Assessment of the Psychological Comorbidity, Pathophysiological Mechanisms, and Treatment Implications in Patients with Chronic Orofacial Pain

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Abstract

Chronic orofacial pain is a multifaceted health problem that like many other forms of chronic pain bears deleterious effects upon quality of life as well as psychological and physiological well-being. Due to a poorly understood etiology, effective treatment strategies are lacking and tend to lack a guiding integrative conceptual framework to form the basis and development of intervention. This review seeks to provide an updated review of the comorbid psychological disorders and characteristics that are common among chronic orofacial pain patients, while also examining the pathophysiological mechanisms underlying orofacial pain. Rather than consider the emotional, cognitive, and neuroendocrine influences upon pain perception and severity individually, these factors should be viewed as working in concert with one another. It is this interplay amongst distinct psychological characteristics governing the patient along with physiological mechanisms that exacerbate the pain. Together, the goal is to identify unique characteristics surrounding orofacial pain and offer some plausible insights for effective treatment outcomes.

Keywords: Chronic orofacial pain; Temporomandibular joint; Periaqueductal gray

Introduction

Chronic Orofacial Pain (COP) represents a complex pain condition with an etiology comprised of many factors including those falling within biological, psychological, and social domains. The complexity of this condition underscores the urgency to evaluatethese domains from an integrative perspective rather than one that simply addresses the potential etiological mechanisms in a singular fashion. Indeed, a review of the trajectory of this pain condition reveals a dynamic pathway in which numerous factors seemingly play a role in its manifestation, as well as its chronicity.

By definition, “chronic” orofacial pain represents a pain that has persisted for a period of time that is longer than the believed recovery time for that body site to heal. Approximately 40-70% of the US reportedly demonstrate a symptom of orofacial pain, and 10% meet the criteria for having COP to the point that it is considered disabling and significantly compromising activities of daily living [1]. The intention of this paper will not center on providing an exhaustive review, but instead, to highlight key features of COP from a biopsychosocial perspective. Specifically, the transition that lead sorofacial pain from the acute to the chronic stage will be reviewed by underscoring well established mechanisms believed to facilitate this transition. Embedded in this discussion, the psychophysiological mechanisms that are less established in the manifestation of COP will also be reviewed. These mechanisms may distinguish COP from other types of pain. Much of the data presented stem from studies that have included a wide range of orofacial pain conditions including, but not limited to, temporomandibular disorders, trigeminal pain, and headaches.

The Psychological Pathogenesis from Acute to Chronic Pain

There are a number of factors that contribute to the transition from acute pain to chronic pain. It is suspected that the identification of psychological issues serves as an indicator that acute pain is becoming more chronic in nature [2,3]. This is logical in that chronic pain appears to be associated with diagnoses of psychological disorders (e.g., mood disorders and anxiety disorders) [4,5] and other adverse psychological constructs whose presence has often been suspected in complicating the clinical picture of chronic pain. As depicted by the model below (Figure 1), these factors are intertwined with physiological and behavioral factors that further maintain the pain condition.

Gatchel et al. [6] propose an empirically supported model, consisting of three stages, which explain the transition by which acute pain evolves into chronic pain. According to this model, Stage 1 involves the emergence of acute stage of pain coupled with the anticipated preoccupation that results from the emergence of the unpleasant stimulus. At this point, the individual with pain becomes

