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The objective imperative: advancing chronic orofacial pain research with the brain-heart axis

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Abstract

The biopsychosocial model is the prevailing framework for chronic orofacial pain (COP). While COP is a heterogeneous clinical entity involving nociceptive and neuropathic components, it is increasingly defined by its nociplastic features—a systemic, non-nociceptive state in which psychological factors significantly influence symptoms. Current research frequently suffers from the conflation of constructs. Psychosocial predictors (e.g., self-efficacy) and outcome measures (e.g., pain interference) are often conceptually inseparable. To advance beyond this, we advocate for the integration of the brain-heart axis (BHA). The BHA provides objective, quantifiable markers of autonomic nervous system (ANS) dysregulation, the physical manifestation of chronic stress rooted in large-scale brain network imbalance. The present study proposes a theoretical framework in which psychological distress is reflected in corrected QT interval (QTc) changes, while low self-efficacy is mirrored by reduced heart rate variability (HRV). This integration is supported by the neurochemical roles of *N*-methyl-*D*-aspartate (NMDA) receptors in central sensitization and dopamine D2 receptor dysfunction in the basal ganglia. The present paper delineates a framework for research and clinical implementation within advanced dental training.

Keywords

chronic orofacial pain (COP), brain-heart axis (BHA), heart rate variability (HRV), autonomic nervous system (ANS), nociplastic pain, neuroscience, QTc

The methodological blind spot in assessing psychosocial load in COP

The biopsychosocial model is indispensable for comprehending chronic orofacial pain (COP), which is characterized as a non-nociceptive, neuropathic, or nociplastic pain state. Recent research highlights the significant, systemic relationship between psychological factors, specifically psychological distress and reduced self-efficacy/quality of life (QOL), and reported pain intensity [1]. These studies correctly emphasize that a patient's psychological state often has a greater impact on the prediction of pain severity

than diagnostic classification. However, a thorough examination of the research methodologies employed to discern this relationship unveils a critical limitation pertaining to the independence of the measured constructs [2]. When a study utilizes a composite metric, such as the brief pain inventory (BPI) total score, which calculates the mean of both pain severity and pain interference, as the primary outcome, the results may be statistically misleading. The BPI pain interference subscale is, by definition, a measure of reduced function and diminished social engagement. These factors are conceptually inseparable from the psychosocial components identified through techniques such as principal component analysis. Examples of these components include the self-efficacy/QOL component. Future research must either isolate the pain severity subscale or employ structural equation modeling to ensure findings are not methodologically conflated.

The brain-heart axis: objective physical markers

In order to resolve this methodological dilemma and advance the biopsychosocial model from mere correlation to mechanistic understanding, it is proposed that objective physiological markers be integrated in a mandatory manner. The brain-heart axis (BHA) provides a non-invasive, objective framework for addressing the biological underpinnings of COP [3]. It utilizes the autonomic nervous system (ANS) as a proxy for the bidirectional communication between the brain and heart.

The NMDA receptor and central sensitization

A primary driver of the nociplastic state is central sensitization, defined as a heightened state of responsiveness within the central nervous system (CNS) [4]. Chronic pain has been demonstrated to act as a profound, perpetual stressor, leading to the dysregulation of the sympathetic and parasympathetic branches of the ANS [5]. Research has demonstrated that this delicate balance is disrupted in cases of COP, suggesting a global impairment of autonomic function [5]. This process is facilitated by the *N*-methyl-*D*-aspartate (NMDA) receptor. Typically, the NMDA channel is blocked by a magnesium ion (Mg^{2+}). The sustained nociceptive input has been demonstrated to induce protracted depolarization, resulting in the expulsion of the Mg^{2+} block and the subsequent influx of calcium (Ca^{2+}) [6]. This influx has been shown to trigger intracellular signaling, which in turn increases receptor density at the synapse. This, in turn, has been demonstrated to "tune up" the volume of pain signals. This molecular hyperactivity contributes to the hyperactive state of the salience network (SN), driving the autonomic imbalance observed in the BHA [7].

Basal ganglia and dopamine dysfunction

The basal ganglia modulate the BHA, exerting influence on the central autonomic network (CAN) [8]. Dysfunction of dopamine D2 receptors within the basal ganglia has been implicated in the pathogenesis of COP [9]. Dopamine signaling impairment, attributable to genetic factors or pharmaceutical interventions such as selective serotonin reuptake inhibitors (SSRIs) or angiotensin-converting enzyme inhibitors (ACEIs), has been demonstrated to result in the sustained activation of nociceptive pathways, thereby maintaining the "gate" for pain perception in a state of openness [10]. This disruption in the balance between the SN and the default mode network (DMN) results in sympathetic dominance, which can be measured using cardiac biomarkers.

