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Orofacial musculoskeletal pain: an evidence-based bio-psycho-social matrix model

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Highlights

- Chronic orofacial pain is a highly prevalent and clinically relevant condition
- Social, psychological and biological factors may all facilitate and modulate the orofacial pain process.
- Pain-, negative emotions, insomnia and stress-related cortical activity promote a feedforward neural network.

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- Cortical, subcortical and cerebellar areas disrupt the homeostatic state which may result in pain chronicity.
- An interdisciplinary therapeutic strategy based on a biopsychosocial model is essential for effective pain management.

Abstract

Pain is a multidimensional experience comprising sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. Clinical and research findings have demonstrated a complex interplay between social burdens, individual coping strategies, mood states, psychological disorders, sleep disturbances, masticatory muscle tone, and orofacial musculoskeletal pain. Accordingly, current classification systems for orofacial pain require psychosocial assessments to be an integral part of the multidimensional diagnostic process. Here, we review evidence on how psychosocial and biological factors may generate and perpetuate musculoskeletal orofacial pain. Specifically, we discuss studies investigating a putative causal relationship between stress, bruxism, and pain in the masticatory system. We present findings that attribute brain structures various roles in modulating pain perception and pain-related behavior. We also examine studies investigating how the nervous and immune system on cellular and molecular levels may account for orofacial nociceptive signaling. Furthermore, we review evidence pointing towards associations between orofacial musculoskeletal pain and neuroendocrine imbalances, sleep disturbances, and alterations of the circadian timing system. We conclude with several proposals that may help to alleviate orofacial pain in the future.

Keywords: Orofacial pain, pain, chronic pain, pain experience, cognition, emotional motor system, biopsychosocial, neuroimmunology, sleep disorders, circadian timing.

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Introduction

Pain in the orofacial area has an estimated lifetime prevalence of 26% (Macfarlane et al., 2002). The most common chronic pain conditions in this region are attributed to a heterogeneous family of musculoskeletal disorders widely known as temporomandibular disorders (TMDs) (Maixner et al., 2011). Painful TMDs have a 4% annual incidence in the US, are diagnosed most commonly in 20- to 50-year-olds, and females are approximately twice as often

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affected as men (Bueno et al., 2018). About 49% of patients with TMD demonstrate persistence of the painful state (Slade et al., 2016).

The term TMD is derived from anatomical structures. The connection between the temporal bone and the C-shaped mandible forms the two jaw joints, i.e., the temporomandibular joints (TMJs). Under normal circumstances, masticatory muscles receiving neural signals from cortical structures regulate the static and dynamic TMJ load that occur during physiological activities such as speech, mastication, swallowing, etc. (Avivi-Arber and Sessle, 2018). On the other hand, jaw muscle relaxation is characterized by minimal electromyographic (EMG) activity and results in the so-called "habitual position" of the mandible, also referred to as physiological "rest position" or "postural position", with a vertical distance of approximately 3 mm between maxillary and mandibular teeth (Michelotti et al., 1997; Rugh and Drago, 1981).

Findings of the prospective clinical study titled Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) suggest that TMD is a complex disease with a number of risk factors in many domains that may contribute to TMD development (e.g., genetics, environment, behavior, medication, psychological stress, anxiety, obsessive-compulsive feelings, pain-coping strategies, and sleep quality) (Slade et al., 2016). Notably, the relationship between psychological factors and pain persistence is bidirectional (Edwards et al., 2016). Yet, it largely remains an enigma how neuromuscular, biomechanical, neurobiological, and psychosocial aspects interact in a given subject experiencing TMD signs or symptoms.

Patient reports and experimental evidence imply a unique salience of head region pain compared to other bodily pain (Meier et al., 2014). Regardless of origin, painful TMDs are associated with poor quality of life, impaired psychosocial functioning, anxiety, insomnia, and depression (John et al., 2007; La Torre Canales et al., 2018; Meira e Cruz et al., 2019). Orofacial musculoskeletal pain hence disrupts the homeostatic state of various systems, interferes with goal-oriented behavior, and generates stress. Vice versa, psychosocial burdens impact negatively on the central nervous system and facilitate neuropathology and psychopathology, insomnia, musculoskeletal pain, as well as autonomic nervous system (ANS) dysregulation (Critchley et al., 2013). Since the psychiatrist George Engel called for a new “medical model” in his seminal article published in *Science* in 1977*,* the conceptual framework, which integrates biological, psychological, social, and behavioral dimensions, has received broad recognition (Engel, 1977). Terms like personalized or patient-centered medicine increasingly reflect the consideration of the inter-relationships between contextual social burden, psychological state, and neurobiological processes (Fillingim, 2017). The exaggerated focus on biological parameters in medicine can partly be explained by the lack of validated instruments to quantify psychosocial