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for sufferers with orofacial pain. Moreover, the form of COP also psychological disorders inpatients with COP; however, the type of populations have comparable rates of psychological disorders to that epidemiological investigations have collectively shown that non-pain of psychological morbidity in a COP population, numerous research ploy to circumvent a longitudinal examination of psychiatric to a particular type of pain if injury occurred in that body site. Studies whether psychological status may have served as a diathesis for patients comorbidity in patients with COP. Many of these empirical efforts have Psychological Comorbidity of pain through a grimace may encourage similar behaviours [11]. For instance, if pain is elicited from an activity (e.g., bending down), social cues may facilitate or discourage engaging in pain behaviors. Through operant conditioning. Feedback from the environment or from that chronic pain can develop from the reinforcement of acute pain to become chronic once the pain sufferer begins to seek treatment, adequate coping and treatment-seeking behaviour [9]. From a behavioral standpoint, acute pain can be seen as progressing to become chronic once the pain sufferer begins to seek treatment, which would indicate that the pain has reached a level that has reached clinical importance [10]. A vast literature has consistently established that chronic pain can develop from the reinforcement of acute pain through operant conditioning. Feedback from the environment or from social cues may facilitate or discourage engaging in pain behaviors. For instance, if pain is elicited from an activity (e.g., bending down), it is likely that such an activity will be avoided in the future whereas secondary gains (e.g., attention from a physician) upon experience of pain through a grimace may encourage similar behaviours [11]. Psychological Comorbidity There is a vast literature establishing a high rate of psychological comorbidity in patients with COP. Many of these empirical efforts have involved the administration of structured clinical interviews to ascertain the presence of present and lifetime co-existing psychological disorders. Efforts to collect data surrounding the premorbid psychological status provided investigators with a less-than-ideal means to establish whether psychological status may have served as a diathesis for patients to a particular type of pain if injury occurred in that body site. Studies citing lifetime psychiatric comorbidity has been criticized by relying excessively on patient self-reports and have often been perceived as a research ploy to circumvent a longitudinal examination of psychiatric status in a chronic pain population. Although much data have supported a high incidence of psychological morbidity in a COP population, numerous epidemiological investigations have collectively shown that non-pain populations have comparable rates of psychological disorders to that of COP. Our review of these data does support a greater incidence of psychological disorders inpatients with COP; however, the type of disorder may represent a key explanation in the observed differences for sufferers with orofacial pain. Moreover, the form of COP also influences the psychosocial profile of the patient. Nifosi et al. [12] compared patients presenting with myofascial pain alone, patients with Temporomandibular Joint (TMJ) pain alone, and patients presenting with both myofascial and TMJ pain. They found that those with myofascial pain alone scored higher on several psychopathological domains compared to the other pain groups. Comorbidity of Specific Psychological Disorders and Orofacial Pain Anxiety disorders represent a common syndrome comprised of both emotional and psychophysiological symptoms (i.e., muscular bracing, muscular tension, gastrointestinal distress, respiratory difficulties). There has been support for anxiety to be more commonly observed during the acute stage of pain versus the chronic one. Specifically, Gatchel et al. [13] observed higher levels of anxiety among patients with acute TMD relative to those with chronic TMD. These and related findings underscore the notion that anxiety may represent a potential mechanism in the persistence of pain. However, other investigations have consistently found clinical levels of anxiety in chronic pain. For example, Posttraumatic Stress Disorder (PTSD) is frequently observed in patients suffering from all forms of orofacial pain [14]. Its prevalence, is believed to be the second largest to depression, and has been estimated from 10-30% in TMD [15-17]. These rates do exceed those rates observed in a non-clinical population. Moreover, patients with TMD report having experienced more traumatic events than persons without TMD [18-20]. Gender differences have emerged from these data with females exhibiting a higher degree of TMD and PTSD symptoms compared to males. Consistent with other pain populations, the presence of PTSD in TMD increases the likelihood of a greater pain severity, lower pain threshold, poorer treatment outcomes, reduced functionality, and a higher level of disability [17,21]. Many of the aforementioned data involved patients whose traumas stem from motor vehicle accidents. In a population exposed to combat-related traumas, veterans with co-occurring PTSD and TMD reported more physical symptoms including headaches, Temporomandibular Joint (TMJ) clicking, and increased facial tenderness relative to those without PTSD [22]. Mood disorders including depression represent a common factor in chronic pain. Their presence influences numerous germane endpoints to pain patients including pain severity, pain-related disability, treatment response, and quality of life. According to Yap et al. [23,24], approximately 40% of TMD patients in their sample met criteria for clinical depression. Other studies have found that the presence of depression to range from a few symptoms of mood decline to actual full blown major depressive episodes [25]. The manner in which depression mediates and/or moderates these outcomes continues to be debated. Conditions such as TMD do not seem to present in isolation, forin one large-scale study, nearly two-thirds of patients had 3 or more comorbid conditions including depression [26]. While many conclusions from previous investigations have viewed depression as secondary to the pain, the directionality of the relationship between depression and pain remains unclear. Breslau et al. [27] found a bidirectional association between migraine and depression; specifically, each condition predicted the onset of the other condition. Although depression alone is associated with negative outcomes, the combination of depression and anxiety may pose even a greater challenge for clinicians and patients. Lithgort et al. [28] recently reported that patients with combined depression and anxiety reported a higher number of pain sites than those who presented with anxiety or depression alone. Somatoform disorders are characterized by heightened somatic awareness and preoccupation, which lead to considerable impairment as well as distress. Full-blown somatoform disorders do not necessarily imply a psychogenic etiology;
instead, their presence often indicates that psychological factors may be aggravating whatever organic factors underlie the pain condition. Further, the presence of a somatoform disorder is often indicative of patients who will resist any psychological interpretation of their symptoms. Indeed, preoccupation with any deterioration in symptoms or the prolonging of symptoms can lead to patient reports of increased pain duration, pain-related disability, and pain intensity. A significant number of studies examining psychological comorbidity have found high incidences of somatoform disorders as well as patients scoring high on somatization scales [29].

