 37%, and also in TMD where its frequency has been recognized as 28.6%[80]. In addition, in the OPPERA study, high likelihood of OSA has been associated with the incidence of first onset TMD in the prospective cohort study (n=2604, adjusted hazard ratio = 1.73; 95% confidence interval, 1.14, 2.62), and also with chronic TMD in the case-control one (n= 1716, adjusted odds ratio = 3.63; 95% confidence interval, 2.03, 6.52) [68].

Other sleep-related breathing disorder is upper airway resistance syndrome (UARS), which is less prevalent than OSA and is characterized by episodes of increased RERAs and sleep disruption but without meeting apnea/hypopnea definition [99]. As OSA, UARS can cause fatigue, daytime sleepiness and sleep fragmentation [99], and it has been associated with the presence of other conditions such as irritable bowel syndrome, insomnia or depression [100]. Despite UARS can be considered as a different syndrome than OSA, its acceptance as a different syndrome remains controversial. However, it appears that UARS has a bigger impact on subjective sleep quality and fatigue than mild OSA [101], reason why its presence needs to be investigated in TMD patients.

SCREENING OF SLEEP DISORDERS IN TMD

Given the prevalence of sleep disorders and their association with negative pain-related outcomes, the screening of sleep disorders and the identification of subjective sleep disturbances is pivotal to the management of patients with TMD. Recently, an

algorithm based on clinical interview and a physical evaluation was proposed to identify sleep disorders in chronic orofacial pain patients [3,102].

During the clinical anamnesis, the importance of evaluating sleep complains (problems in sleep initiation and/or maintenance, sleepiness during the day, snoring, witnessed apneas, etc.), comorbidities and lifestyle habits (diagnosed sleep disorders, caffeine or tobacco intake, exacerbating or initiating factors, etc.) and sleep routine (sleep environment, bedtime routine, etc.) are highlighted and warranted.

During the physical exam, extraoral examination looking for signs of daytime sleepiness (droopy eyelids, repetitive yawning, irritability, etc.) or risk factors for OSA (increased neck circumference, nasal examination, retrognathia/micrognathia, etc.) should be also accompanied by an intraoral exam assessing other risk factors for OSA (soft palate, uvula, Mallampati score, tongue, nose obstruction-deviation, etc.) and by a systemic diagnostic work-up evaluating blood pressure, heart rate, or body mass index.

The identification of a possible sleep disorder by the dentist should be followed by a referral to a sleep physician for evaluation and possible PSG assessment.

MANAGEMENT OF SLEEP DISORDERS IN TMD

When treating sleep disorders in chronic pain, patients can have benefit from strategies targeting the sleep disorder or also from treatments that can help to manage both sleep and pain. Ideally, an individualized management approach should be implemented considering several aspects and characteristics of the individual, such as morphology, comorbidities, existing treatments and medications, or genetics (Figure 2.2).

Figure 2.2. Management avenues for primary insomnia and obstructive sleep apnea (OSA) concomitant to temporomandibular disorders (TMD).

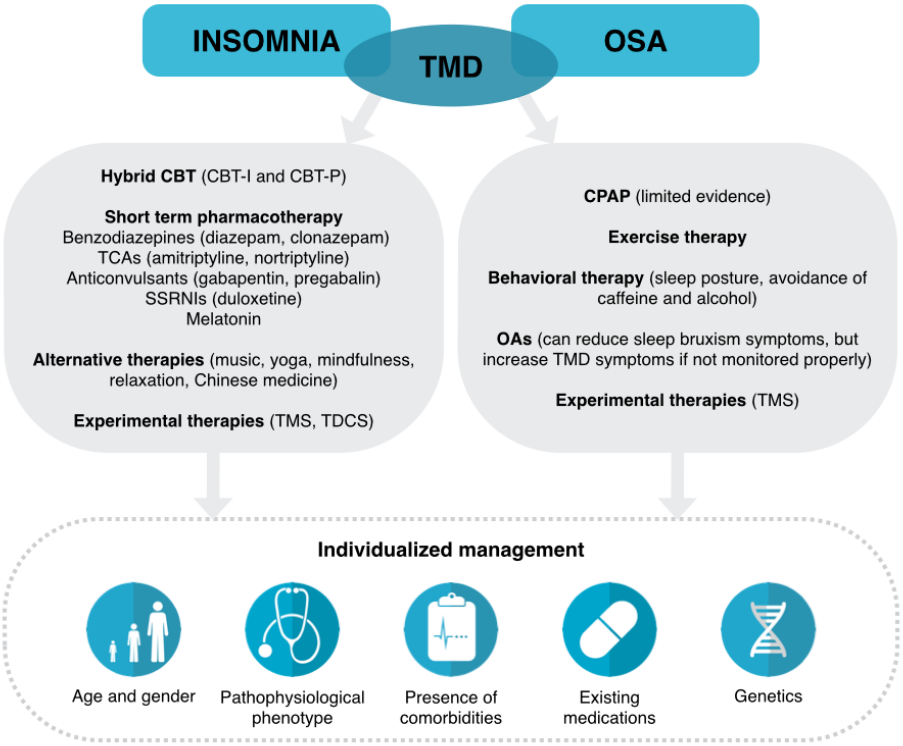


Figure 2.2 abbreviations. CBT: cognitive behavioral therapy; CBT-I: cognitive behavioral therapy for insomnia; CBT-P: cognitive behavioral therapy for pain; TCAs: tryciclic antidepressants; SNRIs: serotonin and norepinephrine reuptake inhibitors; TMS: transcranial magentic stimulation; tDCS: transcranial direct current stimulation; CPAP: continuous positive airway pressure; OAs: oral appliances.

Insomnia. Currently, the first treatment option for the management of chronic insomnia is cognitive behavioral therapy focused on insomnia (CBT-I). CBT-I is a structured program that helps to identify and replace thoughts and behaviors that cause

or worsen sleep problems with habits that promote sleep, usually including sleep hygiene, sleep restriction, and relaxation [103]. CBT-I has been shown to be effective in the long term for different sleep parameters such as sleep onset or efficiency, and also in a small manner for pain outcomes [104] also in TMD [105]. CBT can also be focused on pain (CBT-P), and hybrid models of CBT for both sleep and pain have been proposed as a synergic management plan [106,107]. CBT is a safe, non-invasive modality with good long-term outcomes, but it can suppose a high initial cost requiring as well high level of compliance, which limits its implementation.

Another approach, especially for short-term periods of time, is the use of pharmacological interventions. Their effects are usually immediate and can have lower cost than CBT, but may be accompanied by side effects, drug-drug interactions, short-term efficacy and a risk of addiction [3]. Medications that can be used to treat sleep but with less evidence of their effects on pain are the atypical antidepressant trazodone, the hypnotic agent zolpidem, or the orexin receptor antagonist suvorexant [108-110]. Evidence indicates that benzodiazepines such as diazepam or clonazepam, can be beneficial for improving sleep and reducing pain outcomes in chronic pain populations including TMD [111]. The use of tricyclic antidepressants (TCAs) in low doses such as amitriptyline or nortriptyline has shown to be effective in reducing pain levels in TMD [112] and also in improving sleep quality in different chronic pain populations[113,114]. Anticonvulsant medications such as pregabalin and gabapentin may also be good options for managing pain and sleep [114,115] in chronic pain and in TMD. Other medications that may be effective in improving sleep and pain in TMD are the muscle relaxant cyclobenzaprine [58], melatonin [116], and the selective serotonin and norepinephrine reuptake inhibitors (SSRNI)

duloxetine [114,117]. In general, opioid should be avoided as much as possible, due to the risk of addiction, central sleep apnea and deleterious effect on insomnia [118,119].

Combination of CBT-I and short-term pharmacotherapy, hypnosis, physical exercise, music therapy, yoga, mindfulness, or traditional Chinese medicine are other alternatives to improve pain and sleep disturbances in chronic pain [3,103]. Other alternative strategies may include the use of non-invasive neurostimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation, which have shown promising results in chronic insomnia as a main treatment and as an adjuvant therapy, and also in chronic pain including orofacial pain conditions [120-123].

Sleep breathing disorders. Depending on the AHI, OSA's severity can be classified into mild (AHI>5 but <15), moderate (AHI>15 but <30) and severe (AHI>30). For all of them, the gold standard treatment is the continuous positive airways pressure device (CPAP), which has been proved to reduce AHI as well as morbidity and mortality associated with it [124,125]. There is also small evidence about CPAP efficacy reducing experimental pain sensitivity, perhaps as an indirect improvement of OSA. However, this was not the case in chronic pain populations [126,127]. Adherence to the CPAP treatment remains challenging, and in these cases, other treatment options are available [128].

In a recent meta-analysis, exercise therapy (general exercise to oropharyngeal programs) was found to be the second most effective treatment option in reducing AHI. These findings highlight the use of exercise therapy not only as an adjuvant therapy but also as a first option in indicated cases [125]. Moreover, physical exercise can improve sleep quality and pain related outcomes in chronic pain populations, thus becoming a very relevant option in TMD patients with sleep disturbances[129,130].

Oral appliances (OA) are indicated in mild and moderate cases of OSA and in cases where patients are unable to tolerate CPAP. OAs also become a good option in cases where OSA and sleep bruxism (SB) co-exist, as it can also help to decrease bruxism effects. As OA work moving the jaw forward in order to open the airway, its use can produce jaw discomfort, bite changes, and sometimes aggravate TMD cases [131]. Therefore, if indicated, more conservative advancements and TMD symptoms monitoring while using is preferable. Nevertheless, they are considered as a good alternative to CPAP, having higher adherence and being preferred by OSA patients [132].

Other treatment alternatives include other behavioral therapies such as weight loss, positional therapy, or alcohol avoidance, adjunctive therapies such as bariatric surgery or medications, surgical options such as orthognathic surgery and uvulopalatopharyngoplasty, and more experimental ones as upper airways stimulation or TMS [128,133].

Additional consideration in patients where SB (frequently comorbid with TMD) coexists with OSA, is the election of oral devices to manage SB. Empirically, it appears that mandibular flat planes in maximal intercuspation rather than in a retruded position may be a reasonable alternative do diminish the risk of airway obstruction.

Moreover, the dentist should know that a personalized management of OSA, individualizing treatments according to different phenotypes/traits is now considered the best management strategy for these patients [134] (Lavigne et al. 2019 JDR under review). A multidisciplinary approach where dentists collaborate with physicians, health psychologists, and physical therapists among others emerges as an ideal approach to manage TMD patients OSA and also with sleep disturbances.

CONCLUSIONS

Sleep disturbances are present in TMD patients when measured subjectively and objectively. Dentists need to screen for behavioral and somatic sleep related problem (e.g., sleepiness, fatigue, mood instability) that may guide them to identify sleep disorders such as insomnia, sleep apnea and sleep bruxism. In presence of a suspected sleep disorder, the collaboration with sleep physician is mandatory. Individualized management and a multidisciplinary approach must be pursued when managing patients with TMD and comorbid sleep disturbances and/or sleep disorders, such as insomnia or OSA.

REFERENCES

1. Meira ECM, Lukic N, Wojczynska A, Steiger B, Guimaraes AS, Ettlin DA. Insomnia in Patients Seeking Care at an Orofacial Pain Unit. *Frontiers in neurology.* 2019;10:542.
2. Herrero Babiloni A, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. *Journal of neural transmission.* 2019.
3. Klasser GD, Almoznino G, Fortuna G. Sleep and Orofacial Pain. *Dental clinics of North America.* 2018;62(4):629-656.
4. Lavigne GJ, Sessle BJ. The Neurobiology of Orofacial Pain and Sleep and Their Interactions. *Journal of dental research.* 2016.
5. Almoznino G, Benoliel R, Sharav Y, Haviv Y. Sleep disorders and chronic craniofacial pain: Characteristics and management possibilities. *Sleep medicine reviews.* 2017;33:39-50.
6. Treede RD. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain reports.* 2018;3(2):e643.
7. Williams AC, Craig KD. Updating the definition of pain. *Pain.* 2016;157(11):2420-2423.
8. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and

Orofacial Pain Special Interest Groupdagger. *Journal of oral & facial pain and headache.* 2014;28(1):6-27.

9. Macfarlane TV, Blinkhorn AS, Davies RM, Worthington HV. Association between local mechanical factors and orofacial pain: survey in the community. *Journal of dentistry.* 2003;31(8):535-542.
10. Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: a systematic review and meta-analysis. *Pain.* 2018;159(8):1441-1455.
11. Cairns BE. Pathophysiology of TMD pain--basic mechanisms and their implications for pharmacotherapy. *J Oral Rehabil.* 2010;37(6):391-410.
12. Harper DE, Schrepf A, Clauw DJ. Pain Mechanisms and Centralized Pain in Temporomandibular Disorders. *Journal of dental research.* 2016;95(10):1102-1108.
13. Moana-Filho EJ, Herrero Babiloni A, Nisley A. Endogenous pain modulation assessed with offset analgesia is not impaired in chronic temporomandibular disorder pain patients. *J Oral Rehabil.* 2019.
14. Costa YM, Conti PC, de Faria FA, Bonjardim LR. Temporomandibular disorders and painful comorbidities: clinical association and underlying mechanisms. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2017;123(3):288-297.
15. Velly AM, Fricton J. The impact of comorbid conditions on treatment of temporomandibular disorders. *Journal of the American Dental Association.* 2011;142(2):170-172.

16. Dahan H, Shir Y, Velly A, Allison P. Specific and number of comorbidities are associated with increased levels of temporomandibular pain intensity and duration. *J Headache Pain.* 2015;16:528.

17. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. *J Pain.* 2016;17(9 Suppl):T93-T107.

18. Fillingim RB, Ohrbach R, Greenspan JD, et al. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain.* 2011;12(11 Suppl):T46-60.

19. Slade GD, Ohrbach R, Greenspan JD, et al. Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies. *Journal of dental research.* 2016.

20. Ogilvie RD. The process of falling asleep. *Sleep medicine reviews.* 2001;5(3):247-270.

21. Siegel JM. Clues to the functions of mammalian sleep. *Nature.* 2005;437(7063):1264-1271.

22. Siegel JM. REM sleep: a biological and psychological paradox. *Sleep medicine reviews.* 2011;15(3):139-142.

23. Chokroverty S. Overview of sleep & sleep disorders. *The Indian journal of medical research.* 2010;131:126-140.

24. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep medicine reviews.* 2012;16(1):27-45.

25. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age

groups. *Electroencephalography and clinical neurophysiology.* 1998;107(6):439-450.

26. Rizzi M, Radovanovic D, Santus P, et al. Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients. *Clinical and experimental rheumatology.* 2017;35 Suppl 105(3):74-80.
27. Carra MC, Rompre PH, Kato T, et al. Sleep bruxism and sleep arousal: an experimental challenge to assess the role of cyclic alternating pattern. *J Oral Rehabil.* 2011;38(9):635-642.
28. Hublin C, Kaprio J, Partinen M, Koskenvuo M. Insufficient sleep--a population-based study in adults. *Sleep.* 2001;24(4):392-400.
29. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Progress in cardiovascular diseases.* 2009;51(4):294-302.
30. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Seminars in neurology.* 2009;29(4):320-339.
31. Orzel-Gryglewska J. Consequences of sleep deprivation. *International journal of occupational medicine and environmental health.* 2010;23(1):95-114.
32. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep medicine reviews.* 2006;10(5):357-369.
33. He S, Hasler BP, Chakravorty S. Alcohol and sleep-related problems. *Current opinion in psychology.* 2019;30:117-122.

34. Deleanu OC, Pocora D, Mihalcuta S, Ulmeanu R, Zaharie AM, Mihaltan FD. Influence of smoking on sleep and obstructive sleep apnea syndrome. *Pneumologia.* 2016;65(1):28-35.

35. Costa M, Esteves M. Cigarette Smoking and Sleep Disturbance. *Addictive Disorders & Their Treatment.* 2018;17(1):40-48.

36. Kidwell KM, Van Dyk TR, Lundahl A, Nelson TD. Stimulant Medications and Sleep for Youth With ADHD: A Meta-analysis. *Pediatrics.* 2015;136(6):1144-1153.

37. Robertson JA, Purple RJ, Cole P, Zaiwalla Z, Wulff K, Pattinson KT. Sleep disturbance in patients taking opioid medication for chronic back pain. *Anaesthesia.* 2016;71(11):1296-1307.

38. Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. *Pain.* 2005;119(1-3):56-64.

39. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *Journal of sleep research.* 2001;10(1):35-42.

40. Sivertsen B, Lallukka T, Petrie KJ, Steingrimsdottir OA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. *Pain.* 2015;156(8):1433-1439.

41. Kundermann B, Spernal J, Huber MT, Krieg JC, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med.* 2004;66(6):932-937.

42. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep.* 2006;29(2):145-151.

43. Smith MT, Jr., Remeniuk B, Finan PH, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: Implications for sex differences in chronic pain. *Sleep.* 2018.

44. Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. *Neuroscience.* 2018;387:191-200.

45. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep.* 2007;30(4):494-505.

46. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep medicine reviews.* 2004;8(2):119-132.

47. Lavigne GJ, Nashed A, Manzini C, Carra MC. Does sleep differ among patients with common musculoskeletal pain disorders? *Current rheumatology reports.* 2011;13(6):535-542.

48. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. *Sleep medicine.* 2018.

49. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. *Pain.* 1996;68(2-3):363-368.

50. Stone AA, Broderick JE, Porter LS, Kaell AT. The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week.

Arthritis care and research : the official journal of the Arthritis Health Professions Association. 1997;10(3):185-193.

51. Raymond I, Ancoli-Israel S, Choiniere M. Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. *Sleep medicine.* 2004;5(6):551-559.

52. Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. *Sleep medicine reviews.* 2018;39:82-97.

53. Harvey AG, Stinson K, Whitaker KL, Moskovitz D, Virk H. The subjective meaning of sleep quality: a comparison of individuals with and without insomnia. *Sleep.* 2008;31(3):383-393.

54. Sommer I, Lavigne G, Ettlin DA. Review of self-reported instruments that measure sleep dysfunction in patients suffering from temporomandibular disorders and/or orofacial pain. *Sleep medicine.* 2015;16(1):27-38.

55. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.

56. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep medicine reviews.* 2016;25:52-73.

57. Yatani H, Studts J, Cordova M, Carlson CR, Okeson JP. Comparison of sleep quality and clinical and psychologic characteristics in patients with temporomandibular disorders. *Journal of orofacial pain.* 2002;16(3):221-228.

58. Herman CR, Schiffman EL, Look JO, Rindal DB. The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: a randomized clinical trial. *Journal of orofacial pain.* 2002;16(1):64-70.

59. Benoliel R, Zini A, Zakuto A, et al. Subjective Sleep Quality in Temporomandibular Disorder Patients and Association with Disease Characteristics and Oral Health-Related Quality of Life. *Journal of oral & facial pain and headache.* 2017;31(4):313-322.

60. Haviv Y, Zini A, Etzioni Y, et al. The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2017;123(1):58-66.

61. De Leeuw R, Bertoli E, Schmidt JE, Carlson CR. Prevalence of post-traumatic stress disorder symptoms in orofacial pain patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;99(5):558-568.

62. Schmitter M, Kares-Vrincianu A, Kares H, Bermejo JL, Schindler HJ. Sleep-associated aspects of myofascial pain in the orofacial area among Temporomandibular Disorder patients and controls. *Sleep medicine.* 2015;16(9):1056-1061.

63. Rener-Sitar K, John MT, Pusalavidyasagar SS, Bandyopadhyay D, Schiffman EL. Sleep quality in temporomandibular disorder cases. *Sleep medicine.* 2016;25:105-112.

64. Moana-Filho EJ, Herrero Babiloni A. Endogenous Pain Modulation in Chronic TMD: Derivation of Pain Modulation Profiles and Assessment of Its Relationship with Clinical Characteristics. *J Oral Rehabil.* 2018.

65. Fillingim RB, Ohrbach R, Greenspan JD, et al. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. *J Pain.* 2013;14(12 Suppl):T75-90.

66. Ulus Y, Akyol Y, Tander B, Durmus D, Bilgici A, Kuru O. Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clinical and experimental rheumatology.* 2011;29(6 Suppl 69):S92-96.

67. Hita-Contreras F, Martinez-Lopez E, Latorre-Roman PA, Garrido F, Santos MA, Martinez-Amat A. Reliability and validity of the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) in patients with fibromyalgia. *Rheumatology international.* 2014;34(7):929-936.

68. Sanders AE, Essick GK, Fillingim R, et al. Sleep apnea symptoms and risk of temporomandibular disorder: OPPERA cohort. *Journal of dental research.* 2013;92(7 Suppl):70S-77S.

69. Sanders AE, Akinkugbe AA, Bair E, et al. Subjective Sleep Quality Deteriorates Before Development of Painful Temporomandibular Disorder. *J Pain.* 2016;17(6):669-677.

70. Sanders AE, Akinkugbe AA, Fillingim RB, et al. Causal Mediation in the Development of Painful Temporomandibular Disorder. *J Pain.* 2017;18(4):428-436.

71. de Leeuw R, Studts JL, Carlson CR. Fatigue and fatigue-related symptoms in an orofacial pain population. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;99(2):168-174.

72. de la Vega R, Racine M, Castarlenas E, et al. The Role of Sleep Quality and Fatigue on the Benefits of an Interdisciplinary Treatment for Adults With Chronic Pain. *Pain Pract.* 2018.

73. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis care & research.* 2011;63 Suppl 11:S263-286.

74. Dahan H, Shir Y, Nicolau B, Keith D, Allison P. Self-Reported Migraine and Chronic Fatigue Syndrome Are More Prevalent in People with Myofascial vs Nonmyofascial Temporomandibular Disorders. *Journal of oral & facial pain and headache.* 2016;30(1):7-13.

75. Butkov N, Keenan, S.A. An overview of polysomnographic technique. In: *Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects: Fourth Edition.*2017.

76. Landry GJ, Best JR, Liu-Ambrose T. Measuring sleep quality in older adults: a comparison using subjective and objective methods. *Frontiers in aging neuroscience.* 2015;7:166.

77. Camparis CM, Formigoni G, Teixeira MJ, Bittencourt LR, Tufik S, de Siqueira JT. Sleep bruxism and temporomandibular disorder: Clinical and polysomnographic evaluation. *Archives of oral biology.* 2006;51(9):721-728.

78. Rossetti LM, Pereira de Araujo Cdos R, Rossetti PH, Conti PC. Association between rhythmic masticatory muscle activity during sleep and masticatory myofascial pain: a polysomnographic study. *Journal of orofacial pain.* 2008;22(3):190-200.

79. Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *European journal of pain.* 2009;13(10):1043-1047.

80. Smith MT, Wickwire EM, Grace EG, et al. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. *Sleep.* 2009;32(6):779-790.

81. de Siqueira JT, Camparis CM, de Siqueira SR, Teixeira MJ, Bittencourt L, Tufik S. Effects of localized versus widespread TMD pain on sleep parameters in patients with bruxism: A single-night polysomnographic study. *Archives of oral biology.* 2017;76:36-41.

82. Raphael KG, Sirois DA, Janal MN, et al. Sleep bruxism and myofascial temporomandibular disorders: a laboratory-based polysomnographic

investigation. *Journal of the American Dental Association.* 2012;143(11):1223-1231.

83. Raphael KG, Janal MN, Sirois DA, et al. Masticatory muscle sleep background electromyographic activity is elevated in myofascial temporomandibular disorder patients. *J Oral Rehabil.* 2013;40(12):883-891.

84. Dubrovsky B, Raphael KG, Lavigne GJ, et al. Polysomnographic investigation of sleep and respiratory parameters in women with temporomandibular pain disorders. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2014;10(2):195-201.

85. Besteiro Gonzalez JL, Suarez Fernandez TV, Arboleya Rodriguez L, Muniz J, Lemos Giraldez S, Alvarez Fernandez A. Sleep architecture in patients with fibromyalgia. *Psicothema.* 2011;23(3):368-373.

86. Gold AR, Dipalo F, Gold MS, Broderick J. Inspiratory airflow dynamics during sleep in women with fibromyalgia. *Sleep.* 2004;27(3):459-466.

87. Dubrovsky B, Janal MN, Lavigne GJ, et al. Depressive symptoms account for differences between self-reported versus polysomnographic assessment of sleep quality in women with myofascial TMD. *J Oral Rehabil.* 2017;44(12):925-933.

88. Medicine AAoS. International Classification of Sleep Disorders. *Darien, IL American Academy of Sleep Medicine*.3rd ed (2014).

89. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of affective disorders.* 2011;135(1-3):10-19.

90. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation.* 2011;124(19):2073-2081.

91. Morin CM, Benca R. Chronic insomnia. *Lancet.* 2012;379(9821):1129-1141.

92. Agmon M, Armon G. Increased insomnia symptoms predict the onset of back pain among employed adults. *PloS one.* 2014;9(8):e103591.

93. Kim SH, Sun JM, Yoon KB, Moon JH, An JR, Yoon DM. Risk factors associated with clinical insomnia in chronic low back pain: a retrospective analysis in a university hospital in Korea. *The Korean journal of pain.* 2015;28(2):137-143.

94. Quartana PJ, Wickwire EM, Klick B, Grace E, Smith MT. Naturalistic changes in insomnia symptoms and pain in temporomandibular joint disorder: a cross-lagged panel analysis. *Pain.* 2010;149(2):325-331.

95. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep medicine reviews.* 2017;34:70-81.

96. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2017;13(3):479-504.

97. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *Jama.* 2004;291(16):2013-2016.

98. Hoyos CM, Drager LF, Patel SR. OSA and cardiometabolic risk: What's the bottom line? *Respirology.* 2017;22(3):420-429.

99. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest.* 1993;104(3):781-787.

100. Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. *Chest.* 2003;123(1):87-95.

101. de Godoy LB, Luz GP, Palombini LO, et al. Upper Airway Resistance Syndrome Patients Have Worse Sleep Quality Compared to Mild Obstructive Sleep Apnea. *PloS one.* 2016;11(5):e0156244.

102. Almoznino G, Benoliel R, Sharav Y, Haviv Y. Sleep disorders and chronic craniofacial pain: Characteristics and management possibilities. *Sleep medicine reviews.* 2016.

103. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of P. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Annals of internal medicine.* 2016;165(2):125-133.

104. Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep medicine reviews.* 2015;19:6-16.

105. Ferrando M, Galdon MJ, Dura E, Andreu Y, Jimenez Y, Poveda R. Enhancing the efficacy of treatment for temporomandibular patients with muscular diagnosis through cognitive-behavioral intervention, including hypnosis: a randomized study. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2012;113(1):81-89.

106. Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. *Sleep medicine clinics.* 2014;9(2):261-274.

107. Tang NK, Goodchild CE, Salkovskis PM. Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. *Behaviour research and therapy.* 2012;50(12):814-821.

108. MacFarlane J, Morin CM, Montplaisir J. Hypnotics in insomnia: the experience of zolpidem. *Clinical therapeutics.* 2014;36(11):1676-1701.

109. Tampi RR, Manikkara G, Balachandran S, et al. Suvorexant for insomnia in older adults: a perspective review. *Drugs in context.* 2018;7:212517.

110. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. *Postgraduate medicine.* 2017;129(1):140-148.

111. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine use among chronic pain patients prescribed opioids: associations with pain, physical and mental health, and health service utilization. *Pain medicine.* 2015;16(2):356-366.

112. Haviv Y, Zini A, Sharav Y, Almoznino G, Benoliel R. Nortriptyline Compared to Amitriptyline for the Treatment of Persistent Masticatory Myofascial Pain. *Journal of oral & facial pain and headache.* 2018.

113. Brown S, Johnston B, Amaria K, et al. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. *Scandinavian journal of pain.* 2016;13:156-163.

114. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic

diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes care.* 2012;35(12):2451-2458.

115. Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. *Rheumatology.* 2010;49(4):706-715.

116. Vidor LP, Torres IL, Custodio de Souza IC, Fregni F, Caumo W. Analgesic and sedative effects of melatonin in temporomandibular disorders: a double-blind, randomized, parallel-group, placebo-controlled study. *Journal of pain and symptom management.* 2013;46(3):422-432.

117. Singh RK, Pal US, Goyal P, Nischal A, Gurung TR, Daga D. TMJ Arthrocentesis Alone and in Combination with Duloxetine in Temporomandibular Joint Pain. *Journal of maxillofacial and oral surgery.* 2018;17(3):270-275.

118. Miller MB, Chan WS, Curtis AF, et al. Pain intensity as a moderator of the association between opioid use and insomnia symptoms among adults with chronic pain. *Sleep medicine.* 2018;52:98-102.

119. Marshansky S, Mayer P, Rizzo D, Baltzan M, Denis R, Lavigne GJ. Sleep, chronic pain, and opioid risk for apnea. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;87(Pt B):234-244.

120. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. *The Cochrane database of systematic reviews.* 2014(4):CD008208.

121. Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. *Journal of pain research.* 2018;11:1445-1457.

122. Huang Z, Li Y, Bianchi MT, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: A randomized, double-blind, sham-controlled pilot study. *Brain stimulation.* 2018;11(5):1103-1109.

123. Zhang YP, Liao WJ, Xia WG. Effect of Acupuncture Cooperated with Low-frequency Repetitive Transcranial Magnetic Stimulation on Chronic Insomnia: A Randomized Clinical Trial. *Current medical science.* 2018;38(3):491-498.

124. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2009;5(3):263-276.

125. Iftikhar IH, Bittencourt L, Youngstedt SD, et al. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. *Sleep medicine.* 2017;30:7-14.

126. Khalid I, Roehrs TA, Hudgel DW, Roth T. Continuous positive airway pressure in severe obstructive sleep apnea reduces pain sensitivity. *Sleep.* 2011;34(12):1687-1691.

127. Jaoude P, Lal A, Vermont L, Porhomayon J, El-Solh AA. Pain Intensity and Opioid Utilization in Response to CPAP Therapy in Veterans with Obstructive Sleep Apnea

on Chronic Opioid Treatment. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2016;12(8):1105-1111.

128. Lorenzi-Filho G, Almeida FR, Strollo PJ. Treating OSA: Current and emerging therapies beyond CPAP. *Respirology.* 2017;22(8):1500-1507.

129. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *The Cochrane database of systematic reviews.* 2017;4:CD011279.

130. Chennaoui M, Arnal PJ, Sauvet F, Leger D. Sleep and exercise: a reciprocal issue? *Sleep medicine reviews.* 2015;20:59-72.

131. Knappe SW, Bakke M, Svanholt P, Petersson A, Sonnesen L. Long-term side effects on the temporomandibular joints and oro-facial function in patients with obstructive sleep apnoea treated with a mandibular advancement device. *J Oral Rehabil.* 2017;44(5):354-362.

132. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *American journal of respiratory and critical care medicine.* 2013;187(8):879-887.

133. Herrero Babiloni A, De Beaumont L, Lavigne GJ. Transcranial Magnetic Stimulation: Potential Use in Obstructive Sleep Apnea and Sleep Bruxism. *Sleep medicine clinics.* 2018;13(4):571-582.

134. Carberry JC, Amatoury J, Eckert DJ. Personalized Management Approach for OSA. *Chest.* 2018;153(3):744-755.

Transition to Chapter 3

The review conducted in Chapter 3 indicated that individuals with TMD who subjective report experiencing sleep problems also show objective indicators of sleep disturbances. These patients commonly report difficulties falling asleep, staying asleep, and experiencing restorative sleep, while also presenting several sleep disorders such as insomnia, sleep apnea, or restless leg sydrome. The bulk of previous work in this area, however, has been conducted based on cross-sectional study designs, with limited generalizability, so our understanding of daily sleep and pain problems among patients with TMD remains limited. Further studies, especially those employing dynamic assessment methods, are thus needed. The use of ecological momentary assessment (EMA) or daily diaries in microlongitudinal studies can help to address some of these knowledge gaps. By collecting data in real-time, EMA can capture fluctuations in sleep quality, pain intensity, and other relevant psychological variables.This approach can help to identify patterns and associations that may not be apparent with traditional retrospective or cros-sectional assessment. Pain fluctuations, or changes in pain intensity that occur within and across days, are important outcomes currently underexplored in the TMD literature that can also be explored.Therefore, in Chapter 3, we will use daily diaries to examine the contribution of day-to-day sleep quality and psychological factors identified in prior reviews from this thesis (i.e., affect, catastrophizing)to within-day pain fluctuations in patients with TMD.

CHAPTER 3. EXPERIMENTAL PAPER 1

Herrero Babiloni A, Provost C, Charlebois-Plante C, De Koninck B, Apinis-Deshaies A, De Beaumont L, Lavigne GJ, Martel MO. " The contribution of sleep quality and psychological factors to the experience of within-day pain fluctuations among individuals with temporomandibular disorders" J Pain. Under review.

The contribution of sleep quality and psychological factors to the experience of within-day pain fluctuations among individuals with temporomandibular disorders

Alberto HERRERO BABILONI, DDS, MS,[1,2] Catherine PROVOST, PT, [2] Camille CHARLEBOIS-PLANTE, MSc, [2] Beatrice P DE KONINCK, MSc, [2,] Amelie APINIS-DESHAIES, PhD,[2] Louis DE BEAUMONT, PhD[2], Gilles J LAVIGNE, DMD, PhD,[1,2,7]Marc O MARTEL, PhD,[1,5,6]

[1] Division of Experimental Medicine, McGill University, Montreal, Quebec, Canada

[2] Sacre-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada

[3] Department of Psychology, University of Montreal, Montreal, Quebec, Canada

[5] Faculty of Dental Medicine and Oral Health Sciences, McGill University, Montreal, QC, Canada.

[6] Department of Anesthesia, McGill University, Montreal, QC, Canada.

[7] Faculty of Dental Medicine, University of Montreal, Montreal, Quebec, Canada

Corresponding: Alberto Herrero Babiloni, DDS, MS; Sacre-Coeur Hospital, CIUSS NIM Research Center, Montreal, Quebec, Canada, CEAMS, 5400 Boul Gouin O, Montréal, QC H4J 1C5 Tel: 514-338-2222; Fax: 514-238-2531; E-mail: alberto.herrerobabiloni@mail.mcgill.ca

Short running title: Contributors of pain fluctuations in TMD

Abstract: We assessed the impact of day-to-day sleep quality and psychological variables (catastrophizing, negative affect, positive affect) to within-day pain fluctuations in 42 females with painful temporomandibular disorders (TMD) using electronic diaries. More specifically, we examined the contribution of these variables to the likelihood of experiencing pain exacerbations defined as: 1.1) an increase of 20 points (or more) in pain intensity on a 0-100 visual analogue scale (VAS) from morning to evening, and/or 1.2) a transition from mild-to-moderate pain over the course of the day; and pain decreases defined as: 1.3) a decrease of 20 points (or more) in pain intensity (VAS) from morning to evening, and/or 1.4) a reduction from moderate to mild pain over the day. Results indicated significantly main effects of sleep on both pain exacerbation outcomes (both p's < .05), indicating that nights with better sleep quality were less likely to be followed by clinically meaningful pain exacerbations on the next day. Results also indicated that days characterized by higher levels of catastrophizing were associated with a greater likelihood of pain exacerbations on the next day (both p's < .05). Daily catastrophizing was the only variable significantly associated with within-day pain decrease indices (both p's < .05). None of the other variables were associated with these

outcomes (all p's > .05). These results underscore the importance of addressing patients' sleep quality and psychological states in the management of painful TMD.

Perspectives: These findings highlight the significance of sleep quality and pain catastrophizing in the experience of within-day pain fluctuations among individuals with TMD. Addressing these components through tailored interventions may help to alleviate the impact of pain fluctuations and enhance the overall well-being of TMD patients.

Keywords: “orofacial pain”; “chronic pain”; “Psychosocial Functioning”; “Pain Measurement”; “Pain flare”.

1. Introduction

Temporomandibular disorders (TMD) is an umbrella term encompassing different conditions that affect the temporomandibular joint and/or masticatory muscles,[80] and when painful, it is considered the most common orofacial pain disorder after odontogenic pain.[69] Painful TMD are often accompanied by mechanical problems, disability, and poor mental health.[61, 80]

To date, the vast majority of studies on TMD have primarily focused on investigating factors contributing to TMD pain intensity,[27, 59, 87] while other important phenotypes that characterize the daily chronic pain experience, such as pain fluctuations, remain less investigated. Fluctuations in the intensity of pain can be debilitating, resulting in a sense of lack of control,[72, 49] which alters patients' mental health and daily function.[12, 17, 82,] One way to categorize pain fluctuations is based on the magnitude of changes in pain intensity, with any increase or decrease of 20 points (or more) in pain on the 0-100 visual analogue scale (VAS) being viewed as a clinically meaningful change.[22, 26, 50] Another relevant operationalization of pain fluctuations is to assess within-day transitions from "mild" (<40/100) to "moderate" pain (≥40/100),[84] and within-day transitions from "moderate" (≥40/100) to "mild" (<40/100) pain. Although this categorization relies on patients' numeric (i.e., 0-100) reports of pain intensity, the categorical classification of patients based on "mild", "moderate", and "severe" pain intensity is slightly different. This type of classification/assessment is commonly seen in clinical settings[84] and clinical trials of chronic pain treatments.[21]

Whereas previous studies have explored the day-to-day determinants of TMD pain intensity,[1, 48, 96] little is known on the determinants of pain fluctuations among patients with

TMD. Factors such as weather,[13] menstrual cycle, hormonal changes,[85, 98] and disability[44] have been linked to fluctuations in TMD pain intensity, but the influence of person-specific factors that can vary on a day-to-day basis (e.g., sleep quality) or within-day basis (e.g., psychological states) have remained largely unexplored. Moreover, studies have indicated a higher prevalence and heightened susceptibility of temporomandibular disorder (TMD) in females across different age demographics.[63, 66, 76] which is believed to stem from a variety of components encompassing hormonal, psychosocial, and anatomical factors. Sleep quality and psychological variables such as pain catastrophizing and affect (e.g., negative affect and positive affect) are some of the most well-established determinants of chronic pain, including TMD.[2, 23, 27, 37, 45, 66] There is evidence linking poor sleep and high pain catastrophizing with increased likelihood of experiencing pain exacerbations in patients with hip osteoarthritis,[33, 34] and higher levels of pain catastrophizing were associated with within-day pain increases in patients with fibromyalgia.[94] Moreover, results from ecological momentary assessment (EMA) studies have consistently shown within-person associations between affective states and pain intensity. For instance, within-person elevations in negative affect (NA) or decreases in positive affect (PA) have been associated with heightened pain intensity.[32] Therefore, there is reason to believe that sleep and psychological variables could be associated with within-day pain fluctuations in patients with TMD.

Thus, the main objective of the present study was to examine the contribution of day-to-day sleep quality and psychological variables (pain catastrophizing and affect) to within-day pain fluctuations. More specifically, we examined the contribution of these variables to the likelihood of experiencing pain exacerbations defined as: 1.1) an increase

of 20 points (or more) in pain intensity on a 0-100 visual analogue scale (VAS) from morning to evening, and/or 1.2) a transition from mild-to-moderate pain over the course of the day; and pain decreases defined as: 1.3) a decrease of 20 points (or more) in pain intensity on a 0-100 VAS from morning to evening, and/or 1.4) a reduction from moderate to mild pain over the course of the day. The decision to incorporate various operational methods for evaluating pain increases and decreases was based on the assessment of concept consistency, clinical significance, and applicability.

2. Methods

2.1. Participants

The study procedures were approved by The Human Subjects Research Ethics Board of Hôpital du Sacré-Cœur de Montréal. Written informed consent was obtained from every participant. Participants included in this study met the following inclusion criteria: a) females (due to the increased prevalence of TMD in females when compared to men, similarly to other TMD studies.[63, 66, 76]); b) between 18 and 65 years of age; c) diagnosed with painful TMD, defined as chronic myalgia (>6 months) with/without accompanying arthralgia per DC/TMD criteria.[80] The DC/TMD is a set of standardized criteria developed by an international group of researchers and clinicians to provide a consistent approach to diagnosing TMD.[80] It was published in 2014 and includes both Axis I and Axis II criteria. While Axis I focuses on the “physical” aspects of TMD and their categorization into muscular disorders, joint disorders and disc displacements, Axis II considers psychosocial factors that may contribute to TMD and includes assessment tools for measuring pain-related disability, psychological status, and psychosocial functioning. Diagnoses were confirmed by a trained dentist/orofacial pain specialist (AHB)

during the baseline visit (see 2.2.1); d) pain present at least 15 days during the last month; e) access to internet and electronic devices. Patients were excluded from the study if they reported f) presence of any dental or orofacial pain disorder not meeting the above definition; g) if they were on non-stable pharmacological treatment (e.g., reporting a change in medication in the last month); c) having alcohol or substance use problems; d) reporting any lifetime presence of major neurological or psychiatric disorders. Recruitment was conducted in Montreal and surroundings from 2021 to 2022 via referrals from orofacial pain clinics and from the general population using social media and posters. Participants received a financial compensation for transport and for their involvement in the study.

2.2. Study procedures

Patients initially underwent a phone screening interview to assess eligibility criteria (see 2.1). Patients meeting eligibility criteria then presented for a baseline visit at the hospital (see 2.2.1) and were then asked to complete daily diaries for 7 consecutive days (see 2.2.2).

2.2.1. Baseline hospital visit

During the baseline visit, participants completed different questionnaires assessing sociodemographic (i.e., age, education, marital status, ethnicity, employment), anthropometric (i.e., height, weight), and orofacial pain characteristics (i.e., pain location, pain duration, pain intensity, pain unpleasantness, pain interference). These questionnaires were part of Axis I of the DC/TMD Questionnaire package.[80] The Gracely Box Scale was used to assess pain unpleasantness [36] and the Fibromyalgia Survey

Questionnaire (FSQ)[41] was used to assess the presence of widespread pain. Finally, a health history questionnaire was used to assess any clinical/medical comorbidities, such as other pain comorbidities (i.e., migraine headache, tension-type headache, chronic fatigue syndrome, chronic pelvic pain, chronic low-back pain, vulvodynia, vulvar vestibulitis syndrome, irritable bowel syndrome, interstitial cystitis, neuropathic pain, osteoarthritis, rheumatoid arthritis, whiplash), sleep comorbidities (i.e., obstructive sleep apnea, restless leg syndrome), and other clinical/medical comorbidities such as premenstrual dysphoric disorder, tinnitus, and post-traumatic stress disorder) similarly to other studies.[62-64]

As for psychosocial variables assessment, instruments from the DC/TMD Axis II were used.[80] Those included validated scales such as the Jaw Function Limitation Scale 20-items (JFLS-20;[68]) for jaw limitation, the Patient Health Questionnaire-9 (PHQ-9;[56]) for depression, the Generalized Anxiety Disorder-7 (GAD-7; [89]) for anxiety, and the Patient Health Questionnaire-15 (PHQ-15;[57]) for somatization. In addition, the Perceived Stress Scale (PSS; [14]) for perceived levels of stress, the Pittsburgh Sleep Quality Index (PSQI; [11]) for sleep quality, the Pain Catastrophizing Scale (PCS; [91]) for pain catastrophizing, and the Positive and Negative Affect Scale (PANAS; [100]) for positive and negative affect were used.

Finally, medication intake, caffeine intake, and menstrual cycle were registered.[63] Menstrual cycle phase (if any) was determined as previously described into the following categories: menstrual, follicular, periovulatory, luteal and premenstrual.[77] Caffeine intake in the last 24 h was divided into three categories: low (< 100 mg/day), moderate (101–200 mg/day) or high (> 201 mg/day).[79] Participants were asked to report all prescription

drugs currently taken and quantified using the Medication Quantification Scale (MQS).[39] As cannabis was not part of the scale, this was asked separately.

At the end of the baseline visit, participants were instructed on how to use RedCap,[74] an electronic data capture software that can be used on any computer, smartphone or tablet, in order to complete electronic diaries.

2.2.2. Daily diaries

Participants filled out diaries for 7 consecutive days, twice a day. Diaries were filled out in the morning and in the evening, at randomized hours, within pre-specified time blocks (i.e., from 6:00am to 12:00pm; and from 6:00pm to 12:00am). Diaries were date- and time-stamped to ensure validity and compliance with the diary protocol. The items of the diaries were:

2.2.2.1 Daily pain-related measures: Participants were asked to rate the average level of pain intensity since their last diary entry using a visual analogue scale (VAS) that ranged between 0 (no pain) to 100 (extreme pain). This item was an adaptation of the standard VAS item used in the BPI assessing pain intensity.[92]

2.2.2.2. Daily sleep quality: Sleep quality was assessed only in the morning entry, using a VAS that ranged from 0 (worst possible sleep quality) to 100 (best possible sleep quality). VAS to assess sleep is known to be a reliable method and is commonly used due to its simplicity in a variety of research and clinical settings.[67, 70, 104]

2.2.2.3. Daily pain catastrophizing: Pain catastrophizing was assessed using a diary version of the Pain Catastrophizing Scale (PCS).[19, 31] Patients were asked to report on different thoughts and emotions related to helplessness, rumination, and magnification

associated with pain. Participants were asked to provide reports of catastrophizing since their last diary entry, using a scale ranging from 0 (very slightly or not at all) to 4 (extremely). Studies have supported the reliability and the validity of the daily Pain Catastrophizing Scale as a measure of daily pain catastrophizing.[19] In this study, the within-person internal reliability coefficient of items used to assess catastrophic thinking was α = 0.725.

2.2.2.4. Positive and negative affect measures: Participants were asked to report the extent to which they experienced five positive emotions (i.e., enthusiastic, excited, alert, determined, and inspired) and five negative emotions (i.e., afraid, upset, nervous, scared, distressed) since their last diary entry on a scale ranging from 1 (not at all) to 5 (extremely). This measure is a diary adaptation of the Positive and Negative Affect Scale (PANAS)[100], which reliability and validity has been supported in several chronic pain studies.[9, 20, 30] As in other studies, items were averaged to create a measure of positive affect (PA) and negative affect (NA) score. [9, 20, 30, 31] In the present study, the within-person internal reliability coefficients of items assessing positive and negative affect were α = 0.713 and α = 0.770 for PA and NA, respectively.

2.3. Data reduction and analyses

Data analysis was performed using IBM-SPSS v.25 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as means and standard deviations for continuous variables and percentages for categorical variables. All study analyses were conducted with an alpha level for significance (p value) set to 0.05

2.3.1. Within-day pain increases

To address the first component of our main objective, a clinically meaningful within-day pain exacerbation index was computed. This index was computed for each participant and for each of the diary days based on absolute (Δ) changes in patients' reports of pain intensity. A clinically meaningful within-day pain exacerbation (= 1) was indicated when patients reported any increase of 20 points (or more) in pain intensity on the 0-100 visual analogue scale (VAS) from morning to evening. No clinically meaningful within-day pain exacerbation (= 0) was indicated if the change in pain intensity was $<$ 20 points on the VAS. This cutoff is consistent with previously established operationalizations of clinically meaningful changes in clinical pain intensity among chronic pain populations.[22, 26, 50]

Another within-day pain exacerbation index was computed based on patients' transitions from "mild" to "moderate" pain levels over the course of the day. More specifically, transitions were coded as = 1 if jaw pain intensity was rated as mild (< 40) in the morning and moderate or severe (> 40) in the evening. Transitions were coded as = 0 if patients experiencing mild pain in the morning did not transition to moderate or severe pain in the evening.

2.3.2. Within-day pain decreases

To address the second component of our main objective, a clinically meaningful within-day pain decrease index was computed. This index was computed, for each participant and for each of the diary days, based on Δ changes in patients' reports of pain intensity. A clinically meaningful within-day pain decrease (= 1) was indicated when patients reported any decrease of 20 points (or more) in pain intensity on the 0-100 VAS

from morning to evening. No clinically meaningful within-day pain decrease (= 0) was indicated if the change in pain intensity was < 20 points on the VAS.

Another within-day pain decrease index was computed based on patients' transitions from "moderate" to "mild" pain levels over the course of the day. More specifically, transitions were coded as = 1 if jaw pain intensity was rated as moderate or severe (≥ 40) in the morning and mild (< 40) in the evening. Transitions were coded as = 0 if patients experiencing moderate or severe pain in the morning did not transition to mild pain in the evening.

2.3.3. Daily contributors to pain fluctuations

In order to examine the association between independent variables (IVs: daily sleep quality, pain catastrophizing, negative affect, positive affect) and dependent variables (i.e., within-day pain exacerbations, within-day pain decreases), multilevel logistic regression analyses were used given the binary outcomes as well as the hierarchical (i.e. nested) data structure of this study, in which repeated daily measures (Level 1 units) were nested within days (Level 2 units), which were also nested within participants (Level 3 units). For variables that were collected twice daily (i.e., pain catastrophizing, negative affect, and positive affect) Level 2 scores were obtained by computing an average of the two Level 1 values.

Multilevel logistic regression models were performed using Level 2 units for the IVs (i.e., sleep, catastrophizing, negative affect, positive affect) using within-day pain increase indices as outcomes. The same models were performed separately using within-day pain decreases indices as outcomes. In order to account for possible floor and ceiling

effects, all multilevel models included morning pain intensity as covariate. All multilevel models followed a sequential procedure,[54, 78, 99] which first involved specifying a random intercept and fixed effects for independent variables (IVs). The main effects of person-level (i.e., Level 3) variables such as patients' demographic characteristics (e.g., age, ethnicity, education, body mass index, marital status, employment status), pain condition characteristics (e.g., number of pain locations, comorbidity index, etc.), menstrual cycle, medication and caffeine intake were all examined separately on main study outcomes. For those significantly associated with main outcomes, their influence was subsequently tested by creating cross-level interaction terms between main IVs (i.e., daily sleep quality, pain catastrophizing, negative affect, positive affect and Level 3 (person) characteristics. Any significant 2-way interaction effect would suggest that the association between IVs and the outcome is moderated (i.e., influenced) by the Level 3-person characteristic.[46, 47]

All multilevel models described above were carried out using maximum-likelihood (ML) estimation and included a first-order autoregressive variance covariance matrix (AR1) to account for the autocorrelation between repeated measures. As recommended, all independent variables were centered before being entered in multilevel models.[24] With the ability of MLM to account for randomly missing Level 1 data [46, 86], all 42 study participants were included in multilevel analyses without the need for any data imputation procedures. Across all assessment time points, compliance with the diary protocol was very high, with an overall completion rate of 97.74%. When combining the variables that were assessed twice daily (i.e., pain intensity, negative affect, positive affect, and catastrophizing) and daily (i.e., sleep), there was a total of 2,650 data points, and a total

of 2,590 data points were observed. Analyses indicated that patients with and without missing data did not differ significantly on any of the main study variables (all p's > .05).

3. Results

Descriptive statistics for the study are presented in Table 3.1.

Table 3.1. Descriptive characteristics at baseline

	Mean (± SD) or frequency (%)
Demographic variables	
Age (y)	26.60 ± 8.38
BMI (kg/m2)	22.31 ± 2.88
Marital status (single, %)	26 (62%)
Education (University bachelor or above, %)	28 (66.7%)
Employment (students, %)	28 (66.7%)
Ethnicity	
White	28 (66.7%)
African American	2 (4.8%)
Asian	7 (16.7%)
Native American	3 (7.1%)
Others	2 (4.8%)
Pain characteristic variables	
Average pain intensity (0-100)	45.0 ± 12.90
Concomitant TMJ arthralgia	27 (64.3%)
Concomitant HA attributed to TMD	26 (61.9%)
GBS pain unpleasantness (0-20)	6.33± 3.58
BPI pain interference (0-100)	20.92 ± 20.95
Pain duration (months)	77.7±116.73
Comorbidity index (0-18)	1.07 ± 1.31
FSQ (0-31)	10.88 ± 4.29
GCPS grade I	17 (40.48%)
GCPS grade II	20 (47.62%)
GCPS grade III	3 (7.14%)
GCPS grade IV	2 (4.42%)
Psychosocial variables	
PANAS-NA (10-50)	11.31 ± 3.84
PANAS-PA (10-50)	16.02 ± 3.67

JFLS-20 (0-10)	1.84 ± 1.08
PHQ-9 (0-27)	6.00 ± 4.80
GAD-7 (0-21)	6.00 ± 4.54
PHQ-15 (0-30)	10.00 ± 6.74
PSS (0-40)	16.07 ± 6.68
PSQI (0-21)	5.90 ± 3.06
Other potential confounders	
Menstrual cycle phase	
No menses	7 (16.66%)
Menstrual	10 (23.81%)
Follicular	5 (11.90%)
Periovulatory	5 (11.90%)
Luteal	7 (16.66%)
Premenstrual	8 (19.05%)
Caffeine intake last 24 h	
None	10 (23.81%)
Low	12 (28.57%)
Moderate	15 (35.71%)
High	5 (11.90%)
MQS score	2.48 ± 4.27

Note: the current use of cannabis was not reported by any of the participants.