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parameters. Still, for comprehensively assessing and managing orofacial pain the use of validated self-report instruments is critical for capturing the various physiological, psychological, and social factors that reciprocally influence one another (Bhalang et al., 2020; Ettlin et al., 2016; Schiffman et al., 2014; Sommer et al., 2019).

Accordingly, current classification systems for pain and specifically facial pain require psychosocial assessments to be an integral part of the multidimensional diagnostic process (1. International Classification of Orofacial Pain, 2020; Fillingim et al., 2014). Such instruments provide helpful information for understanding one's personal suffering and for providing tailored treatment since perception and interpretation of painful sensations burden individuals differently (Fillingim, 2017; Galli et al., 2010; Pigozzi et al., 2021). Yet, the use of psychological screening tools is still poorly integrated in today's dental education (Häggman-Henrikson et al., 2018).

On the other hand, it needs to be borne in mind that validated tools do not capture all personal burdens. For gathering complementary information, narrative medicine (narratology, narrativity) identifies biographical and cultural experiences, social and professional situations, personality traits, and coping strategies with the aim of bringing the patient’s inner world to life. Integrating the perspective of anthropologists, social workers and historians in the training of healthcare professionals may assist in raising shared awareness of the patient’s perspective, which requires an empathic effort on behalf of the clinician beyond the mere diagnosis of classifiable disorders (Bonathan et al., 2014; Yawar, 2008). Ignoring such dimensions may prolong suffering as evidenced by patient narratives (Durham et al., 2011; Zakrzewska, 2006).

Given these observations and related conceptual frameworks, in this review we discuss evidence on how the interaction of social, psychosocial, and biological factors may generate and perpetuate musculoskeletal orofacial pain (figure 1). To this purpose, this review is divided in five sections with partly overlapping aspects. The first section reviews studies investigating the putative link between cognitive-emotional states, orofacial musculoskeletal pain, and jaw muscle activities during day and nighttime. The second section focuses on the roles of cortical, cerebellar, and subcortical structures related to trigeminal motor functions, cognitive-emotional processing, ANS activity, and pain control. The third section addresses the interplay between nociceptive, immune, neuroendocrine, and ANS processes important to maintain nociceptive signaling. The fourth section looks at the putative role of the circadian timing system (CTS) in processing nociceptive and emotional stimuli, as well as the potential of pain for dysregulating the CTS. Each of these sections is followed by a summarizing paragraph. Finally, several proposals are presented that may help alleviating orofacial pain in the future.

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Associations of cognitive-emotional states with pain appraisal, orofacial musculoskeletal pain, and jaw muscle activity

Human sensations, including pain, depend on personal perceptions, which in turn are modulated by genetic, biographical and contextual factors. Perception is a cognitive function capable of linking the senses to behavior. The concept of reason and emotion as being separate entities has been supported by philosophers such as Plato and Kant, as well as the father of psychoanalysis, Sigmund Freud. Yet, seeing the glass as half-full or half empty depending on mood state exemplifies how emotions can modulate reasoning. Analogously, the emotional state partly determines how we appraise or interpret psychosocial burdens and noxious stimuli (Jinich-Diamant et al., 2020; Zorn et al., 2020). In turn, pain modulates cognitive functioning and emotional well-being (Bhalang et al., 2020; Morogiello et al., 2019). From a neuroscience perspective, it is therefore not surprising that nociception correlates with activation of multiple brain systems and networks that overlap with systems attributed to emotion, cognition, beliefs, and ANS activity (Brügger et al., 2012; Gandhi et al., 2020; Wiech et al., 2008; Yin et al., 2020; Zheng et al., 2020).

