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Review

MRI-Based Neuroimaging of Chronic Orofacial Pain in Temporomandibular Joint Dysfunction Comorbid with Anxiety and Depression

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Abstract: A study of the brain using magnetic resonance morphometry and diffusion tensor imaging in patients with chronic orofacial pain syndrome associated with temporomandibular joint pain dysfunction syndrome revealed changes in regional gray matter volume, namely a decrease in the volume of the primary somatosensory cortex, an increase in gray matter volume in the thalamus, and an increase in both volume and microstructural alterations in the brainstem (in the dorsal horn of the midbrain) accompanied by changes in diffusion properties, specifically an increase in mean diffusivity; in the projection of structures of the descending pain modulation system, including the periaqueductal gray matter of the midbrain and the nucleus raphe magnus, as well as in the integrity of ascending pain pathways (a reduction of fractional anisotropy in the trigeminal root entry zone, the spinal trigeminal tract, and the ventral trigemino-thalamic tract); as well as bilateral increases in the gray matter volume of the pons corresponding to the principal sensory nucleus of the trigeminal nerve.

The aim of this study is to analyze current data concerning MRI neuroimaging methods of the central nervous system in patients with chronic orofacial pain syndrome in temporomandibular joint pain dysfunction syndrome comorbid with anxiety and depression. We analyzed more than 60 articles in English devoted to neuroimaging studies using voxel-based morphometry of the central nervous system in patients with chronic orofacial pain syndrome in temporomandibular joint pain dysfunction syndrome comorbid with anxiety and depression. The rapid development of imaging in recent decades has led to an increase in the number of identified causes of dysfunction in the trigeminal nerve system, which are amenable to specific treatment and functional recovery. A clinically oriented segmental approach to trigeminal nerve pathology is important for conducting specialized high-resolution imaging studies, which are a powerful tool in the examination of patients with trigeminal nerve dysfunction.

Keywords: *anxiety, depression, orofacial pain, masticatory muscles, temporomandibular joint dysfunction, magnetic resonance imaging.*

1. INTRODUCTION

The temporomandibular joint pain dysfunction syndrome (TMJ PDS) is a relevant public health issue, affecting approximately 15–31% of the adult population [1, 2]. It is the most common cause of chronic non-dental pain in the orofacial region [3]. TMJ PDS presents with characteristic symptoms, including pain in the temporomandibular joint (TMJ) and muscles, headache, joint noises (clicking), tenderness in the masticatory muscles, and parafunctions [4, 5]. The symptoms of TMJ PDS can be observed across a wide age range, with a peak incidence between the ages of 20 and 40 years [6].

An increasing number of studies using magnetic resonance imaging (MRI) have demonstrated the presence of structural and functional changes in the brain of patients with TMJ PDS. Some studies employing voxel-based morphometry revealed cortical

thickening in specific brain regions in patients with chronic TMJ pain, including the primary somatosensory cortex, the frontal pole, and the ventrolateral prefrontal cortex [7]. Other studies have reported decreased gray matter volume in such brain regions as the left anterior cingulate cortex, the right posterior cingulate gyrus, and the right anterior insular cortex [8], as well as reduced cortical thickness in the right sensorimotor cortex and decreased volume in the left putamen [9].

Nevertheless, it has not yet been proven whether these structural changes are a direct result of prolonged orofacial pain or compensatory brain mechanisms aimed at alleviating the pain syndrome.

The aim of this study is to analyze current data concerning MRI neuroimaging methods of the central nervous system in patients with chronic orofacial pain syndrome in TMJ PDS comorbid with anxiety and depression.

2. MATERIALS AND METHODS

We analyzed 128 articles in English devoted to neuroimaging studies using magnetic resonance imaging of the central nervous system in patients with chronic orofacial pain syndrome in TMJ PDS comorbid with anxiety and depression. The inclusion criteria for the search were as follows: (1) full original articles and reviews cited in databases such as PubMed, MedLine, Web of Science, and Scopus; (2) articles in English; (3) a search time frame of 25 years; (4) keywords: anxiety, depression, orofacial pain, masticatory muscles, temporomandibular joint dysfunction, magnetic resonance imaging. The exclusion criteria included abstracts, monographs, and guidelines. The review was conducted in accordance with the PRISMA 2020 statement (Figure 1).