Aside from identifying specific psychological disorders, there have been fewer efforts to measure the presence of other psychological constructs believed to influence pain symptoms. For example, stress burden has begun to receive increased attention as a pivotal variable in the manifestation and course of orofacial pain. Studies have examined differences in stress levels for patient with jaw pain to those with other forms of pain (e.g., low back pain, fibromyalgia) with both self-report and physiological measures. Central to this work has been the enhanced understanding of endocrine measures of stress, including but not limited to the Hypothalamic-Pituitary-Adrenal axis (HPA).

Pain catastrophizing is a construct defined as a tendency to magnify, ruminate, and experience helplessness in response to pain [30]. To date, the catastrophizing of pain has been shown to be one of the most robust predictors of pain outcomes. In part, the influence of catastrophizing has been associated with heightened activation of neural regions believed to influence the emotional components of pain. In one exquisitely sophisticated design, investigators found that high pain catastrophizers reported increased pain when experiencing high threat than when experiencing low threat as a result of both affective and cognitive mechanisms that assist in the processing of both threat and pain [31].

Collectively, the data establishing a robust association between orofacial pain and psychological comorbidity has lead to the question of whether treatment approaches need to be reformulated to adequately address this form of pain. Further, it does underscore the potential etiological pathways in which pain emerges. For example, the presence of psychological distress may trigger muscular activity that eventually might elicit pain via mechanical pathways. The documented psychological comorbidity also allows us to speculate that the processing of pain has been compromised by the same abnormal neurotransmitter imbalances observed in psychological disorders [32]. A shared biological substrate bolsters the argument that orofacial pain is an expression of underlying psychological distress (i.e., depression and/or anxiety).

**Nociceptive Transmission of Orofacial Pain**

The orofacial region is innervated by the trigeminal nerve (i.e., cranial nerve V), which branches into three divisions; the ophthalmic, extending to the infra-orbital area, the maxillary, surrounding the nasal region and above the mouth, and the mandibular, including the tongue, teeth, oral mucosa, and muscles of mastication [33,34]. Other primary afferent nerves such as C fibers, A-β, and A-γ fibers also innervate the orofacial region and are responsible for encoding sensory inputs such as pain, temperature changes, tactile, and mechanical stimulation. During acute pain such as when a painful stimulus reaches the face, primary afferent neurons transmit nociceptive inputs from the orofacial area to the trigeminal ganglion, and then project into the brainstem and spinal cord, and terminate in the cerebral cortex where the affective and discriminative aspects of pain are processed. When pain becomes chronic, such as when inflammation is present or when a nerve injury occurs, this nociceptive processing pathway becomes altered via various physiological mechanisms [35,36].