Maladaptive cognitive processes, psychological disorders, and psychosocial burdens can increase the likelihood of developing orofacial pain and headache (Asquini et al., 2021; Dinan et al., 2021; Emodi-Perlman et al., 2020; Fillingim et al., 2013; Glaros et al., 2016; Jeong et al., 2021; Khawaja et al., 2015; Reiter et al., 2018; Wieckiewicz et al., 2017; Yap et al., 2002). In clinical practice, it is common to observe a correlation between pain onset and social burdens in the form of chronic daily hassles (e.g., high workload, time pressure, conflicts, financial strains) or traumatic life events (e.g., loss of a loved one, unemployment, migration, domestic violence, injustice experience), other adverse life circumstances, or lack of access to supporting resources (Bhalang et al., 2020; Chandan et al., 2019; Fillingim et al., 1997; Hinwood et al., 2012). It is worth noting that even seemingly pleasurable events can be stressful. Diverse social burdens can impact on emotional well-being and lead to increased neural signaling of the emotional motor system (Holstege, 1992), which in turn may augment orofacial muscle activity in the form of tooth grinding or clenching, lip or cheek biting, tongue pressing, or excessive gum chewing. For a long time, abnormal activity of mandibular elevator muscles has been linked to negative emotional experiences (anger, frustration, physical pain), reflected in terms such as gnashing, grinding, and gritting of teeth. Early examples include biblical verses: Psalm 35:16 “Like profane mockers at a feast, they gnash at me with their teeth.” Psalm 112:10 “The sinner shall see and be angry as he shall gnash his teeth and consume away.” Given this historical wisdom of crowds, it is not surprising that scientist have attempted to identify a link between negative emotions and increased jaw muscle EMG. Already in the 1960s, Perry et al. described "a graduated

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sequence running from muscle relaxation, through idiosyncrasy to clenching" as a consequence of intense concentration and stress. They demonstrated in eight dental students that verbal or noise stimulation during an interview can produce an increase in masticatory muscle EMG signaling (Perry et al., 1960). More recently, persistent work-related stress was shown to be associated with an increased level of temporalis muscle activity during sleep (Schmitter et al., 2019).

Given such evidence for the associations between elevated psychosocial scores and 1) the development of orofacial pain and headache as well as 2) abnormal masticatory muscle activity, one would expect a causal connection between TMD symptoms and jaw muscle EMG recordings. To analyze this putative connection, studies measured masticatory muscle activity in TMD patients and healthy controls during sleep (monitored by polysomnography (PSG)) and during wakefulness (monitored by ecological momentary assessment (EMA)). Based on research diagnostic criteria for bruxism defined by Lavigne et al. (Lavigne et al., 1996), an early PSG investigation indeed found a 3.45 higher probability of masticatory myofascial pain occurring in subjects with rhythmic masticatory muscle activities compared to controls (Rossetti et al., 2008). Yet, subsequent studies could not verify such a univariate association between TMD pain and masticatory muscle EMG. Although self-reported bruxism is commonly more prevalent among individuals with painful TMD than among controls, painful symptoms could not be explained by PSG diagnosed sleep bruxism in several studies (Gonzalez et al., 2018; Muzalev et al., 2017; Raphael et al., 2013; Raphael et al., 2012; Wieckiewicz et al., 2020). Some researchers even observed that TMD-pain patients had fewer sleep-bruxism episodes than non-TMD controls (Castrillon and Exposto, 2018; Lavigne et al., 1997; Raphael et al., 2012; Rompré et al., 2007). Still, EMG activity levels not meeting the diagnostic criteria of sleep bruxism were significantly higher in females with myofascial TMD compared to control groups and possibly contribute to persistent pain (Raphael et al., 2013). Analyzing wake-time bruxism, one study using tooth contact time as a proxy measure for jaw muscle tone observed higher activities in TMD pain patients than controls (Chen et al., 2007). However, such an association could not be verified with ambulatory EMG measurements (Gonzalez et al., 2018). An interesting observation of EMA studies is that awake and sleep-time jaw muscle activities are generally low in duration and magnitude (Gonzalez et al., 2018; Schmitter et al., 2019).