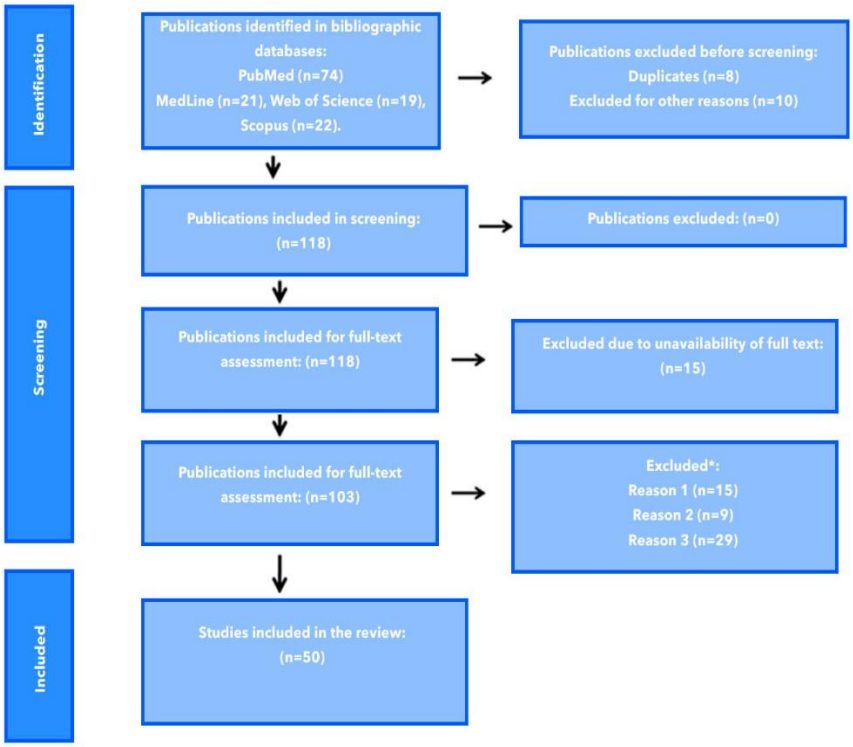

Figure 1. PRISMA 2020 flow diagram of the study selection process. Did not meet PICO criteria or study design (Reason 1, n = 15); Ineligible publication type (Reasons 2, n = 9): narrative reviews; Ineligible publication type (Reasons 3, n = 29) case reports.

3. RESULTS

3.1 Structural brain changes in TMJ PDS with orofacial pain

Pain in TMJ PDS arises in the region innervated by the trigeminal nerve system, and the supraspinal targets of this system are of particular interest in studying this condition. The course of sensory pathways in the examined region is as follows: the trigeminothalamocortical system includes inputs from the spinal trigeminal nuclei, which are then projected via the sensory nuclei of the brainstem to the ventral posteromedial nucleus of the thalamus, and finally, after exiting the thalamus, third-order neurons project to the primary somatosensory cortex [10, 11].

Chronic pain syndrome leads to alterations in the integrity of ascending pain pathways, with a significant reduction in regional gray matter volume (rGMV) in the dorsal horn of the midbrain combined with an increase in mean diffusivity (the relationship between tissue histological structure and diffusion rate is quite complex but can be summarized as follows: higher cell density and reduction of extracellular space volume lead to reduced diffusion) [12]. In individuals with TMJ PDS, an increase in rGMV was noted in the right inferior frontal gyrus, which is known to demonstrate considerable functional laterality, with the right side producing neuronal activations independent of the location of the pain input [13, 14]. The area of greater volume observed in subjects with TMJ PDS was most closely related to the dorsolateral prefrontal cortex (Brodmann area 46).

Changes in volume and mean diffusivity also occurred in patients with TMJ PDS in regions of the descending pain modulation system, including the periaqueductal gray matter of the midbrain and the nucleus raphe magnus. Finally, tractography revealed changes in diffusion properties, specifically a reduction of fractional anisotropy, which provides insights into white matter myelination and the integrity of conducting pathways in the trigeminal root entry zone, the spinal trigeminal tract, and the ventral trigeminothalamic tract (Figure 2).