Abbreviations: BMI: body mass index; BPI: brief pain inventory; FSQ: Fibromyalgia survey questionnaire; GAD: general anxiety disorder; GBS: Gracely box scale; GCPS: graded chronic pain scale; HA: headache; JFLS: jaw functional limitation scale PANAS: positive and negative affect scale; MQS: medication quantification Scale; PHQ: patient health questionnaire; PSQI; Pittsburgh sleep quality index; PSS: perceived stress scale; TMJ: temporomandibular joint; TMD: temporomandibular disorders.

Descriptive statistics for the study are presented in Table 3.1. The sample included 42 women (mean age: 26.60 ± 8.38), being for the most part single (62%) and students (66.7%). Regarding ethnicity, most of the participants reported to be white (66.7%). Other ethnic categories included Asian (16.7%), Native American (7.1%), Black or African American (4.8%), and Others (4.8%). The latter category included one participant who reported to be Hispanic or Latino, and another who reported to be Multiracial. All of the participants had a diagnosis of chronic myalgia as per inclusion criteria, while 62.4% of them presented concomitant TMJ arthralgia and 61.9% fitted the diagnosis of headache

attributed to TMD. The average pain facial pain level was 45.0 ± 12.90 on a 0 to 100 VAS, with a mean duration of 77.7 ± 116.73 months (minimum 6 months maximum 700 months). Seven participants took antidepressant medications in a stable basis, and none of those reported a change of such during the last month or the duration of the study. None of the participants reported being diagnosed with a sleep disorder or the intake of medications or supplements for sleep disorders. Mean and ranges of daily values for the main variables of interest can be found in Table 3.2.

Table 3.2. Average daily reports on measures of pain, sleep and psychological variables.

	Mean ± SD	Range
Pain intensity	31.14 ± 20.53	94 (0-94)
Sleep quality	40.98 ± 24.09	99 (0-99)
Pain catastrophizing	1.45 ± 2.18	11 (0-11)
Positive affect	11.57 ± 4.28	18 (5-23)
Negative affect	7.94 ± 3.54	15 (5-20)

Note: SD = Standard deviations. Range: numbers in parentheses are minimum and maximum

None of the descriptive characteristics at baseline reported in Table 3.1, except ethnicity, were significantly associated with the outcomes of interest.

3.1. Frequency of within-day pain fluctuations

The total number of within-day clinically meaningful pain exacerbations as well as within-day transitions from mild to moderate pain observed across all days and participants is displayed in Table 3.3. The total number of clinically meaningful within-day pain decreases and within-day decreases from moderate to mild pain is also displayed in in Table 3.3.

Table 3.3. Frequency (%) and number of participants experiencing pain fluctuation events.

Pain exacerbations	
Number of participants experiencing at least one within-day pain exacerbation	15/42 (36%)
Total number of clinically-significant within-day pain exacerbations [a]	23/294 (7.8%)
Number of participants experiencing at least one within-day transitions from mild to moderate pain	22/42 (52%)
Total number of within-day transitions from mild to moderate pain [b]	36/192 (18.8%)
Pain decreases	
Number of participants experiencing at least one within-day pain decrease	18/42 (43%)
Total number of clinically-significant within-day pain decreases [c]	23/294 (7.8%)
Number of participants experiencing within-day decreases from moderate to mild pain	10/42 (24%)
Total number of within-day decreases from moderate to mild pain [d]	20/84 (23.8%)

Note: [a] Clinically-significant within-day pain exacerbations: Number of jaw pain intensity increases of magnitude ≥ 20 in a 0–100 VAS occurring within the same day (i.e., from AM measurement to PM measurement). This was calculated across all participants.

[b] Total number of within-day transitions from mild to moderate pain. If jaw pain intensity was rated as mild (<40) in the AM entry and moderate or severe (>40) in the PM entry within the same day, this was considered as moderate pain transition positive.

[c] Clinically-significant within day pain decreases: Number of jaw pain intensity decreases of magnitude ≥ 20 in a 0–100 VAS occurring within the same day (i.e., from AM measurement to PM measurement).

[d] Total number of within day decreases from moderate to mild pain. If jaw pain intensity was rated as moderate or severe (>40) AM entry and mild (<40) in the PM entry of the same day, this was considered as moderate pain reduction positive.

The total number of clinically meaningful within-day pain exacerbations was 23 out of possible 294 (42 participants multiplied by 7 days) (i.e., 7.8%), with 15 unique participants out of 42 (36%) experiencing at least one across the 7 days. Additionally, the total number of within-day transitions from mild to moderate pain was 36 (18.8%), with 22 unique participants (52%) experiencing it at least once.

On the other hand, the total number of within-day pain decreases was 23 (7.8%), where 18 unique participants (43%) experienced it at least once, and the total number of within-day decreases from moderate to mild pain was 20 (23.8%), with 10 unique participants (24%) having them at least once. Twelve unique participants reported to have no pain (i.e., 0/100) at some point during the duration of the study, and in 33 out of the possible 588 (5.6%) instances when considering all days, moments, and participants, the pain was rated as 0/100. Regarding morning pain, nine unique participants reported to have no pain (i.e., 0/100) in the morning at some point, and in 16 out of the possible 294 (5.5%) instances when considering all days and participants, the pain was rated as 0/100 in the morning. Only one participant reported to experience pain rated as 100/100, which was solely in an evening instance.

3.2. Contribution of sleep and psychological factors (catastrophizing, affect) to within-day pain exacerbations

A multilevel logistic regression analysis was first conducted using the within-day pain exacerbation index as the outcome variable, and all Level 2 IVs (i.e., daily sleep, pain catastrophizing, NA and PA) entered simultaneously in the model (see Table 3.4).

Table 3.4. Multilevel logistic regressions examining the factors contributing to within-day pain exacerbations and pain decreases

	(B)	Std. Error	Exp coefficient (OR)†	95% confidence interval Lower bound	Upper bound	p-value
Within-day pain exacerbations [a]						
Sleep quality (0-100)	-0.049	0.016	0.953	0.923	0.983	**0.002***
Pain catastrophizing (0-12)	0.764	0.332	2.147	1.117	4.130	**0.022***
Positive affect (5-25)	-0.241	0.130	0.786	0.655	1.015	0.065
Negative affect (5-25)	-0.074	0.097	0.929	0.713	1.123	0.444
Within-day transitions from mild to moderate pain [b]						
Sleep quality (0-100)	-0.030	0.015	0.970	0.942	1.000	**0.047***
Pain catastrophizing (0-12)	0.891	0.313	2.436	1.314	4.519	**0.005***
Positive affect (5-25)	-0.108	0.133	0.898	0.691	1.166	0.417
Negative affect (5-25)	-0.004	0.129	0.996	0.772	1.283	0.973
Within-day pain decreases [c]						
Sleep quality (0-100)	0.011	0.010	1.011	0.991	1.031	0.280
Pain catastrophizing (0-12)	-0.512	0.165	0.600	0.434	0.829	**0.002***
Positive affect (5-25)	0.177	0.116	1.193	0.949	1.500	0.129
Negative affect (5-25)	0.056	0.107	1.058	0.857	1.306	0.600
Within-day transitions from moderate to mild pain [d]						
Sleep quality (0-100)	0.015	0.017	1.015	0.982	1.049	0.373
Pain catastrophizing (0-12)	-1.001	0.386	0.368	0.170	0.793	**0.011***
Positive affect (5-25)	0.331	0.196	1.392	0.943	2.054	0.095
Negative affect (5-25)	0.120	0.205	1.128	0.750	1.694	0.559

Note: All these models were adjusted for daily morning pain intensity.

* p = 0.05. † Expression coefficients are presented as odds ratio.

[a] Clinically-significant within day pain exacerbations: Number of jaw pain intensity increases of magnitude ≥ 20 in a 0–100 VAS occurring within the same day (i.e., from AM measurement to PM measurement).

[b] Within day pain decreases: Number of jaw pain intensity decreases of magnitude ≥ 20 in a 0–100 VAS occurring within the same day (i.e., from AM measurement to PM measurement).

[c] Total number of within day transitions from mild to moderate pain. If jaw pain intensity was rated as mild (<40) in the AM entry and moderate or severe (>40) in the PM entry within the same day, this was considered as moderate pain transition positive.

[d] Total number of within day decreases from moderate to mild pain. If jaw pain intensity was rated as moderate or severe (>40) AM entry and mild (<40) in the PM entry of the same day, this was considered as moderate pain reduction positive.

Results indicated a significantly main effect of sleep on pain exacerbations (OR = 0.953; 95% LLCI = 0.923; ULCI = 0.983; p = 0.002), indicating that nights with better sleep quality were less likely to be followed by clinically meaningful pain exacerbations the next day. Results also indicated that days characterized by higher greater catastrophic thinking were associated with an increased likelihood of experiencing clinically meaningful pain exacerbations (OR = 2.147, 95% LLCI = 1.117; ULCI = 4.130; p = 0.022). Results indicated that neither negative nor positive affect were significantly associated with the likelihood of experiencing clinically meaningful pain exacerbations.

A multilevel logistic regression analysis was then conducted using the transition from “mild” to “moderate” pain index as the outcome, and all Level 2 IVs (i.e., daily sleep, catastrophizing, NA and PA) entered simultaneously in the model (see Table 3.4). Results indicated that day-to-day increases in sleep quality were associated with a decreased likelihood of experiencing transitions from “mild” to “moderate” pain on the following day (OR = 0.970, 95% LLCI = 0.942; ULCI = 1.000; p = 0.047). Results also indicated that days characterized by higher levels of catastrophic thinking were associated with a higher likelihood of experiencing transitions from “mild” to “moderate” pain (OR = 2.436, 95%; LLCI = 1.314 ULCI = 4.519; p = 0.005). None of the other IVs were significantly associated with the outcome.

3.3. Contribution of sleep and psychological factors (catastrophizing, affect) to within-day pain decreases

A multilevel logistic regression analysis was conducted using the within-day pain decrease index as the outcome variable. As for models described above, all Level 2 IVs (i.e., daily sleep, pain catastrophizing, NA and PA) were entered simultaneously in the

model (see Table 3.4). Results indicated that days characterized by elevations in catastrophic thinking were associated with a decreased likelihood of experiencing a clinically meaningful reduction in pain (OR = 0.600; 95% LLCI = 0.434; ULCI = 0.829; p = 0.002). Day-to-day levels of sleep, negative affect, and positive affect were not significantly associated with the likelihood of experiencing clinically meaningful pain decreases (all p's > .05).

A multilevel logistic regression analysis was also conducted using the transition from “moderate” to “mild” pain index as the outcome, and all IVs (sleep, catastrophizing, NA, PA) were entered simultaneously in the model (see Table 3.4). Results indicated that days with higher catastrophic thinking were associated with a reduced likelihood of experiencing transitions from “moderate” to “mild” pain (OR = 0.368; 95% LLCI = 0.170; ULCI = 0.793; p = 0.011). Day-to-day levels of sleep, negative affect, and positive affect were not significantly associated with the outcome (all p's > .05).

3.4. Sensitivity analyses: Given that the operationalization of within-day pain exacerbations using a binary outcome classification (e.g., > 20/100) prevents from using the full distribution of within-day change scores, a sensitivity analysis was conducted using the absolute (i.e., delta) change scores in pain intensity (from the morning to evening) as the outcome measure. Level 2 IVs (i.e., sleep quality, pain catastrophizing, negative affect, and positive affect) were then included in a multilevel linear model. Results from this analysis indicated that nights characterized by greater sleep quality were associated with lower within-day increases in pain intensity (B = -0.120, p < 0.011). Results from this analysis also indicated that days characterized by higher pain catastrophizing were associated with greater within-day increases in pain intensity (B =

7.671, p < 0.001). Finally, we also found that days characterized by higher levels of positive affect (PA) were associated with a lower magnitude of within-day pain increases (B = -1.591, p < 0.001). Results from this sensitivity analysis are presented in Supplementary Table 3.5.

Supplementary Table 3.5. Multilevel linear regression analysis examining the contribution of sleep and psychological variables on the magnitude of within-day pain increases.

	(B)	Std. Error	95% confidence interval		p-value
			Lower bound	Upper bound	
Sleep quality (0-100)	-0.120	0.47	-0.212	-0.028	**0.011***
Pain catastrophizing (0-12)	7.671	0.926	5.846	9.496	**<0.001***
Positive affect (5-25)	-1.591	0.478	-2.534	-0.649	**0.001***
Negative affect (5-25)	-0.257	0.501	0.608	0.731	0.608

Note: This model was adjusted for daily morning pain intensity. * p = 0.05. The outcome represents the delta (∆) change in pain intensity from morning to evening.

A sensitivity analysis involving a person-level (i.e., Level 3) characteristic (i.e., ethnicity) was also conducted given that analyses revealed a significant main effect of ethnicity on the likelihood of clinically meaningful pain flares (> 20), with White participants being significantly less likely than Non-White participants to experience clinically meaningful pain flares over the 7-day period (B = -1.482, p = 0.01, OR = 0.227). Ethnicity was not associated with any other main outcomes (all p's > 0.05) and ethnicity did not significantly interact with any of the main IVs included in multilevel models (i.e., sleep, catastrophizing, NA, PA) (all p's > 0.05). These non-significant interaction effects suggest that the effects of IVs on main study outcomes was not influenced (i.e., moderated by) ethnicity.

4. Discussion

The results of the present study show that day-to-day sleep quality and pain catastrophizing contribute to fluctuations in pain experienced over the course of the day by individuals with TMD. Our study revealed that nights of greater sleep quality were less likely to be followed by clinically meaningful (i.e., > 20/100) pain increases on the following day. We also found that days characterized by higher levels of catastrophizing were associated with a greater likelihood of pain exacerbations on the next day. Catastrophizing was the only variable significantly associated with within-day pain decreases, with day-to-day elevations in catastrophizing being associated with a lower likelihood of experiencing within-day pain reductions from morning to evening. These findings add evidence to the significant contribution of sleep and catastrophizing to TMD pain, and importantly, provide new insights into the factors that may lead to TMD pain exacerbations in the context of patients' day-to-day lives.

Intraindividual (i.e., within-person) pain variability is currently considered an important topic in pain research, and as such it has been identified as an important clinical and study target.[65, 81] Fluctuations in pain intensity have been associated with poor treatment responses[95] and poor psychological well-being across different types of chronic pain conditions (e.g., arthritis, fibromyalgia, neuropathic pain, sickle cell disease, etc.)[6, 25, 40, 82] in part due to the sense of loss of control and unpredictability.[6] Qualitative studies have also revealed that pain exacerbations may contribute to low self-confidence, vulnerability, and the perception of “being a burden”.[71] Importantly, intraindividual pain variability has been considered an important feature for subgrouping and phenotyping

pain patients,[6, 81] an important avenue to further understand and treat chronic pain. In our study we observed that 36%-42% of our TMD participants experienced at least one pain exacerbation over the course of the 7-diary days, which is similar to what has been found in other studies among patients with other types of chronic pain conditions, such as OA,[5, 72] but also with other studies conducted among TMD patients.[44] Regarding the number of fluctuations, their occurrence across the sample was relatively low (i.e., clinically meaningful pain exacerbations = 7.8%-18.8%, clinically meaningful pain decreases = 7.8%-23.8%), possibly due to the small period of observation (7 days) as well as the relatively modest average self-reported pain intensity (i.e., 45/100) at baseline and the daily pain average of 31/100 across the 7 diary days.

Although some studies have reported that the effects of poor sleep quality on osteoarthritis symptoms can dissipate over the course of the day,[102] our study showed that sleep can contribute significantly to the experience of within-day, clinically meaningful pain increases (i.e., increase of > 20/100), in individuals with TMD. It appears that specific sleep factors, such as longer time in bed and sedentary behaviour, can also contribute to greater odds of next-day pain flares among low back pain patitents.[16] Possible mechanisms include the impairment of endogenous pain modulation, the induction a status of low-grade inflammation, or increased arousal among others.[7, 42, 43, 101] Although better sleep has been linked to pain improvement and remission over time across different conditions,[3, 29] our results showed that sleep did not significantly contribute to within-day pain decreases in TMD participants. This might be due to the outcome or timing used to operationalize pain decreases. For example, a study revealed that better perceived sleep quality was associated with less pain in the earlier, but not later, part of the following day,

suggesting that the analgesic effects of good sleep might be “short-lived”.[93] Another possibility relates to the mild to moderate levels of pain experienced by our sample.

Among the psychological predictors of chronic pain, including TMD, one of the most consistently reported is pain catastrophizing.[10, 23, 27] In our study, we observed that day-to-day elevations in pain catastrophizing were associated with a decreased likelihood of within-day pain decreases. Longitudinal studies have shown that higher pain catastrophizing can predict worse recovery trajectories in post-surgical pain patients,[53] suggesting that catastrophic thoughts might impede recovery from pain episodes. Regarding the possible mechanisms of this association, it is well know that distorted cognitive processes can directly affect pain experience,[58] and catastrophizing has been associated with the use of less effective pain coping strategies.[18, 90] Additionally, there is evidence indicating that high pain catastrophizing could disrupt endogenous pain modulatory pathways by decreasing pain inhibition and/or increasing pain facilitation.[35, 75] Therefore, pain catastrophizing could impede within-day pain reductions in part via alterations in the biological mechanisms involved in pain modulation.

Despite a significant body of literature linking positive and negative affect with chronic pain,[23, 97] we did not observe any significant influence of these variables on main outcomes of interest. A post-hoc power analysis indicated that our study was underpowered to detect statistically significant main effects for daily negative affect (NA) and positive affect (PA) when within-day fluctuations in pain were operationalized based on a binary outcome/cutoff. However, sensitivity analyses indicated that when within-day pain changes were operationalized on a continuum, days characterized by higher levels of positive affect were associated with a lower magnitude of within-day pain increases.

Research has shown that positive affect and negative affect influence pain differently.[28] Indeed, the role of positive affect in chronic pain, which could potentially "buffer" the harmful effects of chronic pain, has been highlighted.[8, 28, 38, 83] Evidence suggests that positive affect influences pain over and above the influence of negative affect, although the impact of these affective states may differ across different pain conditions and study samples.[28] In TMD, a recent study using daily diaries and actigraphy showed that positive affect mediated the association between previous night's total sleep time and next-day's overall pain severity.[66] In fibromyalgia, positive affect was a stronger mediator than pain and negative affect for the association between daily subjective sleep and next day disability.[55] A possible explanation for the mixed findings observed across studies is the use of different items to assess positive affect and the number of diary days. Other reasons include the inherent differences in clinical samples in terms of severity of sleep and pain problems.

A number of other issues need to be considered when interpreting results from this study. First, our sample consisted of only females of a relatively young age, and with relatively mild levels of pain, which could limit the generalizability of these results. Second, we assessed daily outcomes for 7 days. A study conducted over a longer time period could have further our understanding of pain dynamics, in addition to providing a more detailed analysis of psychosocial characteristics as intraindividual pain modulators. Thirdly, while our methodological approach to operationalizing clinically meaningful pain exacerbations and pain decreases was based on commonly used cut-offs viewed as clinically useful,[73, 88,51, 52] the operationalization of within-day pain exacerbations using a binary outcome classification (e.g., > 20/100) has limitations by preventing from using the

full distribution of within-day change scores. Also, floor and ceiling effects must be considered, as these cutoffs might be less applicable among people with higher levels of pain on average. Future studies should explore additional sleep and psychological characteristics and their unique contributions to pain fluctuations in larger samples, including males, and among patients more diverse pain severity levels. Larger samples would also enable examination of how person-specific characteristics potentially interact with daily processes in contributing to pain fluctuations. In our study, sensitivity analyses revealed that ethnicity (i.e., being non-White) was associated with a greater likelihood of clinically meaningful pain fluctuations, which is consistent with previous reports of poorer pain-related outcomes among minorities,[4, 60] but studies with larger sample sized might provide insights into how a host of person characteristics can influence interrelations between day-to-day sleep patterns, psychological states, and pain. In future studies, the clinical relevance and utility of other approaches to operationalize within-person variability will need to be explored,[82] and importantly, other operationalizations of pain fluctuations that include multiple domains beside the sensory aspects of pain (i.e., pain intensity), such as impact on function and emotions[15] could be considered as a way to provide new insights into these dynamic processes. Finally, using other subjective sleep measures, such as sleep duration, sleep latency, number of awakenings, and wake time after sleep onset among others, as well as home sleep quality monitoring (e.g., wearable devices) could contribute to a better understanding of the sleep and pain association. The concurrent incorporation of ambulatory measures assessing daily biological processes (e.g., breathing, heart activity or body movement) could also be useful.[103]

In conclusion, this study highlights the contribution of day-to-day sleep quality and psychological factors to within-day pain fluctuations that may be experienced among female individuals with TMD. Improving sleep quality and/or addressing sleep disturbances and pain catastrophizing through tailored interventions may offer valuable avenues for reducing the occurrence of TMD pain exacerbations. This might also promote the within-day recovery from high pain states and might ultimately contribute to improving the quality of life for TMD patients.

Disclosures and funding:

The authors declare no conflict of interest. GJL received research support from a Canadian Institutes of Health Research Canada Research Chair. LDB received research support from Foundation Caroline Durand Research Chair in Acute Traumatology of Université de Montréal. MOM was supported by grants from the Canadian Institutes for Health Research (CIHR), the International Association for the Study of Pain (IASP), the Canadian Pain Society (CPS), and the Louise and Alan Edwards Foundation (LAEF). AHB was funded by a Vanier Scholarship and the CPS.

References

1. Aaron LA, Turner JA, Mancl LA, Sawchuk CN, Huggins KH, Truelove EL. Daily pain coping among patients with chronic temporomandibular disorder pain: an electronic diary study. *Journal of orofacial pain.* 20:125-137, 2006
2. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. *Pain.* 68:363-368, 1996
3. Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. *Sleep medicine reviews.* 39:82-97, 2018
4. Anderson KO, Green CR, Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. *J Pain.* 10:1187-1204, 2009
5. Atukorala I, Pathmeswaran A, Makovey J, et al. Can pain flares in knee osteoarthritis be predicted? *Scand J Rheumatol.* 50:198-205, 2021
6. Bakshi N, Gillespie S, McClish D, McCracken C, Smith WR, Krishnamurti L. Intraindividual pain variability and phenotypes of pain in sickle cell disease: a secondary analysis from the Pain in Sickle Cell Epidemiology Study. *Pain.* 163:1102-1113, 2022
7. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. *Physiological reviews.* 99:1325-1380, 2019
8. Boselie J, Peters ML. Shifting the perspective: how positive thinking can help diminish the negative effects of pain. *Scandinavian journal of pain.* 23:452-463, 2023

9. Bruneau A, Frimerman L, Verner M, et al. Day-to-day opioid withdrawal symptoms, psychological distress, and opioid craving in patients with chronic pain prescribed opioid therapy. *Drug and alcohol dependence.* 225:108787, 2021

10. Buenaver LF, Quartana PJ, Grace EG, et al. Evidence for indirect effects of pain catastrophizing on clinical pain among myofascial temporomandibular disorder participants: the mediating role of sleep disturbance. *Pain.* 153:1159-1166, 2012

11. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 28:193-213, 1989

12. Carriere JS, Lazaridou A, Martel MO, et al. The moderating role of pain catastrophizing on the relationship between partner support and pain intensity: a daily diary study in patients with knee osteoarthritis. *Journal of behavioral medicine.* 43:807-816, 2020

13. Cioffi I, Farella M, Chiodini P, et al. Effect of weather on temporal pain patterns in patients with temporomandibular disorders and migraine. *J Oral Rehabil.* 44:333-339, 2017

14. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of health and social behavior.* 24:385-396, 1983

15. Costa N, Ferreira ML, Setchell J, et al. A Definition of "Flare" in Low Back Pain: A Multiphase Process Involving Perspectives of Individuals With Low Back Pain and Expert Consensus. *J Pain.* 20:1267-1275, 2019

16. Costa N, Smits EJ, Kasza J, et al. Are objective measures of sleep and sedentary behaviours related to low back pain flares? *Pain.* 163:1829-1837, 2022

17. Costa N, Smits EJ, Kasza J, Salomoni SE, Ferreira M, Hodges PW. Low Back Pain Flares: How do They Differ From an Increase in Pain? *Clin J Pain.* 37:313-320, 2021

18. Crombez G, Viane I, Eccleston C, Devulder J, Goubert L. Attention to pain and fear of pain in patients with chronic pain. *Journal of behavioral medicine.* 36:371-378, 2013

19. Darnall BD, Sturgeon JA, Cook KF, et al. Development and Validation of a Daily Pain Catastrophizing Scale. *J Pain.* 18:1139-1149, 2017

20. Davis MC, Okun MA, Kruszewski D, Zautra AJ, Tennen H. Sex differences in the relations of positive and negative daily events and fatigue in adults with rheumatoid arthritis. *J Pain.* 11:1338-1347, 2010

21. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 113:9-19, 2005

22. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain.* 9:105-121, 2008

23. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. *J Pain.* 17:T70-92, 2016

24. Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. *Psychol Methods.* 12:121-138, 2007

25. Farrar JT, Troxel AB, Haynes K, et al. Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: an ACTTION study. *Pain.* 155:1622-1631, 2014

26. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 94:149-158, 2001

27. Fillingim RB, Ohrbach R, Greenspan JD, et al. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. *J Pain.* 14:T75-90, 2013

28. Finan PH, Garland EL. The role of positive affect in pain and its treatment. *Clin J Pain.* 31:177-187, 2015

29. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain.* 14:1539-1552, 2013

30. Finan PH, Quartana PJ, Smith MT. Positive and negative affect dimensions in chronic knee osteoarthritis: effects on clinical and laboratory pain. *Psychosom Med.* 75:463-470, 2013

31. Frimerman L, Verner M, Sirois A, et al. Day-to-day hedonic and calming effects of opioids, opioid craving, and opioid misuse among patients with chronic pain prescribed long-term opioid therapy. *Pain.* 162:2214-2224, 2021

32. Frumkin MR, Rodebaugh TL. The role of affect in chronic pain: A systematic review of within-person symptom dynamics. *Journal of psychosomatic research.* 147:110527, 2021

33. Fu K, Makovey J, Metcalf B, et al. Sleep Quality and Fatigue Are Associated with Pain Exacerbations of Hip Osteoarthritis: An Internet-based Case-crossover Study. *The Journal of rheumatology.* 46:1524-1530, 2019

34. Fu K, Metcalf B, Bennell KL, et al. The association between psychological factors and pain exacerbations in hip osteoarthritis. *Rheumatology.* 60:1291-1299, 2021

35. Goodin BR, McGuire L, Allshouse M, et al. Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. *J Pain.* 10:180-190, 2009

36. Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. *Pain.* 5:5-18, 1978

37. Haggman-Henrikson B, Bechara C, Pishdari B, Visscher CM, Ekberg E. Impact of Catastrophizing in Patients with Temporomandibular Disorders-A Systematic Review. *J Oral Facial Pain Headache.* 34:379-397, 2020

38. Hanssen MM, Peters ML, Boselie JJ, Meulders A. Can positive affect attenuate (persistent) pain? State of the art and clinical implications. *Current rheumatology reports.* 19:80, 2017

39. Harden RN, Weinland SR, Remble TA, et al. Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians. *J Pain.* 6:364-371, 2005

40. Harris RE, Williams DA, McLean SA, et al. Characterization and consequences of pain variability in individuals with fibromyalgia. *Arthritis and rheumatism.* 52:3670-3674, 2005

41. Hauser W, Jung E, Erbsloh-Moller B, et al. Validation of the Fibromyalgia Survey Questionnaire within a cross-sectional survey. *PloS one.* 7:e37504, 2012

42. Herrero Babiloni A, Brazeau D, Jodoin M, et al. The Impact of Sleep Disturbances on Endogenous Pain Modulation: A Systematic Review and Meta-Analysis. J Pain. 2023. Epub ahead of print Oct 31:S1526-5900(23)00596-5. doi: 10.1016/j.jpain.2023.10.023.