Electrophysiological markers: QTc and HRV

The dysregulation of the sympathetic nervous system (SNS) (threat signaling) and the hypoactivity of the DMN (internal regulation) manifest in the heart's electrical activity [11] (Table 1). As demonstrated in the extant literature, an overactive SNS has the capacity to induce sympathetic over-arousal. The corrected QT interval (QTc) has been demonstrated to serve as a sensitive indicator [12]. Specifically, the shortening of the QTc interval has been associated with intensified adrenergic signaling and the phenomenon of pain catastrophizing [13]. The present study explores the relationship between self-efficacy and heart rate variability (HRV), with a particular focus on the implications of low self-efficacy. The hypothesis posits that

low self-efficacy is associated with hypoactive DMN and parasympathetic withdrawal, as evidenced by low HRV. According to the extant literature, low HRV is indicative of physiological rigidity and a reduced capacity for coping [14].

Table 1. Integrating the BHA to link psychosocial factors and biological function.

Psychosocial component	Core mechanism (BHA)	Proposed biomarker	Measurement/Interpretation	Clinical link
Psychological distress	Hyperactive SN, high sympathetic drive	Corrected QT interval (QTc)	QTc shortening reflects heightened adrenergic signaling.	Confirms biological stress
Self-efficacy/QOL	Hypoactive DMN, low parasympathetic tone	Heart rate variability (HRV)	Low HRV indicates poor ANS adaptability/flexibility.	Objective measure of functional impairment.

BHA: brain-heart axis; SN: salience network; QOL: quality of life; DMN: default mode network; ANS: autonomic nervous system.

Scientific rigor: addressing causality and confounders

The extant evidence is largely correlational in nature. In order to establish BHA as a clinical standard, it is necessary to address the factors that influence cardiac intervals independently, as illustrated in Table 2. To determine whether ANS dysregulation precedes COP symptoms, longitudinal studies are required.

Table 2. Integrating the BHA to link psychosocial factors and biological function.

Variable	Impact on HRV	Impact on QTc	Requirement for research
Age	Decrease with age (vagal decline)	Gradual baseline lengthening	Age-matched controls.
Tricyclics	Reduces HRV (anticholinergic)	Typically lengthens QTc	Medication history screening.
CVD	Marked reduction in HRV	Risk of arrhythmia/long QT	Pre-existing condition screening.
Circadian	Peaks during sleep (vagal)	Fluctuates based on cycle	Standardized time for ECG

BHA: brain-heart axis; QTc: corrected QT interval; HRV: heart rate variability; QTc: corrected QT interval; ECG: electrocardiogram.

Clinical recommendations: implementing BHA in dental settings

In order to establish a connection between theoretical concepts and practical applications, it is recommended that dental practitioners adhere to the following protocol. Initial electrocardiographic screening: In order to establish baseline QTc and HRV levels during the initial assessment, the utilization of medical-grade wearable sensors or a resting 12-lead ECG is imperative. The following is a list of the pharmacological monitoring procedures: It is imperative that practitioners be cognizant of the prevalent interactions between commonly prescribed medications and the BH. The objective of monitoring therapeutic response is to assess the effectiveness of treatment and make adjustments as necessary. The employment of HRV as an objective metric for "physiological recovery" constitutes a pivotal element of this research. An increase in HRV over time has been shown to serve as an objective marker of improved parasympathetic regulation.

The educational imperative

Treating a condition driven by NMDA-mediated sensitization and autonomic imbalance necessitates a clinical approach rooted in neurobiology. The incorporation of a robust neuroscience curriculum within the framework of dental education is of paramount importance [15]. This enables practitioners to administer rational pharmacotherapy targeting receptor pathways and elucidate symptoms to patients.

Conclusion

Recent studies have demonstrated a robust correlation between psychological factors and pain intensity in cases of COP. However, the reliability of these findings may be contingent upon the methodological independence of pain outcome measures and psychosocial predictors. In order to surmount this limitation

and promote the advancement of the field, it is proposed that there be a shift toward the incorporation of BHA biomarkers, including HRV and QTc analysis, as essential, objective physical markers. This approach anchors the psychological components to concrete, quantifiable physiological dysregulation within the ANS, providing a clear, mechanistic understanding of COP pathogenesis that is rooted in neurochemical (NMDA/dopamine) and brain network (SN/DMN) imbalance. This advancement in research must be paired with a foundational commitment to neuroscience education in advanced dental programs, ultimately strengthening the treatment of COP as a truly evidence-based, systemic neurobiological disorder.

Abbreviations

ANS: autonomic nervous system

BHA: brain-heart axis

BPI: brief pain inventory

COP: chronic orofacial pain

DMN: default mode network

HRV: heart rate variability

NMDA: *N*-methyl-*D*-aspartate

QOL: quality of life

QTc: corrected QT interval

SN: salience network

Declarations

Author contributions

TN: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing. The author read and approved the submitted version.

Conflicts of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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