Given these inconsistent study results, it is important to note that long-term EMG recordings revealed that activity in the masseter muscle varied to a large extent in patients reporting TMD symptoms (Lavigne et al., 2001; Rugh and Harlan, 1988). Equally, signs and symptoms of TMD fluctuate substantially (Magnusson et al., 2005). Furthermore, simply participating in an EMA study may cause an increase in self-awareness and self-monitoring

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which may affect involuntary muscle activity. Also, EMG during PSG or EMA cannot by recorded from deep masticatory muscles such as the lateral and medial pterygoid muscles. In addition, the observation that each clinical bruxism symptom seems to relate to different aspects of jaw motor activity deserves consideration (Yoshida et al., 2017). Finally, masticatory muscle activity dysregulation and related orofacial pain can be due to neurological disorders and drugs (Baat et al., 2021; Frucht et al., 2021; Ortega et al., 2008; Patel and Kumar, 2012; Rintakoski et al., 2010; Sude et al., 2021).

In summary, given the limited feasibility to obtain long-term EMG recordings of multiple jaw muscles in subjects' natural environments in combination with psychometric and PSG assessments, current evidence suggests a complex interplay between emotional burdens, individual coping strategies, masticatory muscle tone, and orofacial musculoskeletal pain (figures 1).

Masticatory sensorimotor integration at the central nervous system level

Understanding orofacial musculoskeletal disorders requires the knowledge that the mandible is suspended in a sling of masticatory muscles under complex cortical and subcortical control (Yoshizawa et al., 2019). Proprioceptive information from receptors in the periodontium, skin, muscles, tendons, and joints relay in the mesencephalic trigeminal nucleus and provide the central nervous system with information on mandibular positioning. Proprioceptive afferents project via mesencephalic and thalamic nuclei to the insular cortex and from there to the somatomotor and somatosensory cortices, basal ganglia and the amygdala (Ettlin et al., 2004; Tsutsumi et al., 2018). Some of these cortical structures project onto the trigeminal motor neurons via the parvocellular pontine reticular formation, which is regarded as the "masticatory pattern generator" (Lund et al., 1998; Notsu et al., 2008; Yasui et al., 2004; Yoshida et al., 2009) (figure 2). Evidence for cortical and subcortical modulation of the jaw muscle tone is supported by electrical or chemical stimulation of many of these areas (Ahn et al., 2001; Nakamura et al., 1990; Sasamoto et al., 1990; Uchino et al., 2015). Further evidence indicates that masticatory force correlates differentially with activity in brain areas related to motor function, particularly in the primary sensorimotor cortex and cerebellum (Yoshizawa et al., 2019). In addition, the cerebellum is involved in relaying sensory and motor information to regulate mandibular posture and masticatory movements (Yoshizawa et al., 2019). Along with the basal ganglia and pontine reticular formation, the cerebellum and cerebellar pathology, respectively, have been shown to contribute to the pathophysiology of orofacial dystonia and bruxism (Neychev et al., 2008; Pollack and Cwik, 1989). An interesting observation is that mandibular movements under stressful conditions attenuate stress-induced activation of the hypothalamic-pituitary-adrenal

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axis and of the ANS. Specifically, mastication has been shown to minimize stress-induced changes in the hippocampus and hypothalamus (Sasaguri et al., 2018). A unique effect of extreme masticatory activity on the ANS is illustrated by the trigeminal cardiac reflex that can produce adverse cardiorespiratory changes (hypotension, bradycardia, and asystole), as well as gastric consequences (hypermotility) (Sugrue et al., 2018). This phenomenon possibly relies on suppressed sympathetic outflow of both arms of the baroreflex arc to the blood vessels and the heart via activation of nociception receptors (Tsai et al., 2018).

It is worth noting that the cerebellum contains a variety of neural interconnections with different brain areas that are functionally involved in mediating stress-induced behavioral changes such as hypothalamus, amygdala, prefrontal and cingulate cortex, periaqueductal gray, nucleus raphe magnus, and others (Moreno-Rius, 2019). Thus, in addition to its involvement in controlling motor functions, the cerebellum has an intermediary role in cognitive and emotional processing, ANS activity, and pain (Adamaszek et al., 2017; Claassen et al., 2020; Moreno-Rius, 2019). Yet, although the cerebellum has frequently been shown to respond to painful stimuli including those from orofacial tissues, its specific contributions to pain processing remains elusive (Brügger et al., 2012). Stress triggered by pain or other biological, psychological, and social sources may increase cerebellar signaling. In turn, the cerebellum responds in a feedforward control manner using memory processes and environmental stimuli (Moreno-Rius, 2019). Results of such feedforward neural network activity are, for example, sleep disturbances and muscle hyperactivity that may result in orofacial musculoskeletal pain in vulnerable subjects (Meira e Cruz and Manetta, 2019).