43. Herrero Babiloni A, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. *Journal of neural transmission.* 127:647-660, 2020

44. Herrero Babiloni A, Exposto FG, Peck CM, et al. Temporomandibular disorders cases with high-impact pain are more likely to experience short-term pain fluctuations. *Scientific reports.* 12:1657, 2022

45. Herrero Babiloni A, Martel MO, Lavigne GJ. Sleep disturbances in temporomandibular disorders: a narrative review. *Oral Surgery.* 13:335-348, 2020

46. Hoffman L: Longitudinal analysis: Modeling within-person fluctuation and change, Routledge, 2015.

47. Hox JJ: Multilevel regression and multilevel structural equation modeling. In: The Oxford handbook of quantitative methods: Statistical analysis, Vol. 2. Oxford library of psychology., Oxford University Press, New York, NY, US, 2013, pp. 281-294.

48. Hunt CA, Mun CJ, Owens MA, et al. Sleep, Positive Affect, and Circulating Interleukin-6 in Women With Temporomandibular Joint Disorder. *Psychosom Med.* 84:383-392, 2022

49. Hutchings A, Calloway M, Choy E, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *The Journal of rheumatology.* 34:2291-2300, 2007

50. Jensen MP, Karoly P: Self-report scales and procedures for assessing pain in adults. In: Handbook of pain assessment, 3rd ed., The Guilford Press, New York, NY, US, 2011, pp. 19-44.

51. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain.* 27:117-126, 1986

52. Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain.* 83:157-162, 1999

53. Kent ML, Giordano NA, Rojas W, et al. Multidimensional Perioperative Recovery Trajectories in a Mixed Surgical Cohort: A Longitudinal Cluster Analysis Utilizing National Institutes of Health Patient-Reported Outcome Measurement Information System Measures. *Anesthesia and analgesia.* 134:279-290, 2022

54. Kopala-Sibley DC, Zuroff DC, Russell JJ, Moskowitz DS, Paris J. Understanding heterogeneity in borderline personality disorder: differences in affective reactivity explained by the traits of dependency and self-criticism. *J Abnorm Psychol.* 121:680-691, 2012

55. Kothari DJ, Davis MC, Yeung EW, Tennen HA. Positive affect and pain: mediators of the within-day relation linking sleep quality to activity interference in fibromyalgia. *Pain.* 156:540-546, 2015

56. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 16:606-613, 2001

57. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med.* 64:258-266, 2002

58. Lumley MA, Cohen JL, Borszcz GS, et al. Pain and emotion: a biopsychosocial review of recent research. *J Clin Psychol.* 67:942-968, 2011

59. Maixner W, Greenspan JD, Dubner R, et al. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain.* 12:T75-91, 2011

60. Meints SM, Cortes A, Morais CA, Edwards RR. Racial and ethnic differences in the experience and treatment of noncancer pain. *Pain management.* 9:317-334, 2019

61. Meloto CB, Slade GD, Lichtenwalter RN, et al. Clinical predictors of persistent temporomandibular disorder in people with first-onset temporomandibular disorder: A prospective case-control study. *Journal of the American Dental Association.* 150:572-581 e510, 2019

62. Miller VE, Poole C, Golightly Y, et al. Characteristics Associated With High-Impact Pain in People With Temporomandibular Disorder: A Cross-Sectional Study. *J Pain.* 20:288-300, 2019

63. Moana-Filho EJ, Herrero Babiloni A. Endogenous pain modulation in chronic temporomandibular disorders: Derivation of pain modulation profiles and assessment of its relationship with clinical characteristics. *J Oral Rehabil.* 46:219-232, 2019

64. Moana-Filho EJ, Herrero Babiloni A, Nisley A. Endogenous pain modulation assessed with offset analgesia is not impaired in chronic temporomandibular disorder pain patients. *J Oral Rehabil.* 46:1009-1022, 2019

65. Mun CJ, Suk HW, Davis MC, et al. Investigating intraindividual pain variability: methods, applications, issues, and directions. *Pain.* 160:2415-2429, 2019

66. Mun CJ, Weaver KR, Hunt CA, et al. Pain Expectancy and Positive Affect Mediate the day-to-day Association Between Objectively Measured Sleep and Pain Severity Among Women With Temporomandibular Disorder. *J Pain.* 23:669-679, 2022

67. Nicholson AN, Stone BM, Clarke CH, Ferres HM. Effect of N-desmethyldiazepam (nordiazepam) and a precursor, potassium clorazepate, on sleep in man. *Br J Clin Pharmacol.* 3:429-438, 1976

68. Ohrbach R, Larsson P, List T. The jaw functional limitation scale: development, reliability, and validity of 8-item and 20-item versions. *Journal of orofacial pain.* 22:219-230, 2008

69. Okeson JP. The classification of orofacial pains. *Oral and maxillofacial surgery clinics of North America.* 20:133-144, v, 2008

70. Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. *Psychological medicine.* 8:325-329, 1978

71. Parry E, Dikomitis L, Peat G, Chew-Graham CA. How do people with knee osteoarthritis perceive and manage flares? A qualitative study. *BJGP Open.* 6, 2022

72. Parry E, Ogollah R, Peat G. 'Acute flare-ups' in patients with, or at high risk of, knee osteoarthritis: a daily diary study with case-crossover analysis. *Osteoarthritis Cartilage.* 27:1124-1128, 2019

73. Parry EL, Thomas MJ, Peat G. Defining acute flares in knee osteoarthritis: a systematic review. *BMJ Open.* 8:e019804, 2018

74. Patridge EF, Bardyn TP. Research Electronic Data Capture (REDCap). *J Med Libr Assoc.* 106:142-144, 2018

75. Pulvers K, Hood A. The role of positive traits and pain catastrophizing in pain perception. *Current pain and headache reports.* 17:330, 2013

76. Raphael KG, Janal MN, Sirois DA, et al. Validity of self-reported sleep bruxism among myofascial temporomandibular disorder patients and controls. *J Oral Rehabil.* 42:751-758, 2015

77. Riley JL, 3rd, Robinson ME, Wise EA, Price D. A meta-analytic review of pain perception across the menstrual cycle. *Pain.* 81:225-235, 1999

78. Russell JJ, Moskowitz DS, Zuroff DC, Bleau P, Pinard G, Young SN. Anxiety, emotional security and the interpersonal behavior of individuals with social anxiety disorder. *Psychological medicine.* 41:545-554, 2011

79. Sawynok J. Caffeine and pain. *Pain.* 152:726-729, 2011

80. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications:

recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. *Journal of oral & facial pain and headache.* 28:6-27, 2014

81. Schneider S, Junghaenel DU, Broderick JE, Ono M, May M, Stone AA. II. Indices of Pain Intensity Derived From Ecological Momentary Assessments and Their Relationships With Patient Functioning: An Individual Patient Data Meta-analysis. *J Pain.* 22:371-385, 2021

82. Schneider S, Junghaenel DU, Keefe FJ, Schwartz JE, Stone AA, Broderick JE. Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. *Pain.* 153:813-822, 2012

83. Seebach CL, Kirkhart M, Lating JM, et al. Examining the role of positive and negative affect in recovery from spine surgery. *Pain.* 153:518-525, 2012

84. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain.* 61:277-284, 1995

85. Sherman JJ, LeResche L, Mancl LA, Huggins K, Sage JC, Dworkin SF. Cyclic effects on experimental pain response in women with temporomandibular disorders. *Journal of orofacial pain.* 19:133-143, 2005

86. Singer JD, Willett JB, Willett JB: Applied longitudinal data analysis: Modeling change and event occurrence, Oxford university press, 2003.

87. Smith SB, Maixner DW, Greenspan JD, et al. Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. *J Pain.* 12:T92-101, 2011

88. Smith SM, Dworkin RH, Turk DC, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. *Pain.* 161:2446-2461, 2020

89. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine.* 166:1092-1097, 2006

90. Sturgeon JA, Zautra AJ. Psychological resilience, pain catastrophizing, and positive emotions: perspectives on comprehensive modeling of individual pain adaptation. *Current pain and headache reports.* 17:317, 2013

91. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological assessment.* 7:524-532, 1995

92. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain.* 5:133-137, 2004

93. Tang NK, Goodchild CE, Sanborn AN, Howard J, Salkovskis PM. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep.* 35:675-687A, 2012

94. Taylor SS, Davis MC, Yeung EW, Zautra AJ, Tennen HA. Relations between adaptive and maladaptive pain cognitions and within-day pain exacerbations in individuals with fibromyalgia. *Journal of behavioral medicine.* 40:458-467, 2017

95. Treister R, Honigman L, Lawal OD, Lanier RK, Katz NP. A deeper look at pain variability and its relationship with the placebo response: results from a

randomized, double-blind, placebo-controlled clinical trial of naproxen in osteoarthritis of the knee. *Pain.* 160:1522-1528, 2019

96. Turner JA, Mancl L, Aaron LA. Pain-related catastrophizing: a daily process study. *Pain.* 110:103-111, 2004

97. Vandekerckhove M, Wang YL. Emotion, emotion regulation and sleep: An intimate relationship. *AIMS Neurosci.* 5:1-17, 2018

98. Vilanova LS, Goncalves TM, Meirelles L, Garcia RC. Hormonal fluctuations intensify temporomandibular disorder pain without impairing masticatory function. *Int J Prosthodont.* 28:72-74, 2015

99. Wallace D, Green SB. Analysis of repeated measures designs with linear mixed models. 2002. In D. S. Moskowitz & S. L. Hershberger (Eds.), Modeling intraindividual variability with repeated measures data: Methods and applications (pp. 103–134). Lawrence Erlbaum Associates Publishers.

100. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* 54:1063-1070, 1988

101. Whibley D, AlKandari N, Kristensen K, et al. Sleep and Pain: A Systematic Review of Studies of Mediation. *Clin J Pain.* 35:544-558, 2019

102. Whibley D, Braley TJ, Kratz AL, Murphy SL. Transient Effects of Sleep on Next-Day Pain and Fatigue in Older Adults With Symptomatic Osteoarthritis. *J Pain.* 20:1373-1382, 2019

103. Yoon H, Choi SH. Technologies for sleep monitoring at home: wearables and nearables. *Biomed Eng Lett.* 13:313-327, 2023

104. Zisapel N, Nir T. Determination of the minimal clinically significant difference on a patient visual analog sleep quality scale. *Journal of sleep research.* 12:291-298, 2003

Transition to Chapter 4

In the previous chapter of this thesis, we found that poorer sleep quality and pain catastrophizing contribute to the occurrence of clinically meaningful pain exacerbations over the course of the day among patients with chronic TMD. Interventions have been previously developed to specifically target sleep disturbances (84, 85) and pain catastrophizing (86) for patients with chronic pain, but these interventions are known to have only a modest impact on patients' levels of pain intensity. Prescription drugs have long been used for the reduction of pain, most drugs usually provide modest pain relief and many of them are accompanied by undesirable side effects (87). Calls have thus been made to develop alternative treatment options for the management of chronic pain and its comorbidities.

In this context, the use of repetitive transcranial magnetic stimulation (rTMS) emerges as an appealing option to be explored among TMD patients. rTMS is a safe non-invasive brain neurostimulation technique that can stimulate cortical and subcortical areas (88), and it has been used as a therapeutic tool to manage several conditions, including chronic pain disorders (83, 89, 90). Although rTMS has been researched in other chronic orofacial pain conditions, its use has never been explored in TMD. We thus conducted a randomized, double-blind, sham-controlled study to explore the effects of TMS among patients with TMD. More specifically, we evaluated the immediate and sustained (over 7 days) effects of a single session of active rTMS compared to sham stimulation. Daily diaries were used to evaluate main outcomes, such as patients' daily levels of TMD pain intensity and pain unpleasantness. Diaries were also used to explore the effects of rTMS on secondary outcomes such as sleep quality.

CHAPTER 4. EXPERIMENTAL PAPER 2

Herrero Babiloni A, Provost C, Charlebois-Plante C, De Koninck BP, Apinis-Deshaies A, Lavigne GJ, Martel MO, De Beaumont L. One session of repetitive transcranial magnetic stimulation induces mild and transient analgesic effects among female individuals with painful temporomandibular disorders. J Oral Rehabil. 2024 Jan 15. doi: 10.1111/joor.13655. Epub ahead of print. PMID: 38225806.One session of repetitive transcranial magnetic stimulation (rTMS) induces mild and transient analgesic effects among female individuals with painful temporomandibular disorders.

Alberto HERRERO BABILONI, DDS, MS,[1,2] Catherine PROVOST, PT,[2] Camille CHARLEBOIS-PLANTE, MSc,[2] Beatrice P DE KONINCK, MSc,[2,] Amelie APINIS-DESHAIES, PhD,[2] Gilles J LAVIGNE, DMD, FRDC, PhD,[1,2,7] Marc O MARTEL, PhD,[1,5,6] Louis DE BEAUMONT, PhD[2]

[1] Division of Experimental Medicine, McGill University, Montreal, Quebec, Canada

[2] Sacre-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada

[3] Department of Psychology, University of Montreal, Montreal, Quebec, Canada

[5] Faculty of Dentistry, McGill University, Montreal, QC, Canada.

[6] Department of Anesthesia, McGill University, Montreal, QC, Canada.

[7] Faculty of Dental Medicine, University of Montreal, Montreal, Quebec, Canada

Corresponding: Alberto Herrero Babiloni, DDS, MS; Hôpital du Sacré-Coeur de Montreal, CEAMS, 5400 Boul Gouin O, Montréal, QC H4J 1C5; Tel: 514-338-2222; Fax: 514-238-2531; E-mail: alberto.herrerobabiloni@mail.mcgill.ca

Declarations: The authors have no conflicts of interest to declare. This research was conducted in accordance with the Declaration of Helsinki.

Acknowledgements: This work was financially supported by the Canada Research Chairs (GL) and the Foundation Caroline Durand Research Chair in Acute Traumatology of Université de Montréal (LDB). The first author (AHB) is funded by a Vanier Scholarship.

Abstract

Purpose: Temporomandibular disorders (TMD) are characterized by chronic pain and dysfunction in the jaw joint and masticatory muscles. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential non-invasive treatment for chronic pain; however, its effectiveness in individuals with TMD has not been thoroughly investigated. This study aimed to evaluate the immediate and sustained (over 7 consecutive days) effects of a single session of active rTMS compared to sham stimulation on pain intensity and pain unpleasantness in individuals with TMD.

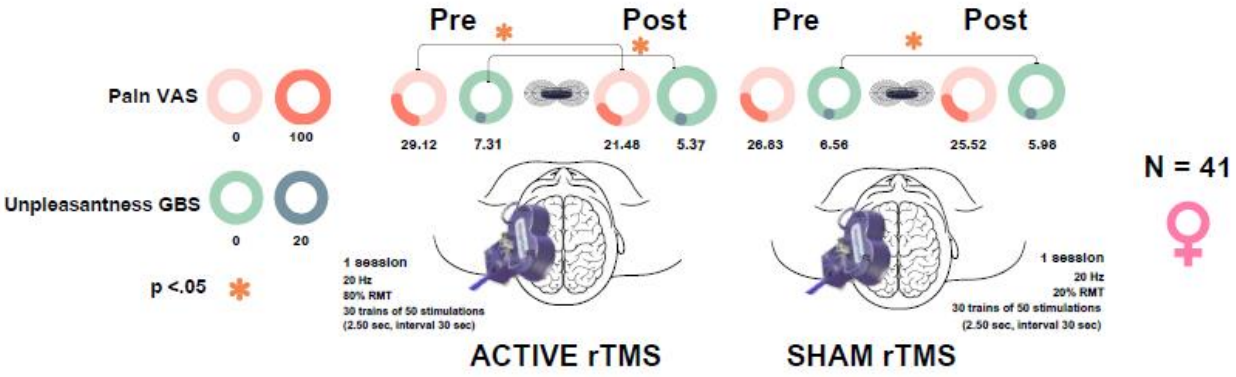
Methods: A randomized, double-blind, sham-controlled trial enrolled 41 female participants with chronic TMD. Pain intensity and pain unpleasantness were assessed immediately pre- and post-intervention, as well as twice daily for 21 days using electronic diaries. Secondary outcomes included pain interference, sleep quality, positive and negative affect, and pain catastrophizing. Adverse effects were monitored. Repeated

measures ANOVA and multilevel modeling regression analyses were employed for data analysis.

Results: Active rTMS demonstrated a significant immediate mild reduction in pain intensity and pain unpleasantness compared to sham stimulation. However, these effects were not sustained over the 7-day post-intervention period. No significant differences were observed between interventions for pain interference, sleep quality, and negative affect. A minority of participants reported minor and transient side effects, including headaches and fatigue.

Conclusion: A single session of active rTMS was safe and led to immediate mild analgesic effects in individuals with TMD compared to sham stimulation. However, no significant differences were observed between interventions over the 7-day post-intervention period. Based on this study, rTMS stimulation appears to be a promising safe approach to be tested in TMD patients with longer stimulation protocols.

Graphical abstract.



1. Introduction

Temporomandibular disorders (TMD) is an umbrella term describing different disorders that affect the temporomandibular joint (TMJ) and/or muscles of mastication [92]. One of the most common TMD symptoms is pain. TMD is the most common chronic orofacial pain condition after odontogenic pain, and the second most commonly occurring musculoskeletal condition, affecting around 12% of the general population and up to 36% of adults aged 20–49 years [60; 81]. Females are usually more affected than males, and although it can present at any age, it is most common in young and middle-aged adults [42; 60]. The diagnosis of TMD is based on clinical examination [92], and when it becomes chronic (i.e., more than 3 or 6 months) [101], it can significantly impact patients' function, quality of life, and psychological well-being [63; 93; 95].

The standard of care for TMD is based on a multidisciplinary approach consisting mainly on self-care measures, cognitive behavioral therapy (CBT), physical therapy, oral appliances and short-term pharmacotherapy, among others [42]. Although these strategies are effective for some patients, the chronification of the disorder due to the neural sensitization process, the frequent comorbidities accompanying it, can make TMD a condition difficult to manage in a significant proportion of patients [42; 104]. Thus, research to develop new avenues to manage chronic TMD is encouraged.

Repetitive transcranial magnetic stimulation (rTMS) is a safe non-invasive neurostimulation technique based on magnetic fields that has the ability to stimulate cortical and subcortical areas [4], and it has been used as a therapeutic tool to manage several conditions, including chronic pain disorders [55]. While the stimulation over different brain areas (e.g., dorsolateral prefrontal cortex, insula) seem to reduce pain

intensity and other related psychological and functional outcomes [11; 25; 55], it appears that the stimulation of the motor cortex (M1) leads to better and more reliable results, being identified as the main target area to manage chronic pain [2; 55]. The mechanisms behind the analgesic effects of rTMS are not fully elucidated, but it is thought that rTMS can enhance pain inhibition by stimulating brain areas involved in pain modulation, such as the periaqueductal grey, insula, anterior, cingulate cortex, or basal ganglia, among others [18; 34]. Different preclinical and clinical studies have also reported the involvement of opioidergic, GABAergic, serotonergic, and glutamatergic pathways, and it seems that rTMS can also modify N-Methyl-D-aspartic acid (NMDA) receptors and induce long-term potentiation and depression-like mechanisms [18; 34]. Additionally, rTMS over M1 can also improve psychological function and sleep in chronic pain populations [35; 44], which can be secondary to pain improvement but also independent due to the potential stimulation of subcortical structures and connection with other structures such as the basal ganglia via the cortico-striato-thalamocortical circuit [29; 35], or the default mode and attention networks [41]. Although a higher number of rTMS sessions produces larger and more durable effects [45; 55], it has been shown that only one session can have short-term analgesic effects that can last 3-5 days after the treatment [1; 3; 6; 71], thus becoming an option to investigate initial effects in a pain disorder before developing more time consuming and costly intervention protocols.

The analgesic use of rTMS has been explored not only in spinally mediated chronic pain disorders, but also in chronic orofacial pain conditions, such as burning mouth syndrome, atypical neuropathic pain, and trigeminal neuralgia [23; 36; 47; 90; 102]. However, to the best of our knowledge, the effects of rTMS among patients with painful

TMD have never been explored. Therefore, we aimed to compare the analgesic and adverse effects of a single session of active rTMS with sham stimulation in patients with chronic TMD. More specifically, we evaluated the a) immediate (within session, pre-intervention vs post-intervention) effects of rTMS on TMD pain intensity. We also examined b) the effects of rTMS on daily levels of TMD pain intensity and pain unpleasantness over 7 consecutive days. Secondary outcomes included daily pain interference, pain catastrophizing, positive/negative affect, and sleep quality.

2. Methods

2.1. Participants

The study procedures were approved by *The Human Subjects Research Ethics Board* of Hôpital du Sacré-Cœur de Montréal within the CIUSSS du Nord-de-l'île-de-Montréal. Participants were recruited from Orofocial pain clinics in Montreal and from the community through advertisements placed on university campuses and social media. All the procedures were performed in a TMS laboratory located at the Hôpital du Sacré-Coeur de Montréal from 2021 to 2022. Written informed consent was obtained from every participant, in accordance with the Declaration of Helsinki.

Participants included in this exploratory study met the following inclusion criteria: a) females (due to the increased prevalence of TMD in females [67; 72; 83]); b) between 18 and 65 years of age; c) diagnosed with painful TMD, defined as chronic myalgia (>6 months) with/without accompanying arthralgia per DC/TMD criteria [92]. Diagnoses were confirmed by a trained dentist/orofacial pain specialist (AHB) during the baseline visit; e) pain present at least 15 days during the last month; f) patients that were on stable

medications (i.e., not reporting a change in the last month) with direct analgesic properties; g) access to internet and electronic devices. Individuals were excluded from the study if they reported a) presence of any dental or orofacial pain disorder not meeting the above criteria; b) if they were on non-stable pharmacological treatment (e.g., reporting a change in medication in the last month), if they; c) reported having alcohol or substance use problems; d) reported any lifetime history of major neurological or psychiatric disorders; e) presented any TMS contraindication [40]. All participants were screened for TMS tolerability and safety using the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) questionnaire [43; 86].

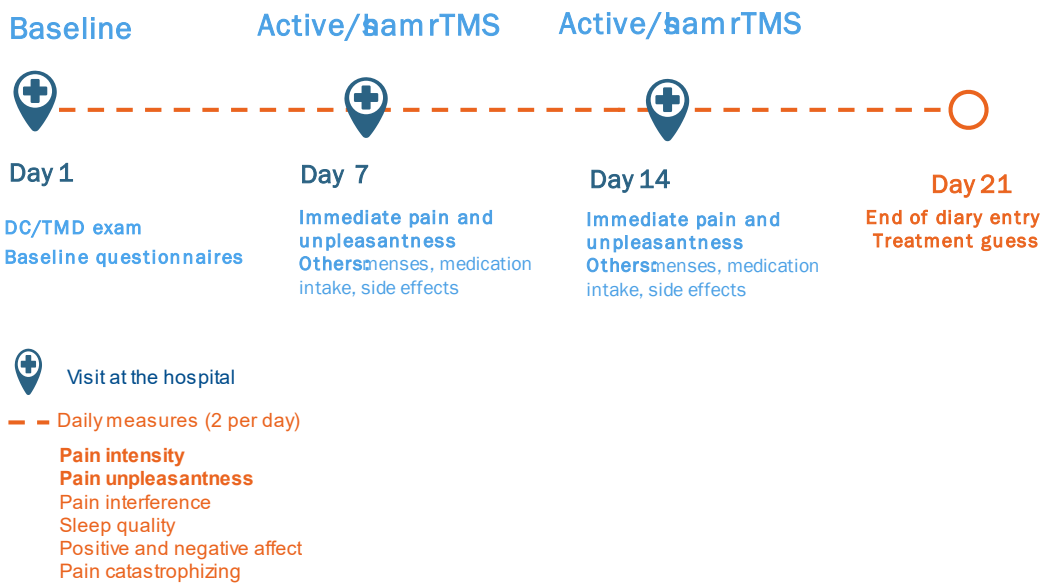
Participants received an economical compensation and transport for their involvement in the study.