**Central and Peripheral Sensitization during Chronic Pain**

As mentioned previously, chronic pain is pain that persists beyond the healing of injury and is often clinically defined as pain lasting longer than 6 months. Although chronic pain affects various parts of the body and can be inflammatory or neuropathic in nature, several common physiological changes in pain processing neurons occur among chronic pain conditions that are responsible for maintaining the pain. When pain becomes chronic, the term "sensitization" is often used as an umbrella term to describe the many specific changes within the cells and anatomical pathways that process nocestration. Sensitization refers to an increase or enhancement of neuronal activity and occurs both centrally and peripherally to maintain pain. Further, the neural mechanisms underlying sensitization are the main factors distinguishing chronic pain from acute pain. Much like other forms of chronic pain, chronic orofacial pain is characterized by several broad mechanisms of sensitization that contribute to ongoing pain. First, primary afferent neurons become hyperactive in transmitting nociceptive sensory inputs to the spinal cord and brain, and this hyperactivity is facilitated by the release of various neurotransmitters and neuromodulators. Second, the major excitatory and inhibitory neurotransmitters such as glutamate and GABA that facilitate and inhibit nociceptive inputs become "unbalanced," and sufficient pain inhibition mechanisms become impaired. Third, nociceptive neurons undergo changes within their firing thresholds and membrane excitability, which alter intracellular signalling pathways and produce functional changes. Lastly, phenotypic changes occur in primary afferent neurons that change their response to various sensory stimuli [37-39]. Together, these events create and maintain a state of peripheral and central sensitization that governs chronic pain conditions.

**Trigeminal Brainstem Nuclear Sensory Complex (VBSNC) and Orofacial Pain**

Chronic orofacial pain shares many of the same major pathophysiological changes in nociceptive processing neurons as other forms of chronic pain. However, chronic orofacial pain does appear to differ in terms of where, anatomically, the majority of the nociceptive inputs are processed. Orofacial pain is unique in that the central mechanisms for nociceptive processing occur not only in the spinal cord but also in a specific region of the brainstem. This region is known as the trigeminal brainstem nucleus sensory complex (VBSNC), or simply, the trigeminal sensory nucleus. Anatomically, this bilateral region is located dorsolateral within the brainstem and contains a main sensory nucleus and three subnuclei; the nucleus oralis (Vo), the nucleus interpolaris (Vi), and the nucleus caudalis (Vc) [34,40].

The subnuclei within the VBSNC, in particular the nucleus caudalis, are responsible for orofacial nociceptive processing and share some similar anatomical and physiological properties with spinal dorsal horn neurons [41,42] (Table 1 and 2). For this reason, the VBSNC is also known as the "medullary dorsal horn." However, of important note is that the caudal portion of the nucleus caudalis extends anatomically to the top portion of the spinal cord. Given this anatomical proximity, there is likely some overlap of orofacial nociceptive processing between the nucleus caudalis and spinal cord. Nevertheless, the caudalis region of the VBSNC is considered a separate anatomical region with...
Despite some differences in sensory innervation, the VBSNC and spinal cord do share similar anatomical ascending and descending projections that are involved with nociceptive processing. For example, the VBSNC also projects to adjacent brainstem areas such as the reticular formation, the cerebellum, the pontine brachial nucleus, the Periaqueductal Gray (PAG), the Rostral Ventromedial Medulla (RVM), and to the cervical region of the spinal cord. Both the PAG and RVM are regions responsible for the descending inhibition of nociceptive inputs within the spinal dorsal neurons, and have also been shown to influence nociceptive inputs to the nucleus caudalis. Much like spinal cord neurons, neural projections within the VBSNC also ascend to the thalamus and various cortical areas such as the somatosensory cortex, anterior cingulate cortex, insula, and prefrontal cortex, where various sensory and affective dimensions of pain are processed [42,43].