In summary, it is plausible to suggest that various cortical, cerebellar and subcortical structures play a central role in channeling emotions, perception, cognition, and motor activity to control mandibular posture and movements. In susceptible individuals, negative thoughts and emotions in response to overwhelming psychosocial burdens can lead to dysregulation of various interactive neurobiological systems. In consequence, orofacial musculoskeletal pain may develop (figure 2).

Interactions between nociceptive, immune, neuroendocrine and autonomic nervous system

Both the immune and nervous systems detect deviations in homeostasis and initiate protective responses, usually by direct interactions known as neuroimmune interface (Bonfante et al., 2018; Grace et al., 2014). Such interplay is mediated by immune cell receptors that bind neuropeptides and neuromodulators released by nociceptors. These receptors are located on glial, endothelial, and T cells as well as resident tissues macrophages (Bonfante et al., 2018;

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Grace et al., 2014; Shinoda et al., 2019). Therefore, nociceptor activation in orofacial myalgia or arthralgia may amplify and perpetuate pain via immune cell responses to substances released from sensory neuron terminals (Glaros et al., 2016). Although masticatory muscle pain is rarely accompanied by clinical signs of injury or inflammation, increased intramuscular levels of cytokines and chemokines have been reported (Louca Jounger et al., 2017). It can be hypothesized that immune cell–driven changes may occur in nociceptors of masticatory muscles, tendons, and joints that possibly underlie the increased membrane excitability of these receptors (Antel et al., 2020; Jain et al., 2020). When nociceptive signaling exceeds physiological adaptive capacity, structural changes may occur along the nociceptive pathways triggering central sensitization and consequently pain (Shinoda et al., 2019; Zheng et al., 2020).

Neuroimmune-linked pain sensitivity may be further heightened by activation of the neuroendocrine hypothalamus-pituitary-adrenal axis and ANS alterations due to psychosocial stress (del Rey and Besedovsky, op. 2017; Lin et al., 2019). Sympathetic outflow is regulated by sympathetic premotor neurons located in the lower brain stem and hypothalamus. It is generally accepted that sympathetic system activity controls blood pressure and night-time masticatory muscle activity. However, it is less known that secondary lymphoid organs such as the spleen and lymph nodes are richly innervated by the sympathetic nervous system (Bottasso, 2019; Nashed et al., 2012). It is currently unknown if neuroplasticity of this system has implications for neuroimmune-mediated nociception and pain. But a bidirectional neuroimmune interaction is increasingly recognized on the level of the trigeminal ganglion, brainstem sensory and motor nuclei, as well as higher brain structures (Albrecht et al., 2019; Dantzer, 2018; Hossain et al., 2017; Jeong et al., 2021; Shinoda et al., 2019). Since clinical pain per se is a form of stress and often accompanied by other sources of distress, it is interesting to note that chronic stress may alter the morphology of microglial cells in the cerebral cortex. In addition, microglial-induced inflammation is an important neurobiological mechanism by which microglia mediates the behavioral effects of chronic psychological stress (Couch et al., 2013; Hinwood et al., 2012; Yasui et al., 2004). Sex-specific variations in pain sensitivity may also in part be encoded in differential changes of microglia and the peripheral immune system, respectively (Lopes et al., 2017; Woodburn et al., 2021).

The above-mentioned cellular and molecular findings have not yet yielded biomarkers applicable in clinical settings. This lack of methods for demonstrating putative tissue changes in the presence of pain reports inspired the terminology task force of the International Association for the Study of Pain (IASP) to adopt the term “nociplastic pain” (Kosek et al., 2016). The chosen definition for nociplastic pain is “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors

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or evidence for disease or lesion of the somatosensory system causing the pain". Symptoms originating from augmented CNS pain and sensory processing are mechanistically different from nociceptive or neuropathic pain. Still, patients can have a combination of nociceptive, neuropathic and nociplastic pain (Kosek et al., 2016). At the time of submitting this manuscript, defining criteria for this new mechanistic pain descriptor were not yet published. The term is suggested to cluster pain disorders that appear to share similar pain pathophysiology given that they are accompanied by diverse hypersensitivities (e.g., touch, pressure, temperature, sound, light, odors), sleep disturbances, fatigue, cognitive problems, and others. Patients experiencing TMDs and overlapping disorders such as headaches, fibromyalgia, and other forms of widespread pain often complain about such phenomena.