2.2. Experimental design

A randomized, crossover, double-blind design was used. After telephonic screening comprising orofacial pain and TMS questionnaires verbally administered by a phone interviewer to assess eligibility criteria, participants took part into three laboratory assessment visits at the hospital. After randomization, each participant took part in a baseline assessment visit (Visit 1). Upon confirmation of the diagnosis by an orofacial specialist (AHB) who was blinded to study arm allocation (TMS active/sham), participants completed several demographics, clinical and psychosocial questionnaires (see section 2.3). During Visit 1, participants were also asked to complete electronic diaries up until study completion (i.e., for 21 consecutive days). Participants were then asked to come to the hospital for a second visit (i.e., Visit 2) to either receive active or sham rTMS (see treatment randomization, section 2.5). Finally, participants came to the

hospital for a third visit (i.e., Visit 3), where they received the alternate treatment condition (i.e., active if in visit 2 they received sham, or vice versa). Hospital visits were 7 days apart, mainly to avoid any potential treatment carry-over effects [58; 89]. Participants were asked to avoid (when possible) using analgesic medications the day of the visit and they were allowed to resume usual TMD treatments (i.e., mouthguards or physical therapy) during the study period. Analgesic and other TMD treatments were assessed via self-report during the visits. A schematic representation of the study design and timeline can be observed in Figure 3.1.

Figure 4.1. Study timeline.



2.3. Baseline hospital visit

During the baseline visit, participants filled out different questionnaires assessing sociodemographic (i.e., age, education, marital status, ethnicity, employment),

anthropometric (i.e., height, weight), and orofacial pain characteristics (i.e., pain location, pain duration, pain intensity, pain unpleasantness, pain interference). These questionnaires were taken from the Axis I of the DC/TMD Questionnaire package [92]. Pain intensity was rated based on an average from the last six months prior to the visit as well as at the precise moment of each visit. The Gracely Box Scale was used to assess pain unpleasantness [30], and the Fibromyalgia Survey Questionnaire (FSQ)[33] was used to assess the presence of widespread pain. Finally, a health history questionnaire was used to assess any clinical/medical comorbidities, such as other pain comorbidities (i.e., migraine headache, tension-type headache, chronic fatigue syndrome, chronic pelvic pain, chronic low-back pain, vulvodynia, vulvar vestibulitis syndrome, irritable bowel syndrome, interstitial cystitis, neuropathic pain, osteoarthritis, rheumatoid arthritis, whiplash), sleep comorbidities (i.e., obstructive sleep apnea, restless leg syndrome), and other clinical/medical comorbidities such as premenstrual dysphoric disorder, tinnitus, and post-traumatic stress disorder)[65; 67].

For the assessment of psychosocial variables, instruments from the DC/TMD Axis II were used.[92] These included the Jaw Function Limitation Scale 20-items (JFLS-20;[74]) for jaw limitation, the Patient Health Questionnaire-9 (PHQ-9;[51]) for depressive symptoms, the Generalized Anxiety Disorder-7 (GAD-7; [96]) for Generalized Anxiety Disorder symptoms, and the Patient Health Questionnaire-15 (PHQ-15;[52]) for somatization. In addition, the Perceived Stress Scale (PSS; [12]) for perceived levels of stress, the Pittsburgh Sleep Quality Index (PSQI; [9]) for sleep quality, the Pain Catastrophizing Scale (PCS; [97]) for pain catastrophizing, and the Positive and Negative Affect Scale (PANAS; [108]) for positive and negative affect were used.

Finally, prior to each testing session, besides pain intensity and pain unpleasantness, participants reported on medication intake, caffeine intake, and menstrual cycle, because these variables may impact the study main outcomes [67]. When applicable, the menstrual cycle phase was categorized based on previous studies into the following categories: menstrual, follicular, periovulatory, luteal and premenstrual.[85] Caffeine intake in the last 24 h was divided into three categories: low (< 100 mg/day), moderate (101–200 mg/day) or high (> 201 mg/day).[91] Participants were asked to report all the prescription drugs currently taken and quantified using the Medication Quantification Scale (MQS)[32].

At the end of the baseline visit, participants were instructed on how to use RedCap,[77] an electronic data capture software that can be used on any computer, smartphone or tablet, in order to complete electronic diaries.

2.4. Daily diaries

Participants completed diaries, twice a day, for 21 consecutive days. Diaries were filled in the morning and in the evening, at random hours, within pre-specified time blocks (i.e., from 6:00am to 12:00pm; and from 6:00pm to 12:00am). Diaries were date- and time-stamped to ensure validity and compliance with the diary protocol. Diary measures included:

2.4.1 Daily pain-related measures: participants were asked to rate the average level of pain intensity since their last diary entry using a visual analogue scale (VAS) that ranged between 0 (no pain) to 100 (extreme pain). This item was an adaptation of the standard VAS item used in the BPI assessing pain intensity.[98] Participants also

rated their pain interference with daily activities using a VAS scale ranging from 0 (no interference) and 100 (extreme interference)[98]. Finally, patients were asked to provide reports of pain unpleasantness using a diary adaptation of the Gracely Box Score.[30]

2.4.2. Daily sleep quality: sleep quality was assessed only in the morning entry, using a VAS that ranged from 0 (worst possible sleep quality) to 100 (best possible sleep quality). VAS to assess sleep is known to be a reliable method and is commonly used due to its simplicity in a variety of research and clinical settings[73; 75; 111].

2.4.3. Daily pain catastrophizing: pain catastrophizing was assessed using a diary version of the Pain Catastrophizing Scale (PCS).[16; 24] Patients were asked to report on different thoughts and emotions related to helplessness, rumination, and magnification associated with pain. Participants were asked to provide reports of catastrophizing since their last diary entry, using a scale ranging from 0 (very slightly or not at all) to 4 (extremely). Studies have supported the reliability and the validity of the daily Pain Catastrophizing Scale as a measure of daily pain catastrophizing.[16]

2.4.4. Positive and negative affect measures: participants were asked to report the extent to which they experienced five positive emotions (i.e., enthusiastic, excited, alert, determined, and inspired) and five negative emotions (i.e., afraid, upset, nervous, scared, distressed) since their last diary entry on a scale ranging from 1 (not at all) to 5 (extremely). This measure is a diary adaptation of the Positive and Negative Affect Scale (PANAS)[108], which reliability and validity has been supported in several chronic pain studies.[7; 17; 22] As in other studies, items were averaged to create a measure of positive affect (PA) and negative affect (NA) score [7; 17; 22; 24]

2.5. Randomization, Concealment, and Blinding

The order of the interventions (active rTMS or sham at first or second visit) were randomized and counterbalanced using a computer-based random sequence generation program (https://www.random.org/lists/). The allocation procedure was conducted by an external member of the research group and consisted of 42 sealed, opaque and numbered envelopes that contained information about intervention order in accordance with the randomization. When a participant was recruited, the research assistants involved in rTMS administration opened the envelope. This research assistant was the only person knowing the treatment order. The rTMS assistant adjusted stimulus parameters and coil used (active or sham coil) while the rTMS operator and participant were outside the room. Both active and sham coils were identical in aspect and emitted similar sounds. In that way, participants and TMS operators were blinded to the order of intervention.

2.6. Treatment

At the first visit (V1), optimal stimulation site over the left motor cortex M1 of the hand was determined through exploration near the C3 cortical electrode site as per the 10/20 International system of electrode placement [46]. The optimal stimulation position was determined based on the stimulation site that elicited the largest and most consistent motor evoked potentials (MEPs), which were recorded from the contralateral first dorsal interosseous muscle of the hand. The “hot-spot” was marked on a swim cap with a dermatograph pencil to allow accurate repositioning of the coil between interventions and throughout the whole experiment. This site was recorded using a 3D tracking system (Northern Digital Instruments, Waterloo, Canada) to ensure consistent

coil positioning. The angle of inclination of the coil was determined using a level and the distance between the bathing cap and the nasion and between the bathing cap and each earlobe. The resting motor threshold (rMT) was defined as the lowest stimulator output needed to induce a MEP of >50 μV peak-to-peak amplitude in at least 6/10 consecutive trials [87]. Once the rMT was determined, the marked cap was used for the location of M1 in the subsequent visits, similar to other studies [82]. Thus, the resting motor threshold was used to individually adjust the stimulation in each participant. During the stimulation visits, after M1 location, the experimenter in charge of the rTMS administration and the participant left the rTMS room while waiting for the TMS assistant to set the stimulation modalities and coil used, as previously described. Then, the cap and previous angle measurements were used to position the coil and the participant in an adequate position for an optimal stimulation.

All participants sat in a comfortable reclining chair remaining as relaxed as possible, protected by earplugs during both stimulation sessions. Following previous studies [1; 2; 39; 59], we elected to stimulate the contralateral M1 of the hand representation to the most painful face side, as studies have shown that stimulating these area rather than the face/masseter representation of M1 may lead towards more consistent and reproducible results [1]. If TMD pain was bilateral, left M1 was stimulated, in a similar manner than fibromyalgia studies [55].

2.6.1. Active and sham conditions

The rTMS protocol included 30 consecutive trains of 50 stimuli delivered at 20 Hz at an intensity of 80% RMT. Trains of 50 stimuli lasted 2.5 seconds and the intertrain interval was 30 seconds. This methodology is consistent with previous clinical studies

(20, 21). Total treatment duration including localization was ~20 minutes for a total of 1500 stimuli, using the Magstim Double 70mm AirFilm R Coil (Magstim, Whitland, Wales, UK) on a Super Rapid^2 Plus Magstim rTMS device ((Magstim, Whitland, Wales, UK)). The TMS coil was positioned tangentially to the head at a 45◦ angle to induce a posterior-anterior current flow [45]. The coil was centered and fixed directly over the stimulus site using a tripod so that the coil handle pointed to the back. Sham treatment was applied using the same procedure with the Magstim AirFilm R SHAM coil (Magstim, Whitland, Wales, UK) entering the same TMS parameters as in the active treatment. For a graphical depiction of TMS administration, including coil positioning and orientation, and experimental set up please see [45; 59]

2.7. Safety and blinding success assessment

The occurrence of any adverse event was collected over the entire study period using qualitative open-ended questions. At the end of the study, participants were also asked to guess the order of treatment (i.e., active during the first session and sham during the second, or vice versa).

As we considered the study as exploratory given the lack of previous studies using rTMS with TMD participants, we did not plan adjustment for multiple comparisons.

2.8. Data reduction and analyses

Data analysis was performed using IBM-SPSS v.25 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as means and standard deviations for continuous variables and frequencies/percentages for categorical variables. Baseline variables were

collected primarily for characterization purposes and rather than as potential confounding factors considering the exploratory nature of this study and modest sample size. Additionally, the cross-over design provides a way to control for between-person differences and to reduce the impact of potential confounding factors. In cross-over designs baseline measures are not necessary confounders because each participant acts as their own baseline, reducing error from between-participant variability [109]. All study analyses were conducted with an α level (i.e., p value) for significance set to .05.

For the first objective (i.e., evaluate the immediate effects of rTMS vs sham), the primary outcomes included mean changes in pain intensity and pain unpleasantness immediately before and after treatment, during the same day (i.e., (testing/treatment) session. In order to assess our first objective (immediate effects of rTMS vs sham), two-way (type of intervention x time interaction). Repeated measure analyses of variance (ANOVAs) were used. In this ANOVA, the type of intervention (active or sham) and time (pre or post) were the independent variables, and the dependent variables were pain intensity and pain unpleasantness, respectively. Post-hoc pairwise comparisons were done using the Bonferroni test.

In order to assess our second objective (i.e., effects of rTMS on daily TMD pain intensity and pain interference), multilevel modeling (MLM) analyses were used given the hierarchical (i.e., nested) data structure of this study, in which repeated daily measures (Level 1 units) were nested within days (Level 2 units), which were nested within participants (Level 3 units). In the first two multilevel regression analyses, the independent variables were type of treatment (no intervention, active rTMS, sham), and daily pain intensity and daily pain unpleasantness were used as dependent (i.e., outcome) variables

in separate analyses. Multilevel regression analyses were then used to examine rTMS effects on secondary outcomes such as daily sleep quality, daily pain catastrophizing, and daily negative/positive affect using identical multilevel regression analysis models. For all the daily variables described above, participants' ratings provided in the AM and PM were aggregated at the day-level (i.e., Level 2).

All of the multilevel models followed a sequential procedure, [48; 88; 106] which first involved specifying a random intercept and fixed effects for independent variables (IVs). Person-level (i.e., Level 3) variables such as participants' demographic characteristics (e.g., age, ethnicity, education, body mass index, marital status, employment status), pain condition characteristics (e.g., number of pain locations, comorbidity index, etc.), menstrual cycle, medication and caffeine intake were all examined as potential effect modifiers. All multilevel models described above were carried out using maximum-likelihood (ML) estimation and included a first-order autoregressive variance covariance matrix (AR1) to account for the autocorrelation between repeated measures. As recommended, all independent variables were centered before being entered in multilevel models [20]. With the ability of MLM to account for randomly missing Level 1 data [38; 94], 41 participants were included in multilevel analyses without the need for any data imputation procedures. Across all assessment time points, compliance with the diary protocol was very high, with an overall completion rate of 96.2%. When combining the four main Level 1 variables that were assessed in this study (i.e., pain intensity, negative affect, positive affect, and catastrophizing) and Level 2 (i.e., sleep), there was a total of 11,402 possible data points, and10,996 data points (96.2%) were

observed. Analyses indicated that participants with and without missing data did not differ significantly on any of the main study variables (all p's > .05).

In addition, paired T-Tests were conducted to determine if participants' pain intensity and unpleasantness at baseline differed across the two treatment order conditions (i.e., active rTMS at V1 and sham rTMS at V2, or vice versa), in order to assess if the randomization was successful.

Regarding sample size calculation, an a priori power analysis conducted using G*Power 3.1.9.6 software, revealed that using the proposed analysis and cross-over design, a total sample size of 36 participants would suffice to detect a mild effect size (np2 = 0.2) with a power of 0.80 at a given alpha of 0.05 [1; 36].

3. Results

We screened 55 participants from which 42 complied with eligibility criteria and were enrolled on the study. One participant withdrew before visit 2 due to anxiety related to the intervention. Therefore, the data presented corresponds to a total of 41 female participants (age: 26.63 ± 8.57). Participants' baseline demographic, pain, and psychosocial characteristics are shown in Table 4.1. Seven participants took antidepressant medications in a stable basis.

Table 4.1. Descriptive characteristics at baseline

	Mean (± SD) or frequency (%)
Demographic variables	
Age (y)	26.63 ± 8.57
BMI (kg/m2)	22.34 ± 2.94
Marital status (single, %)	29 (70.7%)
Ethnicity (white, %)	27 (63.4%)
Education (University bachelor or above, %)	26 (64.4%)
Employment (students, %)	28 (66.7%)
Pain characteristic variables	
Average pain intensity (0-100)	50.49 ± 11.17
Concomitant TMJ arthralgia	26 (63.4%)
Concomitant HA attributed to TMD	26 (63.4%)
GBS pain unpleasantness (0-20)	7.21± 2.90
BPI pain interference (0-100)	19.87 ± 20.05
Pain duration (months)	79.0±117.93
Comorbidity index (0-18)	1.05 ± 1.32
FSQ (0-31)	10.98 ± 4.30
GCPS grade 0	16 (39.0%)
GCPS grade I	20 (48.8%)
GCPS grade IIa	3 (7.3%)
GCPS grade IIb	2 (4.9%)
Psychosocial variables	
PANAS-NA (10-50)	11.33 ± 3.80
PANAS-PA (10-50)	16.03 ± 3.64
JFLS-20 (0-10)	1.85 ± 1.07
PHQ-9 (0-27)	6.04 ± 4.75
GAD-7 (0-21)	6.05 ± 4.47
PHQ-15 (0-30)	10.02 ± 6.68
PSS (0-40)	16.10 ± 6.61
PSQI (0-21)	5.92 ± 3.03
TMS variables	
Resting motor threshold	56.98 ± 12.24
Other potential confounders	
Menstrual cycle phase	
No menses	7 (17.1%)
Menstrual	9 (22.0%)
Follicular	5 (12.2%)
Periovulatory	5 (12.2%)
Luteal	7 (17.1%)
Premenstrual	8 (19.5%)

Caffeine intake last 24 h	
None	10 (24.4%)
Low	11 (26.8%)
Moderate	15 (36.6%)
High	5 (12.2%)
MQS score	2.37 ± 4.26

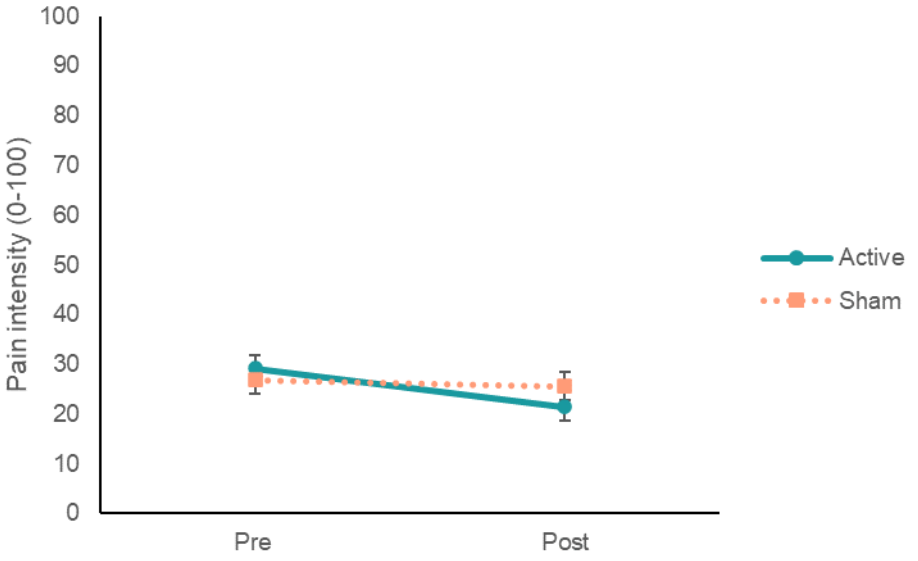
Notes: BMI: body mass index; BPI: brief pain inventory; FSQ: Fibromyalgia survey questionnaire; GAD: general anxiety disorder; GBS: Gracely box scale; GCPS: graded chronic pain scale; HA: headache; JFLS: jaw functional limitation scale PANAS: positive and negative affect scale; MQS: medication quantification Scale; PHQ: patient health questionnaire; PSQI; Pittsburgh sleep quality index; PSS: perceived stress scale; TMJ: temporomandibular joint; TMD: temporomandibular disorders; TMS: transcranial magnetic stimulation

Notes: Medications used were: Fluoxetine, Citalopram (2), Escitalopram (2), Wellbutrin (2), Levothyroxine, and Formoterol.

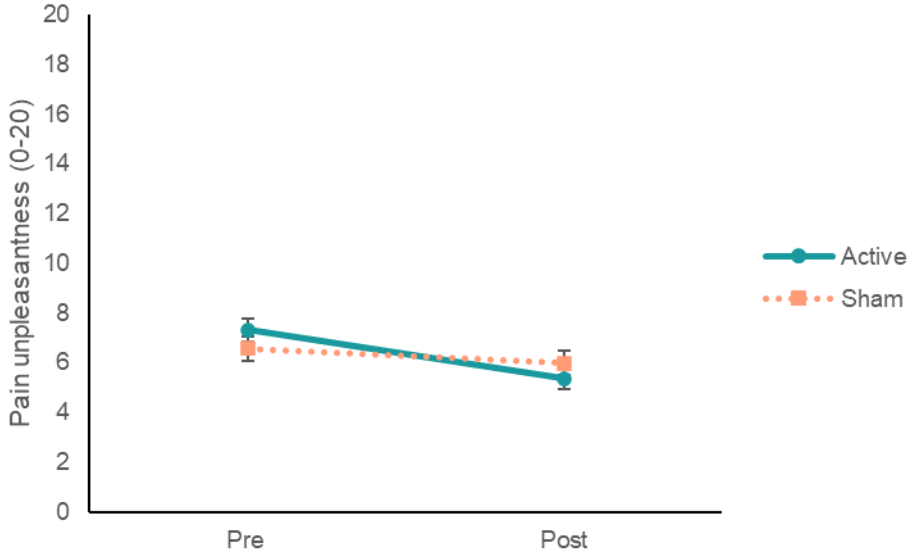
3.1. *Immediate effects of rTMS on pain intensity and pain unpleasantness*

Regarding our first objective, results from the 2 x 2 ANOVA showed a significant interaction (type of treatment X time) effect on TMD pain intensity, $F(1, 40) = 6.054$, $p = 0.018$ (see Figure 4.2).

Figure 4.2. Immediate effects of active and sham rTMS on pain intensity (A) and pain unpleasantness (B).



A)



B)

Legend: Immediate effects of active and sham rTMS on pain intensity (A) and pain unpleasantness (B). VAS, visual analogue scale. GBS, Gracely Box scale. rTMS, repetitive transcranial magnetic stimulation.

Results indicated a significant mild immediate decrease in TMD pain intensity from pre-to-post treatment, but the magnitude of the decrease in TMD pain intensity was only significant in the active rTMS condition (m = 29.12 vs 21.48; $p < 0.001$), not in the sham condition (m = 26.83 vs 25.52; $p = 0.522$). Results also indicated a significant interaction (type of treatment X time) effect on TMD pain unpleasantness $F(1, 40) = 12.881$, $p < 0.001$. Results indicated a significant mild decrease in TMD pain unpleasantness from pre-to-post treatment (i.e., from pre-to-post treatment). While the magnitude of the decrease in TMD pain unpleasantness was significant in both active rTMS condition (m = 7.31 vs 5.37; $p < 0.001$), and sham condition (m = 6.56 vs 5.98; $p = 0.011$), this was more pronounced in the active condition (Figure 4.2).

3.2. Effects of rTMS on daily pain intensity and pain interference

Results from MLM indicated a significant interaction effect between treatment type and time on pain intensity and pain unpleasantness (both p's < 0.001).

Post-hoc contrast analyses indicated that mean TMD pain intensity across the 7-day period (i.e., main effect of time) was significant when comparing active rTMS and the baseline (no treatment) condition (m = 31.50 vs. 28.10; $p < 0.001$) and when comparing sham and baseline (m = 31.50 vs. 27.65; $p < 0.001$). However, post-hoc analyses indicated that the decreases in mean pain intensity over the 7-day period between the active rTMS and sham conditions were not significantly different (m = 28.10 vs. 27.65; $p = 0.468$).

In other words, lower levels of pain intensity and pain unpleasantness were observed in both interventions (active and sham), but the difference between them was not statistically significant (see Table 4.2).

Table 4.2. Multilevel modeling results assessing the effects of active rTMS and sham rTMS on primary and secondary outcomes over a 7-day period, expressed as means and standard errors of mean.

				p-value		
	No intervention	Active rTMS	SHAM rTMS	No Intervention vs Active	No Intervention vs Sham	Active vs Sham
Pain intensity (0-100)	31.50 (2.41)	28.10 (2.41)	27.65 (2.41)	**<0.001**	**<0.001**	0.468
Pain unpleasantness (0-20)	6.23 (0.39)	5.63 (0.39)	5.62 (0.39)	**<0.001**	**<0.001**	0.945
Pain interference (0-100)	19.68 (2.66)	17.34 (2.66)	16. 50 (2.66)	**<0.001**	**<0.001**	0.252
Sleep quality (0-100)	41.72 (2.09)	36.31 (2.09)	34.79 (2.09)	**<0.001**	**<0.001**	0.186
Negative affect (5-25)	7.96 (0.45)	7.82 (0.45)	7.68 (0.45)	0.190	**0.004**	0.150
Positive affect (5-25)	11.75 (0.56)	11.79 (0.56)	12.09 (0.56)	0.799	**0.005**	**0.012**
Pain catastrophizing (0-12)	1.48 (0.27)	1.22 (0.27)	1.05 (0.27)	**<0.001**	**<0.001**	**0.002**

Notes: rTMS: repetitive transcranial magnetic stimulation

3.3. Effects on secondary outcomes

Similar results were obtained with secondary outcomes such as pain interference and sleep quality, as a significant difference was observed between no intervention and both interventions, but no significant difference was observed between active and sham in any of those models (Table 4.2). However, negative and positive affect did not change with the active intervention when compared to no intervention (m = 7.89 vs. 7.82; p =

0.190 and m = 11.75 vs 11.79; p = 0.799, respectively), but they slightly improved under sham compared to no intervention (m = 7.89 vs. 7.68; p = 0.004 and m = 11.75 vs 12.09; p = 0.005, respectively). Additionally, positive affect (m = 11.79 vs 12.09; p = 0.012) and pain catastrophizing (m = 1.22 vs 1.05; p = 0.002) improved slightly more with the sham intervention than with the active.

3.4. Adverse effects

One participant withdrew from the study after completing the baseline visit and 7 days of baseline daily diaries due to anxiety prior to the interventional visits. Three participants reported mild headaches only after the active rTMS intervention, two participants only after the sham intervention, and three after both active and sham. In all cases, headaches resolved within a few hours after the interventions without the need of using any of medication. Moreover, one participant reported generalized transient fatigue immediately after both active and sham interventions. No other adverse effects were reported.

3.5. Participant blinding & randomization

Our results indicated that 60.1% of the participants (25 out of 41) guessed the order of treatment correctly, hence being considered as an acceptable blinding success[5]. Participants assigned to the two different treatment order options (i.e., active rTMS at V1 and sham rTMS at V2, or vice versa) did not differ significantly on pain intensity (39.01 ± 13.40 vs 37.98 ± 13.68; p = 0.89) and pain unpleasantness (5.81 ± 3.53 vs 7.00 ± 3.66; p = 0.30) at baseline.