### Mechanisms of Sensitization within the VBSNC

The VBSNC contains Nociceptive Specific (NS) neurons, or neurons that encode noxious stimuli, along with Wide Range Neurons (WDR), which encode a broad spectrum of stimuli ranging from slight tactile stimuli to more pronounced mechanical and pain stimuli [51].
During acute pain, both types of neurons are active at transmitting nociceptive and non-nociceptive inputs. However, as pain becomes chronic, both types of neurons become more sensitive and less discriminative of sensory stimuli. When a nerve injury or inflammation persists, both the NS and WDR neurons become more active; that is, the membrane excitability increases, and the thresholds for firing decrease. Evidence of hyperactivity in NS and WDR neurons has been found in electrophysiological studies showing that the ectopic firing patterns of these neurons increase, along with the post firing discharge [52-57]. The sensitivity and phenotype of primary afferents also change such that Aβ fibers that typically respond to tactile and lighter pressure stimulation, now respond to noxious stimulation. Once the discriminatory abilities and the firing thresholds of these neurons weaken, a greater amount of sensory inputs are processed and in turn contribute to increased excitation, or facilitation of nociceptive inputs. Further, as pain becomes chronic, primary afferents undergo changes in plasticity, or synaptic reorganization that facilitates nociceptive processing [58]. For example, several adjacent neurons will form new synaptic connections onto a single neuron, which allows for increased convergence of nociceptive inputs. Plasticity changes also involve new “sprouting” of neurons, often within the periphery that further facilitate central processing of nociceptive sensory inputs. Orofacial nerve injuries are associated with sprouting of sensory afferents peripherally and appear to maintain pain, yet sprouting within the trigeminal ganglion appears to be spared [56,59].

Central sensitization involves physiological changes in pain processing such that nociceptive inputs are facilitated more than inhibited. Under conditions of acute pain, nociceptive facilitation and inhibition are in equilibrium, where afferent nociceptive inputs are adequately inhibited by efferent outputs. Descending inhibitory supraspinal-structures such as the Periaqueductal Gray (PAG) and Rostral Ventromedial Medulla (RVM) send descending projections to inhibit incoming nociceptive inputs within the spinal cord [60,61]. However, when pain becomes chronic, the equilibrium becomes "unbalanced" and nociceptive input outweighs nociceptive inhibition [62]. Given that the VBSCN is part of the brainstem; this region is not exempt from the imbalance of nociceptive facilitation and inhibition. For example, the ViVc transition region and the RVM have bidirectional projections and following temporomadibular injury or inflammation, the RVM neurons have been shown to facilitate nociceptive processing within the ViVc region [63,64]. In addition to peripheral inputs influencing nociceptive facilitation, various neurotransmitters and neuromodulators are released during chronic pain that exacerbate facilitation [34]. Like spinal neurons, neurons within the VBSCN Crease excess glutamate, causing neurons to become more active, and hence more efficient at transmitting nociceptive signals to the brain. During nerve injury or inflammation to the orofacial region primary afferents, including the trigeminal nerve, release neurotransmitters and neuromodulators such as substance P, Brain-Derived Neurotrophic Factor (BDNF), and Calcitonin Gene-Related Peptide (CGRP) which facilitate nociceptive transmission. In contrast, inhibitory neurotransmitters such as GABA and glycine cannot adequately inhibit the influx of nociceptive inputs [65]. Evidence for this imbalance comes from animal studies where GABA agonists such as baclofen are administered into the dorsal horn spinal neurons, and pain behavior decreases, suggesting that increasing inhibitory tone during chronic pain helps with restoring tonic inhibition [66]. Various other physiological factors are responsible for maintaining central and peripheral sensitization and include but are not limited to neurotransmitters, neuromodulators, receptor subtypes, changes in intercellular signalling proteins, and chemical mediators such as cytokines and chemokines.