In summary, orofacial musculoskeletal pain and associated psychological disturbances affect parts of the stress and immune system in bidirectional, complex, multifaceted, and partly sex-specific ways (figures 1 and 2). Knowledge on the nature and role of nociceptor-immune crosstalk in the generation and perpetuation of orofacial pain is still sparse and thus deserves further investigation.

Circadian timing system, sleep, and pain

The CTS and its behavioral manifestation in an individual chronotype have not received much consideration in a comprehensive orofacial pain model. The CTS evolved as an adaptation to the 24-h light/darkness cycle resulting from Earth rotation. It controls sleep and wakefulness, body temperature, thirst, appetite, and many other cellular, behavioral, and physiological processes. In mammals, the CTS is composed of a light-responsive central pacemaker ("master clock") located in the suprachiasmatic nucleus of the hypothalamus which responds to photostimulation of the retina, as well as genetically encoded and coordinated peripheral clocks in virtually all other tissues. The discovery of interacting genes that pace the clocks ("clock genes") led to a Nobel prize in 2017 (www.nobelprize.org/prizes/medicine/2017/prize-announcement). Apart from gene regulation, the CTS is synchronized via environmental cues ("zeitgebers" or time givers), as well as neuroendocrine and ANS interactions. Interestingly, neurotransmitters involved in nociception also influence the CTS (Palada et al., 2020).

The best-characterized phenotypic presentation of CTS is the sleep-wake cycle. This cycle is regulated by a circadian process (reflected by the endogenous circadian time) and by a homeostatic process (reflected by sleep need). Restorative sleep is a necessity for proper functioning of physiological and psychological systems. Activity of these systems can be investigated by electrophysiology and neuroimaging. Such techniques have made it possible to demonstrate that the clearance of metabolic waste products from the brain by cerebrospinal

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fluid occurs in an orchestrated fashion with cortical oscillations. Specifically, waves of fluid flow are synchronized with delta waves (<4Hz) (Fultz et al., 2019). These low-frequency oscillations are generated by cortico-thalamocortical loops under modulatory control of brainstem and forebrain systems (Peigneux, 2014). In patients experiencing orofacial pain and insomnia, pain persistence can be linked to disturbances of these mechanisms since inadequate sleep lowers pain thresholds, increases ratings of pain intensity, and is associated with negative mood states (Haack et al., 2020; Meira e Cruz et al., 2019). Vice versa, the origins of insomnia can be traced to emotionally burdening experiences (Babson and Feldner, 2015).

In a clinical context, melatonin and cortisol are commonly used CTS biomarkers. Other examples of homeostatic processes under CTS regulation are body temperature, the immune system, and additional hormones (Scheiermann et al., 2018). Attention has only recently been given to the interaction of the CTS with pain and emotions (Bauducco et al., 2020; Burish et al., 2019; Crodelle et al., 2019). Whereas research and knowledge on the link between CTS and mood are rapidly expanding, investigations on its interaction with pain are scarce. This is likely due to methodological constraints regarding the collection of pain reports at multiple time points throughout the 24-hour cycle. In the orofacial pain field, it has been reported that the dental pain threshold has a nadir in the early morning and peaks in the early afternoon (Pöllmann and Harris, 1978). The intensity of burning mouth and musculoskeletal orofacial pain also tend to increase throughout the day (Forssell et al., 2012; Glaros et al., 2008). Yet dental and joint pain of inflammatory origin as well as some headaches related to masticatory muscle activity prevail in the early morning. A time-based correlation with altered neuroendocrine and immune activities has been reported (Galbo and Kall, 2016; Grushka and Sessle, 1984; Vieira et al., 2020). Bruxism occurs in response to increased sympathetic signaling as one of the CTS pathways (Iwasaki et al., 2019). The putative role of the CTS in processing nociceptive and emotional stimuli warrants further exploration in orofacial pain. Vice versa, it remains to be clarified whether pain-associated psychosocial burdens and sleep impairment result in CTS dysregulation.