4. Discussion

Results of this study revealed that one session of active rTMS induces significantly greater, yet mild, immediate analgesic effects (i.e., reductions in pain intensity and pain unpleasantness) relative to sham among participants with TMD. However, immediate rTMS effects on the latter pain measures were not sustained during the 7 consecutive days post-treatment, at which time pain relief was comparable to sham stimulation. Although speculative, this might be possibly due to the use of only one session of rTMS [55]. Side effects were minor and lasted less than a day. These results highlight the potential analgesic effects of rTMS among individuals with TMD.

Painful chronic TMD is heterogeneous and its exact pathophysiology is unclear, yet several mechanisms have been suggested to explain how biological, psychological and social factors can combine to predispose, perpetuate, or initiate TMD [42]. Similarly to other disorders such as fibromyalgia, from which TMD shares several characteristics [70], some studies have pointed towards alleged neurologic, endocrine and inflammatory pathways, including autonomic dysfunction, chronic inflammation, and altered endogenous pain modulation, as pain perception and processing may be impaired in these individuals[42; 68]. While earlier studies indicated relatively normal cortical excitability in a small sample of TMD participants [15], a recent study found that in patients with persistent idiopathic facial pain (which could include TMD), significant alterations in cortical neurophysiological parameters of cortical excitability, namely defective intracortical GABAergic interneuron activity in the intermediate layers of the M1, were present when compared to healthy individuals [26]. Different studies have also pointed toward impaired cortical excitability and plasticity in myofascial pain syndromes [99; 100].

Therefore, the potential application of rTMS, which can be used to modify cortical excitability and potentially “restore” cortical activity among TMD individuals, could potentially contribute to explaining short-term (i.e., immediate) reductions in TMD pain intensity and pain unpleasantness following the use of rTMS.

Depending on the parameters and areas of stimulation, rTMS can exert different effects (i.e., excitatory or inhibitory) and modulate different pathways, thus having the capacity of being used for different purposes. Regarding chronic pain treatment including orofacial pain, although neural excitatory protocols (i.e., high frequency) over brain areas such as the DLPFC have shown analgesic potential in different pain disorders, independent and comparative research has shown that rTMS applied over the M1 have generated better results in producing analgesic effects (mostly studied in neuropathic pain) [2; 36; 55], and that somatotopic effects are likely not to be obtained by stimulating specific M1 areas but rather by “recruiting” more brain networks known to be involved in analgesia [1]. In light of findings from previous work [1; 36], we elected a high frequency protocol over M1 of the hand rather than the face to induce analgesic effects. Results from the present study revealed that such protocol had immediate analgesic effects by reducing pain intensity and pain unpleasantness, suggesting that rTMS could impact different components (sensory and affective) of the pain experience [64; 80]. These findings are consistent with the literature, as besides pain intensity, rTMS over M1 has shown to reduce affective and emotional dimensions of pain in other pain conditions [69; 78], perhaps due to the indirect stimulation of insular and cingulate cortex [69; 76; 78] . Importantly, we were not able to infer analgesic mechanisms due to the design of this study. The inclusion of cortical excitability measures and imaging methods such as

functional magnetic resonance imaging (fMRI) before and after treatment to assess more objective outcomes, could have given more insight into rTMS analgesic pathways and would be extremely valuable in future trials[66; 105]. Furthermore, such outcomes can also be used to personalize and improve rTMS treatment, as it has been shown in patients with depression [10; 27].

Given the heterogeneity of the disorder and associated mechanisms, future research seeking to stimulate over different cortical areas could also be useful to target more specific phenotypes. For instance, it has been shown that excitatory rTMS stimulation over the face M1 can induce durable results among patients with neuropathic orofacial pain [90], and that inhibitory rTMS stimulation over S1 can successfully alter proprioceptive facial perceptions [49; 50]. In addition, female gender, shorter duration of pain and lower anxiety have shown a certain favorable profile on analgesic facial pain rTMS response [90]. Whereas research identifying predictors of rTMS response in other conditions such as depression is extensive [14; 28; 31; 37; 53; 54], less is known about chronic pain. Therefore, further research with larger samples, different protocols and more specific phenotypic mechanisms are warranted in this population.

Importantly, most of the studies showing consistent and durable analgesic effects utilized a higher number of sessions, as changes in brain function are thought to occur gradually over time and may require multiple sessions to produce significant and lasting effects [55]. For example, a recent randomized multicentre sham-controlled trial using 15 sessions over 22 weeks found that active rTMS was superior to sham in several pain outcomes among neuropathic pain patients for almost 7 months [2], while a study using 10 sessions of rTMS among patients with upper limb fracture observed better pain and

functional outcomes three months following the stimulation (Jodoin et al. 2023 paper under review). Nonetheless, one session rTMS protocols can be beneficial to assess the feasibility and initial effects of this technique on a specific condition that has not been studied before, and thus becoming of value to show initial evidence for the justification of larger and costly high-quality RCTs. Results from our study showed that although active rTMS produced immediate pain reduction in comparison to sham, which was close to the 20-30% cutoff that was established for determining clinically significant changes in pain intensity among chronic pain populations [19; 21] (i.e., 26.3% reduction from before treatment), adding extra treatment sessions could have been justified to explore the potential of rTMS in TMD patients.

Regarding secondary outcomes (pain interference, sleep, positive and negative affect, and catastrophizing), an improvement from baseline was observed with both interventions (active and sham), but a difference across interventions (i.e., active rTMS, sham) was not observed. In that way, one session of active rTMS did not seem to show superiority to sham on those outcomes. Considering that a single session of rTMS has the potential to alter cortical pathways, it is plausible that these outcomes might be influenced, although the likelihood of such influence is relatively low. Indeed, most of the earlier one-session rTMS studies showing analgesic benefits did not measure such secondary outcomes [56; 57; 79], likely because only transient effects on pain were anticipated and the influence of other psychosocial variables was not expected. Nonetheless, as demonstrated previously [2; 35; 61; 76; 110], it is plausible that conducting more rTMS sessions may be able to improve these outcomes directly or indirectly (through pain relief), which becomes critical within a biopsychosocial context.

Importantly, we observed that the sham intervention improved more positive affect and reduced more pain catastrophizing than active rTMS (Table 4.2), highlighting the important non-specific or placebo effect associated to rTMS interventions that is widely reported in the literature [8; 62; 84]. Different placebo responder phenotypes have been identified among chronic pain conditions and TMD individuals [13; 103; 107]. For example, a recent study among TMD individuals and healthy controls showed that those reporting more emotional distress and maladaptive cognitive appraisals of pain, such as pain catastrophizing, may benefit less from certain placebo effects [107]. Therefore, it is possible that as our sample did not have high levels of emotional distress and pain catastrophizing, analgesic non-specific effects could have been greater. As it has already been suggested, addressing the phenomenon of differential placebo effects of sham rTMS interventions compared with other forms of placebo in prospective studies is highly relevant to further understand and enhance rTMS clinical efficacy [62].

This study presents some limitations. First, the use of a neuronavigational system would have been ideal to always ensure stimulation accuracy. As previously mentioned, another limitation was the use of a single session due to the exploratory nature of our study. Future studies aiming to assess efficacy and safety rather than initial effects should use a higher number of sessions (e.g., 5 sessions), different protocols such as theta burst stimulation, and areas of stimulation to potentially optimize rTMS treatment among painful TMD individuals. In addition, we included only females, the majority of young age, and most of our sample presented mild to moderate levels of pain, which limit the generalization of the study findings. More studies including participants of different ages, gender and ethnicity with a wider range of pain intensity or disability are encouraged.

Finally, despite using a double-blind study design, it would have been worthwhile to test success of blinding among main operators as well.

5. Conclusions

This study demonstrates that a single session of active rTMS can lead to significant, yet mild, reductions in pain intensity and pain unpleasantness among individuals with TMD. The immediate analgesic effects observed with active rTMS highlight the potential utility of TMS as a non-invasive treatment option for TMD-related pain. However, when considering improvements from baseline and comparing active rTMS to sham stimulation over a week-long period, no significant difference was found, suggesting that the analgesic effects of a single session may not be sustained in the long term.

The minor and transient side effects reported in a minority of TMD patients from this study, such as headache and fatigue, further support the safety and tolerability of rTMS as a therapeutic intervention for TMD.

Given the heterogeneity of TMD and its elusive underlying mechanisms, further research is warranted to explore the optimal parameters, treatment protocols, and brain areas to be targeted using rTMS in this population. Future studies with larger sample sizes, diverse phenotypic characteristics, and multiple treatment sessions will contribute to understand if the analgesic effects of rTMS is a sustainable avenue for TMD patients or for specific subgroups with specific phenotype clinical characteristic or to a given endotype, mechanism responders.

REFERENCES

[1] Andre-Obadia N, Magnin M, Simon E, Garcia-Larrea L. Somatotopic effects of rTMS in neuropathic pain? A comparison between stimulation over hand and face motor areas. European journal of pain 2017.

[2] Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, Fermanian C, Nizard J, Peyron R, Lefaucheur JP, Bouhassira D. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain : a journal of neurology 2021;144(11):3328-3339.

[3] Ayache SS, Ahdab R, Chalah MA, Farhat WH, Mylius V, Goujon C, Sorel M, Lefaucheur JP. Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain. European journal of pain 2016;20(9):1413-1422.

[4] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1(8437):1106-1107.

[5] Berlim MT, Broadbent HJ, Van den Eynde F. Blinding integrity in randomized sham-controlled trials of repetitive transcranial magnetic stimulation for major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2013;16(5):1173-1181.

[6] Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, Nahas Z, Byrne KT, Morgan K, George MS. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain stimulation 2008;1(2):122-127.

[7] Bruneau A, Frimerman L, Verner M, Sirois A, Fournier C, Scott K, Perez J, Shir Y, Martel MO. Day-to-day opioid withdrawal symptoms, psychological distress, and

opioid craving in patients with chronic pain prescribed opioid therapy. Drug and alcohol dependence 2021;225:108787.

[8] Burke MJ, Kaptchuk TJ, Pascual-Leone A. Challenges of differential placebo effects in contemporary medicine: The example of brain stimulation. Ann Neurol 2019;85(1):12-20.

[9] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research 1989;28(2):193-213.

[10] Cash RFH, Cocchi L, Lv J, Fitzgerald PB, Zalesky A. Functional Magnetic Resonance Imaging-Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. JAMA psychiatry 2021;78(3):337-339.

[11] Ciampi de Andrade D, Galhardoni R, Pinto LF, Lancelotti R, Rosi J, Jr., Marcolin MA, Teixeira MJ. Into the island: a new technique of non-invasive cortical stimulation of the insula. Neurophysiologie clinique = Clinical neurophysiology 2012;42(6):363-368.

[12] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of health and social behavior 1983;24(4):385-396.

[13] Colloca L. The Placebo Effect in Pain Therapies. Annu Rev Pharmacol Toxicol 2019;59:191-211.

[14] Corlier J, Tadayonnejad R, Wilson AC, Lee JC, Marder KG, Ginder ND, Wilke SA, Levitt J, Krantz D, Leuchter AF. Repetitive transcranial magnetic stimulation treatment of major depressive disorder and comorbid chronic pain: response

rates and neurophysiologic biomarkers. Psychological medicine 2023;53(3):823-832.

[15] Cruccu G, Frisardi G, Pauletti G, Romaniello A, Manfredi M. Excitability of the central masticatory pathways in patients with painful temporomandibular disorders. Pain 1997;73(3):447-454.

[16] Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, Burns JW, Sullivan M, Mackey SC. Development and Validation of a Daily Pain Catastrophizing Scale. J Pain 2017;18(9):1139-1149.

[17] Davis MC, Okun MA, Kruszewski D, Zautra AJ, Tennen H. Sex differences in the relations of positive and negative daily events and fatigue in adults with rheumatoid arthritis. J Pain 2010;11(12):1338-1347.

[18] DosSantos MF, Ferreira N, Toback RL, Carvalho AC, DaSilva AF. Potential Mechanisms Supporting the Value of Motor Cortex Stimulation to Treat Chronic Pain Syndromes. Frontiers in neuroscience 2016;10:18.

[19] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9(2):105-121.

[20] Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. Psychol Methods 2007;12(2):121-138.

[21] Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149-158.

[22] Finan PH, Quartana PJ, Smith MT. Positive and negative affect dimensions in chronic knee osteoarthritis: effects on clinical and laboratory pain. Psychosom Med 2013;75(5):463-470.

[23] Fricova J, Klirova M, Masopust V, Novak T, Verebova K, Rokyta R. Repetitive transcranial magnetic stimulation in the treatment of chronic orofacial pain. Physiological research 2013;62 Suppl 1:S125-134.

[24] Frimerman L, Verner M, Sirois A, Scott K, Bruneau A, Perez J, Shir Y, Martel MO. Day-to-day hedonic and calming effects of opioids, opioid craving, and opioid misuse among patients with chronic pain prescribed long-term opioid therapy. Pain 2021;162(8):2214-2224.

[25] Galhardoni R, Aparecida da Silva V, Garcia-Larrea L, Dale C, Baptista AF, Barbosa LM, Menezes LMB, de Siqueira S, Valerio F, Rosi J, Jr., de Lima Rodrigues AL, Reis Mendes Fernandes DT, Lorencini Selingardi PM, Marcolin MA, Duran FLS, Ono CR, Lucato LT, Fernandes A, da Silva FEF, Yeng LT, Brunoni AR, Buchpiguel CA, Teixeira MJ, Ciampi de Andrade D. Insular and anterior cingulate cortex deep stimulation for central neuropathic pain: Disassembling the percept of pain. Neurology 2019;92(18):e2165-e2175.

[26] Galhardoni R, Ciampi de Andrade D, Puerta MY, Brunoni AR, Varotto BL, de Siqueira JT, Teixeira MJ, Siqueira SR. Altered cortical excitability in persistent idiopathic facial pain. Cephalalgia 2019;39(2):219-228.

[27] Ge R, Humaira A, Gregory E, Alamian G, MacMillan EL, Barlow L, Todd R, Nestor S, Frangou S, Vila-Rodriguez F. Predictive Value of Acute Neuroplastic Response to rTMS in Treatment Outcome in Depression: A Concurrent TMS-fMRI Trial. The American journal of psychiatry 2022;179(7):500-508.

[28] Gonterman F. A Systematic Review Assessing Patient-Related Predictors of Response to Transcranial Magnetic Stimulation in Major Depressive Disorder. Neuropsychiatr Dis Treat 2023;19:565-577.

[29] Gonzalez-Garcia N, Armony JL, Soto J, Trejo D, Alegria MA, Drucker-Colin R. Effects of rTMS on Parkinson's disease: a longitudinal fMRI study. J Neurol 2011;258(7):1268-1280.

[30] Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. Pain 1978;5(1):5-18.

[31] Hanlon CA, McCalley DM. Sex/Gender as a Factor That Influences Transcranial Magnetic Stimulation Treatment Outcome: Three Potential Biological Explanations. Frontiers in psychiatry 2022;13:869070.

[32] Harden RN, Weinland SR, Remble TA, Houle TT, Colio S, Steedman S, Kee WG, American Pain Society P. Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians. J Pain 2005;6(6):364-371.

[33] Hauser W, Jung E, Erbsloh-Moller B, Gesmann M, Kuhn-Becker H, Petermann F, Langhorst J, Weiss T, Winkelmann A, Wolfe F. Validation of the Fibromyalgia Survey Questionnaire within a cross-sectional survey. PloS one 2012;7(5):e37504.

[34] Henssen D, Giesen E, van der Heiden M, Kerperien M, Lange S, van Cappellen van Walsum AM, Kurt E, van Dongen R, Schutter D, Vissers K. A systematic review of the proposed mechanisms underpinning pain relief by primary motor cortex stimulation in animals. Neuroscience letters 2020;719:134489.

[35] Herrero Babiloni A, Bellemare A, Beetz G, Vinet SA, Martel MO, Lavigne GJ, De Beaumont L. The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. Sleep medicine reviews 2021;55:101381.

[36] Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. Journal of pain research 2018;11:1445-1457.

[37] Hinchman CA, Fried PJ, Jannati A, Press DZ, Pascual-Leone A, Stern AP. Corticomotor plasticity as a predictor of response to high frequency transcranial magnetic stimulation treatment for major depressive disorder. Journal of affective disorders 2022;303:114-122.

[38] Hoffman L. Longitudinal analysis: Modeling within-person fluctuation and change: Routledge, 2015.

[39] Jette F, Cote I, Meziane HB, Mercier C. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on

pain after spinal cord injury. Neurorehabilitation and neural repair 2013;27(7):636-643.

[40] Jodoin M, Rouleau DM, Bellemare A, Provost C, Larson-Dupuis C, Sandman E, Laflamme GY, Benoit B, Leduc S, Levesque M, Gosselin N, De Beaumont L. Moderate to severe acute pain disturbs motor cortex intracortical inhibition and facilitation in orthopedic trauma patients: A TMS study. PloS one 2020;15(3):e0226452.

[41] Jung J, Bungert A, Bowtell R, Jackson SR. Modulating Brain Networks With Transcranial Magnetic Stimulation Over the Primary Motor Cortex: A Concurrent TMS/fMRI Study. Frontiers in human neuroscience 2020;14:31.

[42] Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg 2020;13(4):321-334.

[43] Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2001;112(4):720.

[44] Kim H, Jung J, Park S, Joo Y, Lee S, Lee S. Effects of Repetitive Transcranial Magnetic Stimulation on the Primary Motor Cortex of Individuals with Fibromyalgia: A Systematic Review and Meta-Analysis. Brain sciences 2022;12(5).

[45] Klein MM, Treister R, Raij T, Pascual-Leone A, Park L, Nurmikko T, Lenz F, Lefaucheur JP, Lang M, Hallett M, Fox M, Cudkowicz M, Costello A, Carr DB,

Ayache SS, Oaklander AL. Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. Pain 2015;156(9):1601-1614.

[46] Klem GH, Luders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. Electroencephalography and clinical neurophysiology Supplement 1999;52:3-6.

[47] Kohutova B, Fricova J, Klirova M, Novak T, Rokyta R. Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial. Physiological research 2017.

[48] Kopala-Sibley DC, Zuroff DC, Russell JJ, Moskowitz DS, Paris J. Understanding heterogeneity in borderline personality disorder: differences in affective reactivity explained by the traits of dependency and self-criticism. J Abnorm Psychol 2012;121(3):680-691.

[49] Kothari SF, Blicher JU, Dagsdottir LK, Kothari M, Kumar A, Sengupta K, Buchholtz PE, Ashkanian M, Svensson P. Facilitatory Effect of Intermittent Repetitive Transcranial Magnetic Stimulation on Perceptual Distortion of the Face. J Pain 2022;23(6):1051-1059.

[50] Kothari SF, Dagsdottir LK, Kothari M, Blicher JU, Kumar A, Buchholtz PE, Ashkanian M, Svensson P. Effect of repetitive transcranial magnetic stimulation on altered perception of One's own face. Brain stimulation 2020;13(3):554-561.

[51] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine 2001;16(9):606-613.

[52] Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64(2):258-266.

[53] Lacroix A, Calvet B, Laplace B, Lannaud M, Plansont B, Guignandon S, Balestrat P, Girard M. Predictors of clinical response after rTMS treatment of patients suffering from drug-resistant depression. Transl Psychiatry 2021;11(1):587.

[54] Lacroix A, Paquet A, Okassa M, Vinais T, Lannaud M, Plansont B, Buisson A, Guignandon S, Malauzat D, Girard M, Calvet B. Distinct Predictors of Clinical Response after Repetitive Transcranial Magnetic Stimulation between Bipolar and Unipolar Disorders. Int J Environ Res Public Health 2023;20(7).

[55] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipovic SR, Grefkes C, Hasan A, Hummel FC, Jaaskelainen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorova I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2019.

[56] Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 2001;12(13):2963-2965.

[57] Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP. Neurogenic pain relief by repetitive transcranial magnetic

cortical stimulation depends on the origin and the site of pain. Journal of neurology, neurosurgery, and psychiatry 2004;75(4):612-616.

[58] Lefaucheur JP, Hatem S, Nineb A, Menard-Lefaucheur I, Wendling S, Keravel Y, Nguyen JP. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. Neurology 2006;67(11):1998-2004.

[59] Lefaucheur JP, Nguyen JP. A practical algorithm for using rTMS to treat patients with chronic pain. Neurophysiologie clinique = Clinical neurophysiology 2019;49(4):301-307.

[60] LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists 1997;8(3):291-305.

[61] Leung A, Shirvalkar P, Chen R, Kuluva J, Vaninetti M, Bermudes R, Poree L, Wassermann EM, Kopell B, Levy R, and the Expert Consensus P. Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-NANS Expert Consensus Panel Review and Recommendation. Neuromodulation 2020;23(3):267-290.

[62] Malhi GS, Bell E. Is the response to rTMS largely the result of non-specific effects? Aust N Z J Psychiatry 2021;55(5):445-450.

[63] Manfredini D, Borella L, Favero L, Ferronato G, Guarda-Nardini L. Chronic pain severity and depression/somatization levels in TMD patients. Int J Prosthodont 2010;23(6):529-534.

[64] Melzack R. Pain and the neuromatrix in the brain. Journal of dental education 2001;65(12):1378-1382.

[65] Miller VE, Poole C, Golightly Y, Barrett D, Chen DG, Ohrbach R, Greenspan JD, Fillingim RB, Slade GD. Characteristics Associated With High-Impact Pain in People With Temporomandibular Disorder: A Cross-Sectional Study. J Pain 2019;20(3):288-300.

[66] Mizutani-Tiebel Y, Tik M, Chang KY, Padberg F, Soldini A, Wilkinson Z, Voon CC, Bulubas L, Windischberger C, Keeser D. Concurrent TMS-fMRI: Technical Challenges, Developments, and Overview of Previous Studies. Frontiers in psychiatry 2022;13:825205.

[67] Moana-Filho EJ, Herrero Babiloni A. Endogenous pain modulation in chronic temporomandibular disorders: Derivation of pain modulation profiles and assessment of its relationship with clinical characteristics. J Oral Rehabil 2019;46(3):219-232.

[68] Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: a systematic review and meta-analysis. Pain 2018;159(8):1441-1455.

[69] Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. European journal of pain 2016;20(5):689-700.

[70] Moreno-Fernandez AM, Jimenez-Castellanos E, Iglesias-Linares A, Bueso-Madrid D, Fernandez-Rodriguez A, de Miguel M. Fibromyalgia syndrome and

temporomandibular disorders with muscular pain. A review. Mod Rheumatol 2017;27(2):210-216.

[71] Mori N, Hosomi K, Nishi A, Oshino S, Kishima H, Saitoh Y. Analgesic Effects of Repetitive Transcranial Magnetic Stimulation at Different Stimulus Parameters for Neuropathic Pain: A Randomized Study. Neuromodulation 2022;25(4):520-527.

[72] Mun CJ, Weaver KR, Hunt CA, Owens MA, Phillips J, Lerman SF, Buenaver LF, Colloca L, Tennen H, Haythornthwaite JA, Finan PH, Smith MT. Pain Expectancy and Positive Affect Mediate the day-to-day Association Between Objectively Measured Sleep and Pain Severity Among Women With Temporomandibular Disorder. J Pain 2022;23(4):669-679.

[73] Nicholson AN, Stone BM, Clarke CH, Ferres HM. Effect of N-desmethyldiazepam (nordiazepam) and a precursor, potassium clorazepate, on sleep in man. Br J Clin Pharmacol 1976;3(3):429-438.

[74] Ohrbach R, Larsson P, List T. The jaw functional limitation scale: development, reliability, and validity of 8-item and 20-item versions. Journal of orofacial pain 2008;22(3):219-230.

[75] Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. Psychological medicine 1978;8(2):325-329.

[76] Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain : a journal of neurology 2007;130(Pt 10):2661-2670.

[77] Patridge EF, Bardyn TP. Research Electronic Data Capture (REDCap). J Med Libr Assoc 2018;106(1):142-144.

[78] Picarelli H, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, Fonoff ET, Pridmore S, Marcolin MA. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain 2010;11(11):1203-1210.

[79] Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neuroscience letters 2004;356(2):87-90.

[80] Price DD, Harkins SW, Baker C. Sensory-affective relationships among different types of clinical and experimental pain. Pain 1987;28(3):297-307.

[81] Progiante PS, Pattussi MP, Lawrence HP, Goya S, Grossi PK, Grossi ML. Prevalence of Temporomandibular Disorders in an Adult Brazilian Community Population Using the Research Diagnostic Criteria (Axes I and II) for Temporomandibular Disorders (The Maringa Study). Int J Prosthodont 2015;28(6):600-609.

[82] Proulx-Begin L, Herrero Babiloni A, Bouferguene S, Roy M, Lavigne GJ, Arbour C, De Beaumont L. Conditioning to Enhance the Effects of Repetitive Transcranial Magnetic Stimulation on Experimental Pain in Healthy Volunteers. Frontiers in psychiatry 2022;13:768288.

[83] Raphael KG, Janal MN, Sirois DA, Dubrovsky B, Klausner JJ, Krieger AC, Lavigne GJ. Validity of self-reported sleep bruxism among myofascial temporomandibular disorder patients and controls. J Oral Rehabil 2015;42(10):751-758.

[84] Razza LB, Moffa AH, Moreno ML, Carvalho AF, Padberg F, Fregni F, Brunoni AR. A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. Prog Neuropsychopharmacol Biol Psychiatry 2018;81:105-113.

[85] Riley JL, 3rd, Robinson ME, Wise EA, Price D. A meta-analytic review of pain perception across the menstrual cycle. Pain 1999;81(3):225-235.

[86] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2011;122(8):1686.

[87] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, Siebner HR, Ugawa Y, Walsh V, Ziemann U. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2015;126(6):1071-1107.

[88] Russell JJ, Moskowitz DS, Zuroff DC, Bleau P, Pinard G, Young SN. Anxiety, emotional security and the interpersonal behavior of individuals with social anxiety disorder. Psychological medicine 2011;41(3):545-554.

[89] Sacco P, Prior M, Poole H, Nurmikko T. Repetitive transcranial magnetic stimulation over primary motor vs non-motor cortical targets; effects on experimental hyperalgesia in healthy subjects. BMC Neurol 2014;14:166.