Cellular Mechanisms of Sensitization

During chronic orofacial pain various receptors act peripherally and centrally within the VBSCN to initiate the development and maintenance of pain [34,67]. Excitation of primary trigeminal afferents occur through ionotropic calcium and sodium ion-gated channels within cell membranes, and become depolarized when excitatory neurotransmitters such as glutamate bind to NMDA receptor subtypes NR2A/B [68]. AMPA receptors, specifically the GluR2 and GluR3 subtypes have also been shown to increase neural excitation within the nucleus caudalis and upper cervical spinal neurons upon injury to the trigeminal nerve [69]. Purinergic receptor subtypes P2X3/7 have also been shown to facilitate both peripheral sensitization among trigeminal nerve afferents, and also central sensitization among neurons within the caudalis region of the VBSCN [56,70-72]. Much like spinal neurons of the dorsal root ganglion, trigeminal ganglion neurons show expression of the transient receptor potential vaniloid 1 (TRPV1) following trigeminal nerve injury or experimentally applied capsicain [73,74]. Pain resulting from tooth pulp inflammation is mediated by the transient receptor potential ankyrin 1 receptor, a subtype of the TRPV1. The TRPA1 receptor also becomes activated by various chemical irritants, cannabinoids, and coldstimuli [75]. During inflammatory chronic orofacial pain conditions, Nerve Growth Factor (NGF) and other inflammatory mediators such as IL-6 facilitate the upregulation of TRPA1 receptors [75]. Depolarization of primary nociceptors also leads to functional changes among G proteins and metabotropic receptors within the neuron. Upon activation, G proteins can produce either excitation or inhibition of specific intracellular pathways. Intracellular pathways involve the activation of various protein kinases and messenger proteins that in turn influence cellular function. Several intracellular pathways have been identified as targets for maintaining central sensitization, including protein Kinase C (PKC), Protein Kinase A (PKA), Extracellular Signal-Related Kinase (ERK), and p38 Mitogen-Activated Protein Kinase (MAPK) [74,76,77]. Many of these intracellular proteins are activated by surface membrane receptors; specifically receptors for glutamate (mGluR), neurokinin (NK1), and calcitonin gene-related peptide (CGRP), which all activate the ERK pathway. Within the VBSCN, ERK activation has been shown in the caudalis region following both trigeminal nerve injuries and during conditions of dentalinflammation [77-79]. These various signalling pathways may partially explain the diversity and complexity of orofacial pain conditions.

Glial Mechanisms of Sensitization

During orofacial pain, in particular, following injuries to the trigeminal nerve branches, glia cells have been shown to facilitate the maintenance of cellular mechanisms of central sensitization within the VBSCN [76,80]. Microglia surrounds and structurally "support"primary afferent neurons within the periphery around the dorsal root ganglion, trigeminalganglion, and centrally within the spinal cord and VBSCN. Microglia and neurons are connected by gap-like junctions that promote the exchange of neurotransmitters, neuromodulators, and chemical mediators. Microglias are thought to further contribute tocentral sensitization by facilitating the release of excitatory neurotransmitters from neurons [80]. For example, excitatory neurotransmitters such as glutamate and kainite enhance the excitability of the gap junctions among microglia via influx of calcium ions, thus causing depolarization of neurons. Additionally, in response to inflammation or injury of the trigeminal nerve, microglia release substance P, Nitric Oxide (NO), neurokinin, and prostaglandins, which
together enhance neuron excitability within the nucleus caudalis of the VBSCN [78,81,82]. During injury of the trigeminal nerve, microglia have also been shown to release proinflammatory cytokines such as IL-1 and TNF, and chemokines such as CCL2, which contribute to central sensitization within the VBSCN, particularly following inflammation [71,83-85]. Astroglia are another type of glial cell that further maintain chronic orofacial pain. Like neurons, astroglia have receptors for glutamate (e.g. NMDA) substance P, and GABA, which make them sensitive to changes in excitatory and inhibitory neurotransmitter release during sensitization. Specifically, when mechanisms of central sensitization develop, astroglia appear to function as “cleaner cells” by eliminating excess glutamate via reuptake mechanisms. Thus, astroglia are also thought to serve as a means of dampening central sensitization.

Conclusion

Categorical efforts to identify, assess, and treat orofacial pain is limited by a certain degree of heterogeneity within this pain population. Indeed, the highlighting of specific mechanisms does imply that we propose a definitive pathophysiological model of orofacial pain. Instead, the intention is to identify distinct mechanisms in which COP may manifest. Future studies should focus on the role of the physiological mechanisms and the manner in which they work in concert with psychosocial variables to influence the course of COP and the response of patients to treatment interventions. In conclusion, the mechanisms identified here that distinguish chronic orofacial pain from other pain populations provide testable hypotheses concerning its development and course. Continued efforts to empirically investigate these questions in COP should focus on furthering a guiding conceptual framework that can include some of the understudied psychophysiological variables. With an enhanced understanding of this population’s psychological and psychophysiological landscape, a greater need for more tailored interventions further emerges. Ultimately, the testing of such a framework would allow researchers to determine whether the convergence of factors suspected in orofacial pain can lead to better integrative interventional approaches to treat a pain condition often times perceived as treatment reticent. Within that same context, investigators should also examine whether tailored treatments actually yield different results from more “generic” approaches.

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References


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