In summary, considering the pool of evidence, neuroimmune sensitization, neuroendocrine imbalance, sleep and circadian system alterations, and psychological distress may all facilitate the generation and perpetuation of orofacial musculoskeletal pain (figures 1 and 2).

Future directions

In spite of the many years of investigation on pain experience and its management, chronic orofacial musculoskeletal pain remains highly prevalent. Use of self-report instruments

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(Ettlin et al., 2016; Schiffman et al., 2014), an evaluation system for bruxism (Manfredini et al., 2020), somatosensory function assessment (Svensson et al., 2011; van der Cruyssen et al., 2020), sensor technologies for ecological momentary assessment (Chen et al., 2021; Naranjo-Hernández et al., 2020), genome-wide association studies (Broberg et al., 2021; Smith et al., 2019), epigenetic investigations (D'Agnelli et al., 2019), neuroimaging (Lin, 2018; Yin et al., 2020), biomarkers (Davis et al., 2020; Doetzer et al., 2021; Jasim et al., 2018; Mackey et al., 2019), deep learning approaches (Ceglia et al., 2018) and narratology may all serve to further our understanding on the complex relationships among genetic predisposition, anatomical variations, psychosocial burdens, orofacial musculoskeletal pain and related comorbidities. The challenge lies in coordinating comprehensive data collection and in integrating findings in the context of an interdisciplinary management strategy, which requires training that is currently inadequate in many parts of the world.

Granting specialty recognition to orofacial pain and oral medicine experts by the US National Commission on Recognition of Dental Specialties and Certifying Boards was an important step towards attracting young talents and thus enhancing training in this field (Heir, 2020; Stoopler and Murdoch-Kinch, 2020). Despite these hopeful developments, leaders of dental schools in many parts of the world still do not give proper recognition and funds to this clinically relevant and academically rewarding field. For providing adequate care to the many patients suffering from orofacial pain, more professorships are urgently needed to appropriately educate practitioners and researchers alike (Sharma et al., 2020; Ziegeler et al., 2019). Such conclusion is underscored in the recent report published by the U.S. National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division, which identified the following five future research and patient care priorities (Yost et al., 2020): 1) basic research focused on improving clinical outcomes, 2) sex differences in TMDs and orofacial pain, 3) population-based research to further understand the burden and costs of TMDs, 4) comparative effectiveness research on TMD treatments, and 5) artificial intelligence and novel data approaches.

Authors Contribution

DAE & JTC-N conceived the idea, DAE, JTC-N, MHN & MMC contributed equally to searching the literature and writing the manuscript.

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Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content of the paper.

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Legends

Figure 1. Bio-psycho-social matrix model

Orofacial pain and dysfunction are commonly associated with a burdening social context that can overwhelm psychological response mechanisms and dysregulate biological systems. In turn, pain can interfere with biological processes as well as emotional and social functioning. ANS = Autonomic Nervous System. Created with BioRender.com

Figure 2. The potential impact of psychosocial burdens on the neuroimmune, neuroendocrine and autonomic system and related cortical regions

Psychosocial burdens can have a negative impact on different systems that are controlled by interactive brain networks including autonomic systems (circadian timing, neuroendocrine, neuroimmune, and autonomic nervous systems), the mood regulation system, the pain inhibitory system, and the emotional motor system. Imbalance of autonomic systems can occur within a complex neural network that involves the cingulate cortex, hypothalamus, pituitary gland, amygdala, hippocampus, periaqueductal grey, and ventromedial medulla (purple). The neural basis of mood disorders has been attributed to abnormalities of prefrontal cortical projections, structures of the limbic system, and various brainstem structures such as raphe nuclei, locus coeruleus, substantia nigra, and ventral tegmentum (yellow). Putative structures responsible for attenuated central pain inhibition are the pre- and postcentral gyrus, cingulate cortex, thalamus, as well as raphe nuclei and locus coeruleus (blue). Cortical motor regions associated with emotional responses include the primary motor cortex, the basal ganglia, the cerebellum, and brainstem structures (red). Please note that this schematic graph presents only a few representative and not all brain structures considered relevant for the systems listed. For didactic purposes, it oversimplifies the complexity of the structural and functional networks. Created with BioRender.com