[90] Saisanen L, Huttunen J, Hypponen J, Nissen M, Kotiranta U, Mervaala E, Fraunberg M. Efficacy and tolerability in patients with chronic facial pain of two consecutive treatment periods of rTMS applied over the facial motor cortex, using protocols differing in stimulation frequency, duration, and train pattern. Neurophysiologie clinique = Clinical neurophysiology 2022;52(2):95-108.

[91] Sawynok J. Caffeine and pain. Pain 2011;152(4):726-729.

[92] Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF, International Rdc/Tmd Consortium Network IafDR, Orofacial Pain Special Interest Group IAftSoP. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. Journal of oral & facial pain and headache 2014;28(1):6-27.

[93] Schiffman EL, Anderson GC, Fricton JR, Lindgren BR. The relationship between level of mandibular pain and dysfunction and stage of temporomandibular joint internal derangement. Journal of dental research 1992;71(11):1812-1815.

[94] Singer JD, Willett JB, Willett JB. Applied longitudinal data analysis: Modeling change and event occurrence: Oxford university press, 2003.

[95] Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, Dubner R, Diatchenko L, Meloto CB, Smith S, Maixner W. Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies. Journal of dental research 2016.

[96] Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine 2006;166(10):1092-1097.

[97] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychological assessment 1995;7(4):524-532.

[98] Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5(2):133-137.

[99] Thapa T, Graven-Nielsen T, Schabrun SM. Aberrant plasticity in musculoskeletal pain: a failure of homeostatic control? Experimental brain research 2021;239(4):1317-1326.

[100] Thibaut A, Zeng D, Caumo W, Liu J, Fregni F. Corticospinal excitability as a biomarker of myofascial pain syndrome. Pain reports 2017;2(3):e594.

[101] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E,

Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160(1):19-27.

[102] Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The Efficacy of Daily Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Burning Mouth Syndrome (BMS): A Randomized Controlled Single-blind Study. Brain stimulation 2016;9(2):234-242.

[103] Vachon-Presseau E, Berger SE, Abdullah TB, Huang L, Cecchi GA, Griffith JW, Schnitzer TJ, Apkarian AV. Brain and psychological determinants of placebo pill response in chronic pain patients. Nat Commun 2018;9(1):3397.

[104] Velly AM, Fricton J. The impact of comorbid conditions on treatment of temporomandibular disorders. Journal of the American Dental Association 2011;142(2):170-172.

[105] Vucic S, Stanley Chen KH, Kiernan MC, Hallett M, Benninger DH, Di Lazzaro V, Rossini PM, Benussi A, Berardelli A, Curra A, Krieg SM, Lefaucheur JP, Long Lo Y, Macdonell RA, Massimini M, Rosanova M, Picht T, Stinear CM, Paulus W, Ugawa Y, Ziemann U, Chen R. Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2023;150:131-175.

[106] Wallace D, Green SB. Analysis of repeated measures designs with linear mixed models. 2002.

[107] Wang Y, Chan E, Dorsey SG, Campbell CM, Colloca L. Who are the placebo responders? A cross-sectional cohort study for psychological determinants. Pain 2022;163(6):1078-1090.

[108] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070.

[109] Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Deutsches Arzteblatt international 2012;109(15):276-281.

[110] Zhu PA, Xie JY, Liu H, Wen Y, Shao YJ, Bao X. Efficacy of High-Frequency Repetitive Transcranial Magnetic Stimulation at 10 Hz in Fibromyalgia: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil 2023;104(1):151-159.

[111] Zisapel N, Nir T. Determination of the minimal clinically significant difference on a patient visual analog sleep quality scale. Journal of sleep research 2003;12(4):291-298.

CHAPTER 5. DISCUSSION

The present thesis included four distinct chapters. The objective of Chapter 1 was to review the association between sleep and chronic pain, with a specific focus on describing the directionality of the "sleep-pain" association and putative underlying mechanisms. The objective of Chapter 2 was to review the association between sleep and TMD pain, with a specific focus on describing objective and subjective sleep measures and identifying potential areas of study and intervention. The objective of Chapter 3 was to to examine the contribution of sleep quality and psychological factors to within-day pain fluctuations in patients with TMD. The objective of Chapter 4 was to To assess the potential effects of rTMS on pain and other TMD-related outcomes (i.e., sleep) in patients with TMD.

In the following sections, a brief summary of findings and knowledge that has emerged from reviews (Chapters 1 & 2) and from experimental studies (Chapers 3 & 4) will be presented. Given that manuscripts included in the present thesis already offered a detailed interpretation of findings based on previous work in the area, the following discussion will be particularly focused on the general contribution of our findings to the existing theoretical and empirical literature. The clinical implications of our findings will also be discussed, and directions for future research will be addressed.

5.1 The "sleep and pain" association and underlying mechanisms

The reviews conducted in Chapter 1 and Chapter 2 provided important information regarding the relationship between sleep and chronic pain. Results from the reviews suggest that in many cases, sleep appears to have a more substantial impact on pain

than the other way around, and this influence seems relatively consistent across studies. Review results presented in Chapter 1 also suggest that the high co-occurrence of sleep and pain problems involves the interplay of many other factors, including common underlying biological mechanisms involved in the regulation of sleep and pain. For example, the potential predominance of underpinning mechanisms could be different in both sexes, as females potentially experience more pronounced alterations in their pain modulation processes compared to males (91, 92). Additionally, the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may be more prominent in individuals with insomnia, particularly those whose sympathetic systems are predisposed to be overactive (93). Furthermore, low-grade inflammation is intertwined with numerous other pathways, and emerging evidence suggests that the endocannabinoid system, melatonin, and orexin pathways could hold key insights into this intricate relationship (91). Further investigation of these phenotypes and endotypes could potentially lead to a better understanding of how they contribute to the maintenance of comorbid sleep and pain problems. Further research in this area might also lead to the development of interventions specifically targeting these biological mechanisms, which in turn might ultimately lead to improved management of patients presenting with comorbid sleep and pain problems.

In the second review (i.e., Chapter 2), a deeper dive is taken into the sleep problems among patients with temporomandibular disorders (TMD). This condition sets a unique challenge due to its frequent comorbidities with insomnia, obstructive sleep apnea (OSA), and sleep bruxism. Although less frequently, TMD can also be accompanied by upper airway resistance syndrome (UARS) and restless leg syndrome

(RLS) (27, 28, 94). Among patients with TMDs, the directionality of the association between sleep and remains unclear. Similar to other chronic pain conditions, a possible reason is that patients often present with psychological comorbidities, which can influence both sleep and pain, and contribute also independently to amplify the pain experience (95). Second, while subjective sleep quality is consistently reported as compromised in TMD patients, objective measurements through polysomnography (PSG) have revealed minor sleep pattern disruptions, namely increased RERA (respiratory effort related arousal), an index of arousability, in comparison with healthy controls. This suggests that patients with TMD might be characterized by having a higher level of arousability, which could contribute to the frequently observed co-occurrence of sleep and pain problems in this population. The clinical significance of these PSG findings (i.e.,, RERA) and their impact on pain remains to be fully understood. Third, the management of sleep disorders in TMD requires a tailored approach, yet guidelines for optimizing treatments and addressing comorbidities, such as sleep-related breathing disorders, are not well-established (Chapter 2).

5.2. Factors contributing to daily TMD pain fluctuations

Although results from our reviews (Chapter 1 & 2) suggest that research has indicated important interrelationships between sleep, psychological states, and pain, further studies, especially those employing dynamic assessments are needed. It is well known that fluctuations occur over time in chronic pain patients' sleep patterns (96-99). Longitudinal study designs involving repeated measures are needed to provide more reliable and comprehensive insights into the complex interplay between sleep, psychological function, and TMD pain.

Ecological momentary assessment (EMA) is a procedure for data capturing that involves repeated sampling of subjects' current behaviors and experiences in real time, in subjects' natural environments. EMA aims to minimize recall bias, maximize ecological validity, and allow study of microprocesses that influence behavior in real-world contexts (100-102). EMA methods have been used extensively in health and clinical psychology to investigate a variety of health behaviors, including substance use, eating, medication adherence, sleep, and physical activity (103). This method provides a detailed and fine-grained view of individuals' experiences and behaviors over time capturing of within-person variation including daily fluctuations, patterns, and changes, which may be missed in studies involving retrospective/cross-sectional study designs or less frequent assessments.

Studies relying on diaries and/or ecological momentary assessment (EMA) methods have already been used among patients with TMD to capture parafunctional habits or oral behaviours such as awake bruxism (104, 105), but also to explore pain and psychosocial outcomes such as sleep, coping, affect, and pain catastrophizing (106-108). Recently, Mun et al. (2022) assessed if sleep deprivation could induce threat interpretation bias, and impairment in positive affective functioning, using both actigraphy and daily diaries (109). They examined whether morning pain expectancy and positive affect mediated the association between previous night's sleep disturbance and next-day overall pain severity in 144 women with TMD. In that study, it was shown that shorter objectively measured daily total sleep time was associated with an increase in pain severity on the next day via greater morning pain expectancy. Also, on days following shorter nights of sleep, decreases in positive affect, but not necessarily increases in

negative affect contributed to higher levels of pain. As authors recognized, they did not include other important psychological variables, such as pain catastrophizing, which is known to influence both sleep and pain, and even to moderate or mediate such association (110, 111). The longitudinal diary study included in Chapter 3 of the present thesis yielded results that allowed to not only better understand the relative contributions sleep and psychological disturbances on TMD pain, but also on day-to-day TMD pain exacerbations. TMD pain fluctuations, including exacerbations or reductions, are critical in the study of pain for several reasons, including the better understanding of pain mechanisms and the identification of variables that contribute to pain perception and pain modulation. Monitoring these fluctuations can provide valuable information about disease progression, and it can potentially help to assess the impact of treatments and interventions (80). From our study (Chapter 3) we observed that that day-to-day sleep quality and psychological factors can contribute to pain exacerbations (also known as pain “flares”) over the course of the day among individuals with TMD. More specifically, we found that participants reporting poorer sleep were more likely to experience clinically meaningful pain increases (i.e., increases in pain of > 20 points on a 0/100 scale) over the course of the day. We also found that participants reporting higher levels of catastrophizing were more likely to experience clinically meaningful pain increases over the course of the day. While we did not delve into the biological mechanisms underlying these effects, our findings indicated that neither positive nor negative affect were determinants of within-day pain exacerbations among patients with chronic TMD. This is somewhat in contrast to what Mun et al. observed using next day pain intensity as

outcome (109). In their study, though, they had not examined the contribution of sleep to pain fluctuations.

While the vast amount of literature regarding pain fluctuation focuses on pain exacerbations, little is known about the factors that might contribute to reductions in pain and/or clinically meaningful pain decreases over the course of the day. It was conceivable to believe that the factors contributing to within-day pain increases and pain decreases could be different, which is why this was explored in Chapter 3 of the present thesis. In longitudinal studies with up to six waves among an aging population of patients with chronic pain, greater financial wealth and physical activity, better sleep quality and self-reported health were associated with a greater probability of recovery (112), defined as transition from severe to moderate pain. From a daily standpoint, there is reason to believe that factors integrated in the biopsychosocial model such as rest and sleep, circadian rhythms, physical activity and movement, relaxation, distraction, social support and above all psychological factors and emotional states such as affect and catastrophizing are some of the elements that can influence those pain decreases (113), but this had remained unexplored among TMD patients. As noted earlier, results from our study reveled that sleep disturbances were associated with a greater likelihood of clinically meaningful within-day pain exacerbations, but sleep was not associated with within-day pain decreases. A valiant guess would be to assume that sleep disturbances may act as a pain amplifier, but greater sleep quality can have a “time lag effect” in a chronic pain context, as the relationship between sleep quality and pain may not be immediate or linear. While poor sleep may lead to within-day pain exacerbations, better

sleep might have delayed or less direct effects on pain decreases. It is possible as well, that the study did not capture longer-term effects of improved sleep on pain reduction.

One notable finding from Chapter 3 was that that day-to-day reductions in pain catastrophizing were associated with a greater likelihood of clinically meaningful decreases over the course of the next day. Although speculative, catastrophizing could have a more immediate and impactful role in daily pain outcomes, perhaps due to interoceptive sensitivity (i.e., sense of the physiological condition of the body, such as conscious awareness, emotional processes, and behavior related to afferent physiological information arising from the body) (114).

5.3 The potential utility of rTMS for improving TMD pain

Chronic pain is challenging to treat due to its multifaceted nature and not fully elucidated mechanisms, which include psychosocial, social, and biological factors that are part of the Biopsychosocial Model. This is also the case for TMD. Repetitve Transcranial Magnetic Stimulation (rTMS) was originally used in the pain field to predict the effectiveness of surgically implanted epidural motor cortex stimulation for treating neuropathic pain (56). It was later discovered that rTMS to the motor cortex had its own analgesic effects, which could persist beyond the stimulation session and be maintained with repeated sessions (115, 116). This led to the exploration of rTMS as a standalone therapy for chronic pain. Studies found that rTMS to the primary motor cortex (M1) not only influenced the motor cortex but also had effects on distant brain areas, including the anterior cingulate, insular cortex, dorsolateral prefrontal cortex (DLPFC), striatum, and brainstem (83, 117). This suggests that M1 serves as an "entry gate" into the brain,

allowing modulation of activity in connected regions. rTMS also appeared to engage changes in neurotransmitter receptors, particularly mu-opioid receptors, which could contribute to its analgesic effects (60, 61, 118). For instance, it has been shown that serum beta-endorphin levels increased after rTMS (119), that naloxone could block rTMS analgesia (120), and that brain opioid receptor occupancy increased after rTMS stimulation (121). Glutamate NMDA receptors also played a role in some studies (62), but this effect varied between humans and rodents. In addition, the specific effects of rTMS on cortical and subcortical structures seem to depend on the orientation of the magnetic coil and which fibers in the precentral gyrus were preferentially stimulated (122). Posteroanterior coil orientation was found to produce significant analgesic effects, possibly by influencing cortico-cortical fibers and their connections to other brain areas (122). This orientation could impact emotional and coping behaviors related to neuropathic pain via the nucleus accumbens reward circuitry passing through the thalamus, contrasting with the effects of preferentially stimulating somatosensory cortex components (122).

In the past, research on rTMS for chronic pain was hindered by small patient samples, lack of blinding, and limited follow-up data. However, recent well-conducted studies have provided more robust evidence. Influential organizations have suggested that rTMS could be a viable treatment option for patients who have exhausted other available options for chronic pain disorders such as neuropathic pain (83). As a result, rTMS is now recommended as a treatment option for chronic pain patients in various disorders and in guidelines across Europe, Latin America, and the USA (83, 123, 124). Studies have also helped to optimize rTMS protocols, suggesting that stimulating the

primary motor cortex (M1) with specific parameters, such as high pulse frequency and coil orientation, is preferred for pain relief. Although the analgesic benefits of rTMS have been investigated in chronic orofacial pain conditions, such as burning mouth syndrome, atypical neuropathic pain, and trigeminal neuralgia (63, 125-128) its use among patients with painful TMD have never been explored. Therefore, this was the aim of Chapter 4 of this thesis. Given the exploratory nature of this objective, we opted for using a single session of rTMS, as research has demonstrated that even one session of rTMS can yield short-term analgesic effects that persist for approximately 3 to 5 days after the treatment (90, 129-131). This approach allowed us to investigate the initial effects of this technique in TMD before potentially developing more time-consuming and expensive intervention protocols. In addition, it appears that achieving somatotopic effects, which involve targeting specific areas in the primary motor cortex (M1), may not be as effective as engaging a broader range of brain networks associated with pain relief (130). Hence, we chose to apply a high frequency rTMS protocol to the M1 region corresponding to the hand instead of the M1 corresponding to the face for different reasons: a) difficulty in pinpointing the precise "hot spot" and resting motor thresholds in the facial muscles compared to those in the hand muscles; b) the hand's motor representation in M1 has a more extensive connectivity pattern with brain structures involved in natural pain regulation than the facial representation; and c) the presence of thicker layers of cerebral spinal fluid (CSF) in the proximal regions of the M1 representation of the face, which could potentially lead to a reduction in the effectiveness of rTMS (63, 130).

Using the protocol described above, our results revealed that one session of active rTMS can induce significantly greater, yet mild, immediate analgesic effects (i.e., reductions in pain intensity and pain unpleasantness) relative to sham stimulation among participants with TMD. However, immediate rTMS effects on the latter pain measures and other secondary measures such as sleep quality or pain catastrophizing, were not sustained during the 7 consecutive days following treatment, at which time pain relief was comparable to sham stimulation. There are various possible interpretations for these findings, albeit somewhat speculative. One plausible explanation could be the utilization of only a single session of rTMS, which might not have been sufficient to induce more sustained and enduring effects. Most studies demonstrating consistent and long-lasting analgesic effects typically employed a higher number of sessions (83). This is because alterations in brain function are believed to evolve gradually over time, often necessitating multiple sessions to generate substantial and enduring effects. For instance, in a recent randomized multicenter sham-controlled trial, involving 15 sessions over 22 weeks, active rTMS was shown to outperform the sham treatment in various pain-related outcomes among neuropathic pain patients for nearly 7 months (82). Similarly, a study employing 10 sessions of rTMS among patients with upper limb fractures observed improved pain and functional outcomes three months following the stimulation (Jodoin et al. 2023, unpublished)). Nevertheless, employing rTMS protocols with a single session can be advantageous for assessing the feasibility and initial impact of this technique on a particular condition that has not been extensively investigated, thus providing preliminary evidence to justify larger and more resource-intensive randomized controlled trials (RCTs).

Our findings demonstrated that although active rTMS did lead to immediate pain reduction compared to the sham treatment, which came close to the established 20-30% threshold for determining clinically significant changes in pain intensity among individuals with chronic pain (132, 133), the inclusion of additional treatment sessions could have been warranted to fully explore the potential of rTMS in patients with TMD. Another possibility is that most of the improvement observed in both treatment groups, especially during the following 7 days, is due to the presence of non-specific effects, or those effects referring to the impact of the treatment that is not directly related to the active ingredients or mechanisms of the treatment itself (134). These effects can be powerful and play a significant role in a patient's response to treatment, especially when they involve sophisticated equipment (135, 136). The importance of such effects in rTMS, namely placebo or expectations, is now well recognized (135, 136), and research has been undertaken to account for those effects in controlled studies. For example, using a sham condition almost identical to the active one, where participants and operators are blinded to the coil being used, is considered to be a valid and reliable method for blinding in this context (117). In our study, our results indicated that 60.1% of the participants (25 out of 41) guessed the order of treatment correctly, hence being considered as an acceptable blinding success (137). Blinding is essential to minimize the influence of placebo effects and ensure that any observed treatment effects are more likely to be due to the specific properties of the treatment rather than participant expectations or biases. Therefore, successful blinding helps control for placebo effects to some extent, yet it does not eliminate placebo effects entirely.

Another important issue to acknowledge is the presence of individuals who are natural responders and non-responders to rTMS. In the field of depression, it has been estimated that almost 30% of the individuals can be categorized as non-responders based mostly on EGG parameters (138). Indeed, different predictors of response have been identified in this field (139), and the use of new technologies such as machine learning approaches and non-linear processing of extracted components in frontal region to have been employed to predict rTMS treatment response in major depressive disorder (140). Nonetheless, this is yet to be applied to the field of chronic pain, where intra-individual or inter-individual predictors of rTMS analgesic effects are not well-known.

5.4. Clinical implications

All the chapters of this thesis highlight the need of a multidisciplinary treatment approach to manage the complex interplay between sleep and pain, including among patients with temporomandibular disorders (TMD). Whereas in some instances pharmacological interventions may be considered to address sleep disturbances and chronic pain (141), patient education and behavioral interventions such as cognitive-behavioral therapy (CBT) become central via a multidisciplinary approach to target other factors contributing to TMD pain. This includes psychological factors such as negative affect and catastrophizing, two psychological factors that have emerged as robust predictors of negative pain-related outcomes among patients with TMD. The use of CBT interventions for the management of sleep problems can equip patients with valuable tools to develop healthier sleep habits, improve coping strategies, and reduce the impact of pain on their daily lives. While sleep and pain can be targeted independently with CBT interventions, a hybrid approach has been developed and been shown effective in chronic

pain populations with insomnia (142, 143), thus becoming a potentially interesting option for TMD patients as well. Hybrid cognitive-behavioral therapy (H-CBT) programs for individuals with insomnia and chronic pain encompass various components such as general sleep and pain education, sleep restriction therapy, stimulus control for sleep and pain, sleep hygiene instructions, cognitive therapy specific to sleep and pain, relaxation or stress management techniques, and cognition-targeted exercise therapy. These comprehensive programs aim to address the cognitive, affective, perceptive, and coping skills associated with both sleep disturbances and chronic pain, particularly when mood disturbances and hyperarousal mechanisms are present. Research indicates that hybrid CBT can effectively help individuals with insomnia and coexisting chronic TMD pain manage their symptoms and improve overall well-being (142, 144).

Chapter 3 of the present thesis suggests that other outcomes than pain intensity itself, such as the presence of pain fluctuations, could be assessed and provide valuable clinical information in the context of TMD pain assessment . Longitudinal assessments and monitoring of these fluctuations could provide valuable information about disease progression, help assess the impact of treatments and interventions on pain relief, and could offer insights into the factors that contribute to clinically significant pain exacerbations that lead to disruptions in daily life functioning and quality of life (80, 145)

Finally, chapter 4 highlights the potential use other alternative strategies, namely rTMS, for managing TMD. Given its safety, and although more research is needed to optimize the parameters before its application, clinicians could consider this non-invasive brain stimulation technique as a potential option for patients who have exhausted other treatments, or as an add-on treatment to the standard of care. Nonetheless, while one

session of rTMS can yield to some immediate analgesic effects, multiple sessions may be necessary for more sustained and long-lasting results. By embracing the potential of rTMS and further exploring its applications in TMD, clinicians can expand the arsenal of available treatments for patients seeking relief from their pain.

5.5. Thesis Limitations

A number of limitations need to be considered when interpreting the results of these studies. Firstly, for chapters 1 and 2 the conducted reviews were narrative in nature. While these reviews allowed to broaden our scope encompassing a wide range of studies, synthesize diverse evidence, and explore emerging areas (e.g., rTMS), they are more susceptible to subjectivity and bias, and present less rigour and limited replicability in comparison to other type of reviews such as systematic reviews. Therefore, some studies may have inadvertently be omitted.

Secondly, for chapters 3 and 4, it needs to be considered that the sample only included females, and those were of relatively young age and had relatively mild to moderate levels of pain. Although this sample is actually considered to be representative of the TMD clinical population (16, 146), the generalizability of these results to men and other patients with higher levels of pain needs to be taken with caution. The duration of the diary period (i.e., 7 days) could also be viewed as relatively short. For instance, many diary studies involve longer (e.g., 14 days) of diary sampling (100), which provides a more representative and generalizable assessment of patients' day-to-day sleep patterns, psychological function, and pain. Future studies should consider using a longer diary period, especially when examining pain fluctuations, as they might occur less frequently in some patients and thus be undetected with short diary assessment periods.

Thirdly, the methodology used in Chapter 4 was primarily exploratory by nature, but certain methodological issues must be considered for future studies using rTMS among TMD patients. For instance, this includes more days of assessment, a higher number of rTMS sessions, the use of neuronavigation systems, and a larger sample size. However, the presents studies serve as a valuable foundation for future research endeavors by generating preliminary insights.

5.6. Future directions

As it was already highlighted in Chapter 1 and 2, there is a growing body of evidence on sleep and pain disorders such as TMD, but the wide variability in how these conditions present and respond to treatment emphasizes the need for a better understanding from an interdisciplinary perspective. In this context, personalized medicine principles can help identify different subtypes of interactions between sleep and pain and different relations to pain catastrophizing and affect. Among the trendiest techniques with the higher potential to achieve such understanding is machine learning, which have proven to be useful in the analysis of diverse data types within sleep and pain disorders (147, 148), and also in predicting responses to rTMS treatments in other conditions (140, 149). For instance, in sleep disorders, these algorithms can integrate data from polysomnography recordings, actigraphy measurements, sleep diaries, and patient-reported outcomes. By extracting these relevant features, such as sleep stages, sleep efficiency, and sleep architecture, machine learning algorithms can uncover hidden patterns and relationships with other pain variables. This can lead to the identification of different phenotypes of sleep disorders, such as insomnia subtypes characterized by specific sleep disturbances or circadian rhythm disorders with distinct patterns of sleep-

wake cycles (141). Similarly, in pain disorders, machine learning algorithms can analyze a range of data, including self-reported pain ratings and derivates (e.g., pain fluctuations), physiological measures (e.g., heart rate variability, skin conductance, EPM, EEG), and neuroimaging data (e.g., functional magnetic resonance imaging) (147). By leveraging the power of machine learning, researchers can gain a deeper understanding of the heterogeneity within sleep and pain disorders, and this knowledge can inform the development of personalized interventions and treatment strategies. For example, machine learning can help identify individuals who are more likely to respond favorably to a particular sleep therapy or predict the effectiveness of pain management strategies based on the individual's pain subtype, stratifying risks and creating personalized management strategies (45, 150).

Another relevant future direction is the possible use of non-invasive brain stimulation to improve both pain and sleep among patients with painful temporomandibular disorders by stimulating two different brain areas or performing a dual stimulation. There is evidence sowing that rTMS over M1 has improved sleep quality, possibly by improving pain symptoms and stimulating sleep-related networks (64). However, targeting the left dorsolateral prefrontal cortex with low frequencies appears to be more suitable for managing insomnia. This approach helps regulate autonomic function, reduce cortical arousal levels, and promote the release of neurotransmitters like melatonin, brain-derived neurotrophic factor, and GABA, which are crucial for sleep and pain relief (64). High-frequency stimulation protocols targeting the dorsolateral prefrontal cortex can also increase serotonin and dopamine release, potentially benefiting individuals with sleep deprivation, chronic pain, and depression. Therefore, dual rTMS

targeting both M1 and the left dorsolateral prefrontal cortex offers a comprehensive approach to address the complex relationship between sleep and pain by regulating sympathetic function, improving mood, and enhancing pain inhibition (64).