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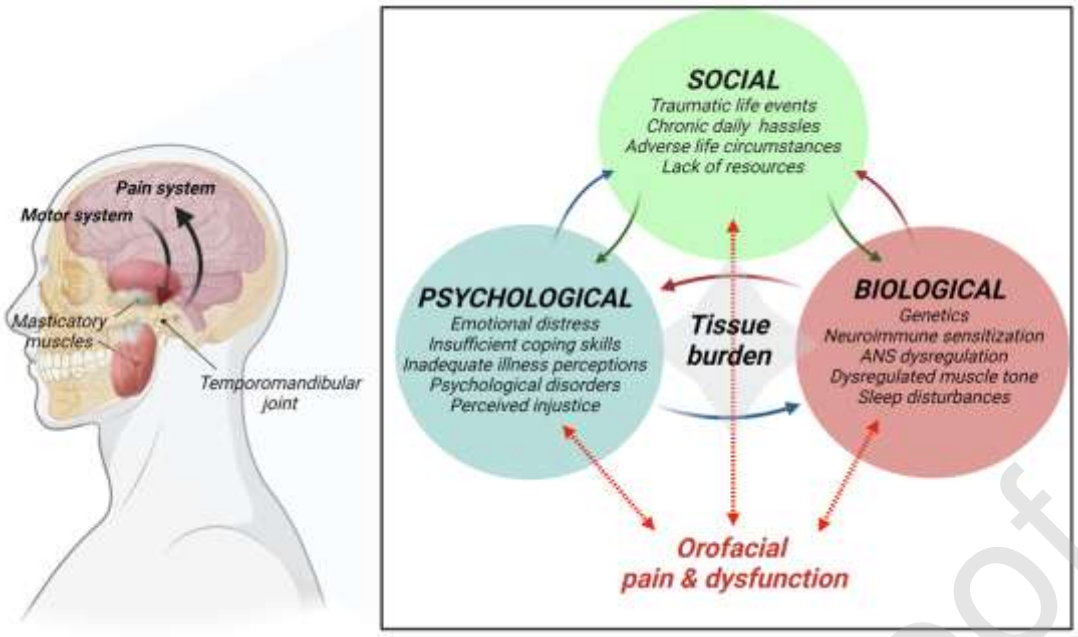

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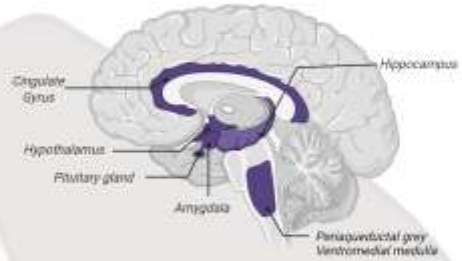
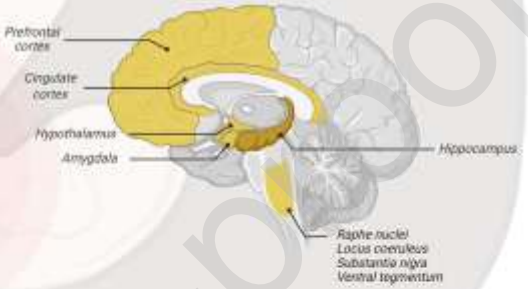
Musculoskeletal orofacial pain has been linked to negative impact of psychosocial burdens on various systems

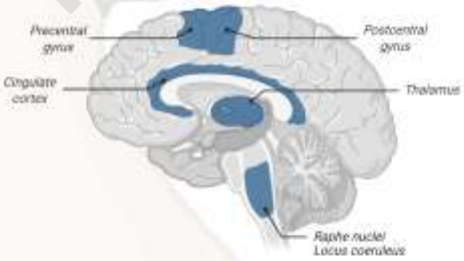
Autonomic Systems
Circadian timing; Neurendocrine; Neuroimmune; Autonomic nervous system



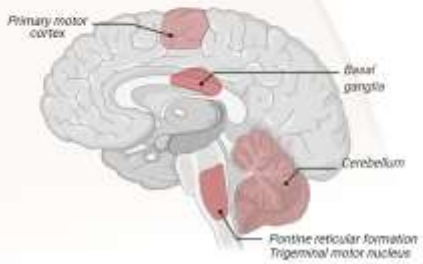
Mood regulation system



Pain inhibitory system



Emotional motor system



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