CHAPTER 6. CONCLUSIONS

The bidirectional relationship between sleep and pain is multifaceted. Research indicates that poor sleep quality can have a significant impact on pain outcomes over time, with studies showing that individuals who experience inadequate or disrupted sleep are more likely to report increased pain intensity and decreased pain tolerance. On the other hand, while chronic pain conditions can disrupt sleep patterns, evidence seems to be less consistent. As highlighted in reviews from Chapter 1 and 2, there is a host of biopsychosocial factors that can contribute to the sleep-pain relationship. This include alterations in endogenous pain modulation, increased inflammation, changes in affect and mood, and pain catastrophizing. Additionally, various endogenous substances such as dopamine, orexin, melatonin, and vitamin D, along with lesser-known mechanisms like the cyclic alternating pattern (CAP) during sleep, may play a role in this intricate interaction between sleep and pain.

Individuals with TMD also present subjective and objective sleep disturbances. Patients with TMD commonly report difficulties with falling asleep, staying asleep, and experiencing restorative sleep. These sleep disturbances can manifest as excessive daytime sleepiness, fatigue, and mood instability. Identifying sleep disorders such as insomnia, sleep apnea, and sleep bruxism in TMD patients via a multidisciplinary approach is important for effective management.

Chapter 3 from the present thesis indicated that catastrophizing is a particularly important factor that is not only linked to poor sleep, but also to an increased likelihood of

experiencing clinically meaningful pain exacerbations among TMD patients. Day-to-day decreases in catastrophizing were linked to an increased likelihood of experiencing clinically meaningful decreases in pain over the course of the day. Overall, these findings add evidence to the significant contribution of sleep and catastrophizing to TMD pain, and provide new insights into the factors that may lead to TMD pain fluctuations in the context of patients' day-to-day lives.

Finally, the use of repetitive transcranial magnetic stimulation (rTMS) has shown promise in providing analgesic effects for individuals with TMD-related pain, as a single session of active rTMS leaded to significant, albeit mild, reductions in pain intensity and pain unpleasantness among these patients. However, when comparing active rTMS to sham stimulation over a week-long period and considering improvements from baseline, no significant difference in pain reduction was found, suggesting that the analgesic effects of a single session may not be sustained in the long term, suggesting that repeated or multiple sessions of rTMS may be necessary to achieve more lasting pain relief. Importantly, the minor and transient side effects reported by a minority of TMD patients, such as headache and fatigue, support the safety and tolerability of rTMS as a therapeutic intervention for TMD-related pain.

7. REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.

2. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain. 2019;160(1):19-27.

3. Grichnik KP, Ferrante FM. The difference between acute and chronic pain. Mt Sinai J Med. 1991;58(3):217-20.

4. Organization WH. Classifications and Terminologies: WHO Family of International Classifications 2022 [Available from: https://www.who.int/standards/classifications.

5. Brennan F, Carr D, Cousins M. Access to Pain Management-Still Very Much a Human Right. Pain medicine. 2016;17(10):1785-9.

6. Force TCPT. An action plan for pain in Canada Ottawa, ON: Health Canada2021 [Available from: https://www.canada.ca/content/dam/

hc-sc/documents/corporate/about-health-canada/public-engagement/externaladvisory-

bodies/canadian-pain-task-force/report-2021-rapport/report-rapport-

2021-eng.pdf.

7. Zimmer Z, Fraser K, Grol-Prokopczyk H, Zajacova A. A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. Pain. 2022;163(9):1740-50.

8. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. Pain. 2005;113(3):331-9.

9. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: understanding the relationships between chronic pain and comorbidity in the general population. Pain. 2012;153(2):293-304.

10. Okeson JP. Bell's Oral and Facial Pain. 7th ed. UK: Quintessence; 2014.

11. Woolf CJ. What is this thing called pain? The Journal of clinical investigation. 2010;120(11):3742-4.

12. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-7.

13. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. Journal of oral & facial pain and headache. 2014;28(1):6-27.

14. Progiante PS, Pattussi MP, Lawrence HP, Goya S, Grossi PK, Grossi ML. Prevalence of Temporomandibular Disorders in an Adult Brazilian Community Population Using the Research Diagnostic Criteria (Axes I and II) for

Temporomandibular Disorders (The Maringa Study). Int J Prosthodont. 2015;28(6):600-9.

15. LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists. 1997;8(3):291-305.

16. Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg. 2020;13(4):321-34.

17. Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, et al. Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies. Journal of dental research. 2016.

18. Manfredini D, Borella L, Favero L, Ferronato G, Guarda-Nardini L. Chronic pain severity and depression/somatization levels in TMD patients. Int J Prosthodont. 2010;23(6):529-34.

19. Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: a systematic review and meta-analysis. Pain. 2018;159(8):1441-55.

20. Cairns BE. Pathophysiology of TMD pain--basic mechanisms and their implications for pharmacotherapy. J Oral Rehabil. 2010;37(6):391-410.

21. Harper DE, Schrepf A, Clauw DJ. Pain Mechanisms and Centralized Pain in Temporomandibular Disorders. Journal of dental research. 2016;95(10):1102-8.

22. Moana-Filho EJ, Herrero Babiloni A, Nisley A. Endogenous pain modulation assessed with offset analgesia is not impaired in chronic temporomandibular disorder pain patients. J Oral Rehabil. 2019;46(11):1009-22.

23. Costa YM, Conti PC, de Faria FA, Bonjardim LR. Temporomandibular disorders and painful comorbidities: clinical association and underlying mechanisms. Oral surgery, oral medicine, oral pathology and oral radiology. 2017;123(3):288-97.

24. Velly AM, Fricton J. The impact of comorbid conditions on treatment of temporomandibular disorders. Journal of the American Dental Association. 2011;142(2):170-2.

25. Dahan H, Shir Y, Velly A, Allison P. Specific and number of comorbidities are associated with increased levels of temporomandibular pain intensity and duration. J Headache Pain. 2015;16:528.

26. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. J Pain. 2016;17(9 Suppl):T93-T107.

27. Meira ECM, Lukic N, Wojczynska A, Steiger B, Guimaraes AS, Ettlin DA. Insomnia in Patients Seeking Care at an Orofacial Pain Unit. Frontiers in neurology. 2019;10:542.

28. Smith MT, Wickwire EM, Grace EG, Edwards RR, Buenaver LF, Peterson S, et al. Sleep disorders and their association with laboratory pain sensitivity in temporomandibular joint disorder. Sleep. 2009;32(6):779-90.

29. Roithmann CC, Silva C, Pattussi MP, Grossi ML. Subjective sleep quality and temporomandibular disorders: Systematic literature review and meta-analysis. J Oral Rehabil. 2021;48(12):1380-94.

30. Benoliel R, Zini A, Zakuto A, Slutzky H, Haviv Y, Sharav Y, et al. Subjective Sleep Quality in Temporomandibular Disorder Patients and Association with Disease Characteristics and Oral Health-Related Quality of Life. Journal of oral & facial pain and headache. 2017;31(4):313-22.

31. Rener-Sitar K, John MT, Pusalavidyasagar SS, Bandyopadhyay D, Schiffman EL. Sleep quality in temporomandibular disorder cases. Sleep medicine. 2016;25:105-12.

32. Trachsel LA, Munakomi S, Cascella M. Pain Theory. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Sunil Munakomi declares no relevant financial relationships with ineligible companies. Disclosure: Marco Cascella declares no relevant financial relationships with ineligible companies.2023.

33. Duncan G. Mind-body dualism and the biopsychosocial model of pain: what did Descartes really say? J Med Philos. 2000;25(4):485-513.

34. Mehta N. Mind-body Dualism: A critique from a Health Perspective. Mens Sana Monogr. 2011;9(1):202-9.

35. Perl ER. Pain mechanisms: a commentary on concepts and issues. Progress in neurobiology. 2011;94(1):20-38.

36. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-9.

37. Moayedi M, Davis KD. Theories of pain: from specificity to gate control. Journal of neurophysiology. 2013;109(1):5-12.

38. Melzack R. Pain and the neuromatrix in the brain. Journal of dental education. 2001;65(12):1378-82.

39. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.

40. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.

41. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988;54(6):1063-70.

42. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001;17(1):52-64.

43. Ogilvie RD. The process of falling asleep. Sleep medicine reviews. 2001;5(3):247-70.

44. Zielinski MR, McKenna JT, McCarley RW. Functions and Mechanisms of Sleep. AIMS Neurosci. 2016;3(1):67-104.

45. Herrero Babiloni A, Beetz G, Tang NKY, Heinzer R, Nijs J, Martel MO, et al. Towards the endotyping of the sleep-pain interaction: a topical review on multitarget strategies based on phenotypic vulnerabilities and putative pathways. Pain. 2021;162(5):1281-8.

46. Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. Sleep medicine. 2018;52:198-210.

47. Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. Sleep medicine reviews. 2018;39:82-97.

48. Korownyk CS, Montgomery L, Young J, Moore S, Singer AG, MacDougall P, et al. PEER simplified chronic pain guideline: Management of chronic low back, osteoarthritic, and neuropathic pain in primary care. Can Fam Physician. 2022;68(3):179-90.

49. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.

50. Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. Health Promot Chronic Dis Prev Can. 2018;38(6):224-33.

51. Fischer B, Pang M, Jones W. The opioid mortality epidemic in North America: do we understand the supply side dynamics of this unprecedented crisis? Subst Abuse Treat Prev Policy. 2020;15(1):14.

52. Ballantyne JC. Opioids for the Treatment of Chronic Pain: Mistakes Made, Lessons Learned, and Future Directions. Anesthesia and analgesia. 2017;125(5):1769-78.

53. Martel MO, Wasan AD, Jamison RN, Edwards RR. Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. Drug and alcohol dependence. 2013;132(1-2):335-41.

54. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The Burden of Opioid-Related Mortality in the United States. JAMA Netw Open. 2018;1(2):e180217.

55. Gomes T, Khuu W, Martins D, Tadrous M, Mamdani MM, Paterson JM, et al. Contributions of prescribed and non-prescribed opioids to opioid related deaths: population based cohort study in Ontario, Canada. Bmj. 2018;362:k3207.

56. Ciampi de Andrade D, Garcia-Larrea L. Beyond trial-and-error: Individualizing therapeutic transcranial neuromodulation for chronic pain. European journal of pain. 2023;27(9):1065-83.

57. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106-7.

58. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2009;120(12):2008-39.

59. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2014;125(11):2150-206.

60. DosSantos MF, Ferreira N, Toback RL, Carvalho AC, DaSilva AF. Potential Mechanisms Supporting the Value of Motor Cortex Stimulation to Treat Chronic Pain Syndromes. Frontiers in neuroscience. 2016;10:18.

61. Henssen D, Giesen E, van der Heiden M, Kerperien M, Lange S, van Cappellen van Walsum AM, et al. A systematic review of the proposed mechanisms underpinning pain relief by primary motor cortex stimulation in animals. Neuroscience letters. 2020;719:134489.

62. Jodoin M, Rouleau D, Larson-Dupuis C, Gosselin N, De Beaumont L. The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients. Prog Neuropsychopharmacol Biol Psychiatry. 2017.

63. Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. Journal of pain research. 2018;11:1445-57.

64. Herrero Babiloni A, Bellemare A, Beetz G, Vinet SA, Martel MO, Lavigne GJ, et al. The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. Sleep medicine reviews. 2021;55:101381.

65. Lanza G, Fisicaro F, Cantone M, Pennisi M, Cosentino FII, Lanuzza B, et al. Repetitive transcranial magnetic stimulation in primary sleep disorders. Sleep medicine reviews. 2023;67:101735.

66. Li M, Zhu Y, Zhang X, Yang H, Zhang S, Liu J, et al. 1Hz rTMS over left DLPFC rewired the coordination with hippocampus in insomnia patients: A pilot study. Brain stimulation. 2022;15(2):437-40.

67. Zhang H, Huang X, Wang C, Liang K. Alteration of gamma-aminobutyric acid in the left dorsolateral prefrontal cortex of individuals with chronic insomnia: a combined transcranial magnetic stimulation-magnetic resonance spectroscopy study. Sleep medicine. 2022;92:34-40.

68. Herrero Babiloni A, Brazeau D, De Koninck BP, Lavigne GJ, De Beaumont L. The Utility of Non-invasive Brain Stimulation in Relieving Insomnia Symptoms and Sleep

Disturbances Across Different Sleep Disorders: a Topical Review. Current Sleep Medicine Reports. 2023;9(2):124-32.

69. Herrero Babiloni A, De Beaumont L, Lavigne GJ. Transcranial Magnetic Stimulation: Potential Use in Obstructive Sleep Apnea and Sleep Bruxism. Sleep medicine clinics. 2018;13(4):571-82.

70. Nardone R, Sebastianelli L, Versace V, Brigo F, Golaszewski S, Pucks-Faes E, et al. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. Sleep medicine. 2020.

71. Zhou WN, Fu HY, Du YF, Sun JH, Zhang JL, Wang C, et al. Short-term effects of repetitive transcranial magnetic stimulation on sleep bruxism - a pilot study. International journal of oral science. 2016;8(1):61-5.

72. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. European journal of pain. 2005;9(4):463-84.

73. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007;55(3):377-91.

74. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.

75. Turk DC, Fillingim RB, Ohrbach R, Patel KV. Assessment of Psychosocial and Functional Impact of Chronic Pain. J Pain. 2016;17(9 Suppl):T21-49.

76. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. J Pain. 2016;17(9 Suppl):T70-92.

77. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539-52.

78. Hutchings A, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. The Journal of rheumatology. 2007;34(11):2291-300.

79. Schneider S, Junghaenel DU, Keefe FJ, Schwartz JE, Stone AA, Broderick JE. Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. Pain. 2012;153(4):813-22.

80. Taylor SS, Davis MC, Yeung EW, Zautra AJ, Tennen HA. Relations between adaptive and maladaptive pain cognitions and within-day pain exacerbations in individuals with fibromyalgia. Journal of behavioral medicine. 2017;40(3):458-67.

81. Fu K, Makovey J, Metcalf B, Bennell KL, Zhang Y, Asher R, et al. Sleep Quality and Fatigue Are Associated with Pain Exacerbations of Hip Osteoarthritis: An Internet-based Case-crossover Study. The Journal of rheumatology. 2019;46(11):1524-30.

82. Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, et al. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain : a journal of neurology. 2021;144(11):3328-39.

83. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic

stimulation (rTMS): An update (2014-2018). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2019.

84. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009;5(4):355-62.

85. Smith MT, Finan PH, Buenaver LF, Robinson M, Haque U, Quain A, et al. Cognitive-behavioral therapy for insomnia in knee osteoarthritis: a randomized, double-blind, active placebo-controlled clinical trial. Arthritis Rheumatol. 2015;67(5):1221-33.

86. Thorn BE. Cognitive Behavioral Therapy for Chronic Pain. Journal of Health Service Psychology. 2018;44(1):25-32.

87. Kouyanou K, Pither CE, Wessely S. Medication misuse, abuse and dependence in chronic pain patients. Journal of psychosomatic research. 1997;43(5):497-504.

88. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and clinical neurophysiology. 1998;108(1):1-16.

89. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. The Cochrane database of systematic reviews. 2014(4):CD008208.

90. Ayache SS, Ahdab R, Chalah MA, Farhat WH, Mylius V, Goujon C, et al. Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain. European journal of pain. 2016;20(9):1413-22.

91. Haack M, Engert LC, Besedovsky L, Goldstein MR, Devine JK, Dang R, et al. Alterations of pain pathways by experimental sleep disturbances in humans: central pain-inhibitory, cyclooxygenase, and endocannabinoid pathways. Sleep. 2023;46(6).
92. Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. Neuroscience. 2018;387:191-200.
93. Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, et al. Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice. Physical therapy. 2018;98(5):325-35.
94. Almoznino G, Benoliel R, Sharav Y, Haviv Y. Sleep disorders and chronic craniofacial pain: Characteristics and management possibilities. Sleep medicine reviews. 2017;33:39-50.
95. Thomas S, Wang Y, Cundiff-O'Sullivan R, Massalee R, Colloca L. How negative and positive constructs and comorbid conditions contribute to disability in chronic orofacial pain. European journal of pain. 2023;27(1):99-110.
96. Hamilton NA, Catley D, Karlson C. Sleep and the affective response to stress and pain. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2007;26(3):288-95.
97. Konjarski M, Murray G, Lee VV, Jackson ML. Reciprocal relationships between daily sleep and mood: A systematic review of naturalistic prospective studies. Sleep medicine reviews. 2018;42:47-58.

98. Freeman LK, Gottfredson NC. Using ecological momentary assessment to assess the temporal relationship between sleep quality and cravings in individuals recovering from substance use disorders. Addictive behaviors. 2018;83:95-101.
99. Littlewood DL, Kyle SD, Carter LA, Peters S, Pratt D, Gooding P. Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. Psychological medicine. 2019;49(3):403-11.
100. May M, Junghaenel DU, Ono M, Stone AA, Schneider S. Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. J Pain. 2018;19(7):699-716.
101. Stone AA, Obbarius A, Junghaenel DU, Wen CKF, Schneider S. High-resolution, field approaches for assessing pain: Ecological Momentary Assessment. Pain. 2021;162(1):4-9.
102. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol. 2008;4:1-32.
103. Stinson L, Liu Y, Dallery J. Ecological Momentary Assessment: A Systematic Review of Validity Research. Perspect Behav Sci. 2022;45(2):469-93.
104. Pereira NC, Oltramari PVP, Conti PCR, Bonjardim LR, de Almeida-Pedrin RR, Fernandes TMF, et al. Frequency of awake bruxism behaviour in orthodontic patients: Randomised clinical trial: Awake bruxism behaviour in orthodontic patients. J Oral Rehabil. 2021;48(4):422-9.
105. Camara-Souza MB, Bracci A, Colonna A, Ferrari M, Rodrigues Garcia RCM, Manfredini D. Ecological Momentary Assessment of Awake Bruxism Frequency in

Patients with Different Temporomandibular Disorders. Journal of clinical medicine. 2023;12(2).

106. Turner JA, Mancl L, Aaron LA. Brief cognitive-behavioral therapy for temporomandibular disorder pain: effects on daily electronic outcome and process measures. Pain. 2005;117(3):377-87.

107. LeResche L, Mancl L, Sherman JJ, Gandara B, Dworkin SF. Changes in temporomandibular pain and other symptoms across the menstrual cycle. Pain. 2003;106(3):253-61.

108. Aaron LA, Turner JA, Mancl LA, Sawchuk CN, Huggins KH, Truelove EL. Daily pain coping among patients with chronic temporomandibular disorder pain: an electronic diary study. Journal of orofacial pain. 2006;20(2):125-37.

109. Mun CJ, Weaver KR, Hunt CA, Owens MA, Phillips J, Lerman SF, et al. Pain Expectancy and Positive Affect Mediate the day-to-day Association Between Objectively Measured Sleep and Pain Severity Among Women With Temporomandibular Disorder. J Pain. 2022;23(4):669-79.

110. Burgess HJ, Burns JW, Buvanendran A, Gupta R, Chont M, Kennedy M, et al. Associations Between Sleep Disturbance and Chronic Pain Intensity and Function: A Test of Direct and Indirect Pathways. Clin J Pain. 2019.

111. Herrero Babiloni A, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. Journal of neural transmission. 2020;127(4):647-60.

112. Li R, Dworkin RH, Chapman BP, Becerra AZ, Yang L, Mooney CJ, et al. Moderate to Severe Chronic Pain in Later Life: Risk and Resilience Factors for Recovery. J Pain. 2021;22(12):1657-71.

113. Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. Physical therapy. 2011;91(5):700-11.

114. Petrini L, Arendt-Nielsen L. Understanding Pain Catastrophizing: Putting Pieces Together. Frontiers in psychology. 2020;11:603420.

115. Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiologie clinique = Clinical neurophysiology. 2001;31(4):247-52.

116. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. Journal of neurology, neurosurgery, and psychiatry. 2005;76(6):833-8.

117. Klein MM, Treister R, Raij T, Pascual-Leone A, Park L, Nurmikko T, et al. Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. Pain. 2015;156(9):1601-14.

118. Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. European journal of pain. 2016;20(5):689-700.

119. Ahmed MA, Mohamed SA, Sayed D. Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurological research. 2011;33(9):953-8.

120. Taylor JJ, Borckardt JJ, Canterberry M, Li X, Hanlon CA, Brown TR, et al. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2013;38(7):1189-97.

121. Lamusuo S, Hirvonen J, Lindholm P, Martikainen IK, Hagelberg N, Parkkola R, et al. Neurotransmitters behind pain relief with transcranial magnetic stimulation - positron emission tomography evidence for release of endogenous opioids. European journal of pain. 2017;21(9):1505-15.

122. Gan Z, Gangadharan V, Liu S, Korber C, Tan LL, Li H, et al. Layer-specific pain relief pathways originating from primary motor cortex. Science. 2022;378(6626):1336-43.

123. Baptista AF, Fernandes A, Sa KN, Okano AH, Brunoni AR, Lara-Solares A, et al. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC(2)-NIN-CP). Pain reports. 2019;4(1):e692.

124. Leung A, Shirvalkar P, Chen R, Kuluva J, Vaninetti M, Bermudes R, et al. Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-NANS Expert Consensus Panel Review and Recommendation. Neuromodulation. 2020;23(3):267-90.

125. Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The Efficacy of Daily Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Burning Mouth Syndrome (BMS): A Randomized Controlled Single-blind Study. Brain stimulation. 2016;9(2):234-42.

126. Fricova J, Klirova M, Masopust V, Novak T, Verebova K, Rokyta R. Repetitive transcranial magnetic stimulation in the treatment of chronic orofacial pain. Physiological research. 2013;62 Suppl 1:S125-34.

127. Kohutova B, Fricova J, Klirova M, Novak T, Rokyta R. Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial. Physiological research. 2017.

128. Saisanen L, Huttunen J, Hypponen J, Nissen M, Kotiranta U, Mervaala E, et al. Efficacy and tolerability in patients with chronic facial pain of two consecutive treatment periods of rTMS applied over the facial motor cortex, using protocols differing in stimulation frequency, duration, and train pattern. Neurophysiologie clinique = Clinical neurophysiology. 2022;52(2):95-108.

129. Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, et al. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain stimulation. 2008;1(2):122-7.

130. Andre-Obadia N, Magnin M, Simon E, Garcia-Larrea L. Somatotopic effects of rTMS in neuropathic pain? A comparison between stimulation over hand and face motor areas. European journal of pain. 2017.

131. Mori N, Hosomi K, Nishi A, Oshino S, Kishima H, Saitoh Y. Analgesic Effects of Repetitive Transcranial Magnetic Stimulation at Different Stimulus Parameters for Neuropathic Pain: A Randomized Study. Neuromodulation. 2022;25(4):520-7.

132. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-21.

133. Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain. 2020;161(11):2446-61.

134. Colloca L. The Placebo Effect in Pain Therapies. Annu Rev Pharmacol Toxicol. 2019;59:191-211.

135. Proulx-Begin L, Herrero Babiloni A, Bouferguene S, Roy M, Lavigne GJ, Arbour C, et al. Conditioning to Enhance the Effects of Repetitive Transcranial Magnetic Stimulation on Experimental Pain in Healthy Volunteers. Frontiers in psychiatry. 2022;13:768288.

136. Malhi GS, Bell E. Is the response to rTMS largely the result of non-specific effects? Aust N Z J Psychiatry. 2021;55(5):445-50.

137. Berlim MT, Broadbent HJ, Van den Eynde F. Blinding integrity in randomized sham-controlled trials of repetitive transcranial magnetic stimulation for major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013;16(5):1173-81.

138. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic

stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychological medicine. 2014;44(2):225-39.

139. Bailey NW, Hoy KE, Rogasch NC, Thomson RH, McQueen S, Elliot D, et al. Differentiating responders and non-responders to rTMS treatment for depression after one week using resting EEG connectivity measures. Journal of affective disorders. 2019;242:68-79.

140. Hasanzadeh F, Mohebbi M, Rostami R. Prediction of rTMS treatment response in major depressive disorder using machine learning techniques and nonlinear features of EEG signal. Journal of affective disorders. 2019;256:132-42.

141. Herrero Babiloni A, Beetz G, Bruneau A, Martel MO, Cistulli PA, Nixdorf DR, et al. Multitargeting the sleep-pain interaction with pharmacological approaches: A narrative review with suggestions on new avenues of investigation. Sleep medicine reviews. 2021;59:101459.

142. Tang NK, Goodchild CE, Salkovskis PM. Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. Behaviour research and therapy. 2012;50(12):814-21.

143. Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. Sleep medicine clinics. 2014;9(2):261-74.

144. Tang NKY. Is cognitive-behaviour therapy for insomnia (CBT-I) the new best pain killer? Sleep medicine reviews. 2021;60:101536.

145. Fu K, Metcalf B, Bennell KL, Zhang Y, Deveza LA, Robbins SR, et al. The association between psychological factors and pain exacerbations in hip osteoarthritis. Rheumatology. 2021;60(3):1291-9.

146. Costa YM, De Koninck BP, Elsaraj SM, Exposto FG, Herrero Babiloni A, Kapos FP, et al. Orofacial pain education in dentistry: A path to improving patient care and reducing the population burden of chronic pain. Journal of dental education. 2021;85(3):349-58.

147. Lotsch J, Ultsch A. Machine learning in pain research. Pain. 2018;159(4):623-30.

148. Shahin M, Ahmed B, Hamida ST, Mulaffer FL, Glos M, Penzel T. Deep Learning and Insomnia: Assisting Clinicians With Their Diagnosis. IEEE J Biomed Health Inform. 2017;21(6):1546-53.

149. Zandvakili A, Philip NS, Jones SR, Tyrka AR, Greenberg BD, Carpenter LL. Use of machine learning in predicting clinical response to transcranial magnetic stimulation in comorbid posttraumatic stress disorder and major depression: A resting state electroencephalography study. Journal of affective disorders. 2019;252:47-54.

150. Whibley D, Braley TJ. The pursuit of mechanistic links between sleep disturbances and pain: are we getting warmer? Sleep. 2023;46(6).