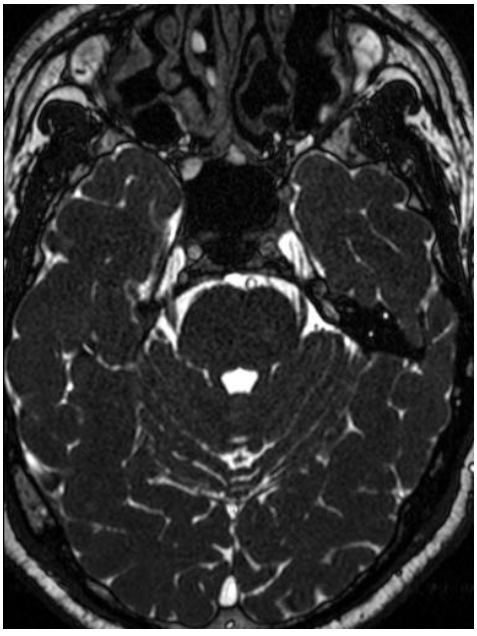

Figure 2. MRI of the brain, FIESTA IP, axial plane. Cisternal segments of the trigeminal nerves are visualized. The trigeminal nerves are asymmetrical due to a decrease in the left (own material).

These data show that chronic musculoskeletal pain in humans is associated with discrete changes in the anatomy of the dorsal horn of the medulla, as well as its afferent and efferent projections [15]. Neuronal alterations may be crucial for the maintenance of pathological pain [12]. Chronic pain syndrome leads not only to changes in functional

state but also to structural reorganization—according to the principle of central plasticity [16]. It remains unknown whether the observed brain abnormalities are the cause or the consequence of chronic pain [17]. One hypothesis suggests that the gray matter abnormalities observed in patients with chronic pain represent neuroplastic "chronification" [18] or "learning" [19] of pain. It is also possible that the observed brain differences reflect pre-existing vulnerabilities to chronic pain.

Gray matter abnormalities were observed at multiple levels of the trigemino-thalamo-cortical system. First, bilateral increases in rGMV were found in the pons, corresponding to the principal sensory nucleus of the trigeminal system. The presence of neural abnormalities may indicate dysregulation of spinal and/or peripheral nervous system function in TMJ PDS. After exiting the trigeminal brainstem nuclei, second-order projections continue to the ventral posterior (VP) nucleus of the thalamus, the main relay in the trigeminal sensory pathway [20]. As in the thalamus, it is possible that the gray matter increases observed in individuals with TMJ PDS represent somatotopic reorganization associated with persistent temporomandibular pain.

The results obtained by Younger J.W. et al. [11] diverged from previous studies in that they observed primarily increases in rGMV in chronic pain rather than reductions. Bilateral increases in GMV were found in the pons, corresponding to the principal sensory nucleus of the trigeminal system. The presence of neural abnormalities in the early trigeminal system is an important finding, as it may indicate dysregulation of the spinal and/or peripheral nervous system in TMJ PDS with myotonic syndrome. After exiting the trigeminal brainstem nuclei, second-order projections continue to the VPL nucleus of the thalamus. The VP relays nociceptive and other sensory inputs originating from the body and the trigeminal system. It was identified as a site of greater GMV in pain patients. On the right side of the brain, the ventral lateral (VL) nucleus of the thalamus demonstrated increased GMV. Bilateral thalamic GMV increases may indicate somatotopic adaptation and reorganization associated with enhanced nociceptive signaling from trigeminal nerves. One possible explanation for the differing results is that the duration of chronic orofacial pain (mean = 4.4 years) was shorter than typically reported by other investigators. Disease duration varied considerably: mean values of 20.6 years [21], 14.7 years [22], 8.5 years [23], and 14.4 years [24]. Limited evidence suggests that peripherally induced pain may increase regional GMV in humans over short time periods [25], and it is plausible that this regional increase may be followed by compensatory reductions over longer periods. The observed GMV increase may also represent a specific feature of pain in TMJ PDS and may identify a peripherally mediated pain condition compared to centrally mediated ones, highlighting significant CNS abnormalities in individuals with TMJ PDS [11].

Similarly, Gerstner G. et al. [26] also reported reductions in gray matter volume in the left anterior cingulate gyrus, right posterior cingulate gyrus, right anterior insular cortex, left inferior frontal gyrus, and superior temporal gyrus in individuals with pain syndrome due to TMJ dysfunction, supporting the presence of morphological changes in brain areas integrated into the central pain system. Limited data suggest that peripherally induced pain may increase regional GMV in humans over short periods [25], and that such increases may be followed by compensatory volume reductions over longer timeframes.

According to Apkarian A.V. et al. [19], the fact that most neuroimaging studies conducted in chronic pain conditions have revealed significant correlations between brain gray matter changes and pain duration or intensity suggests that these brain alterations may be consequences of pain.

This hypothesis was confirmed by Rodriguez-Raecke R. et al. [27], who found that pathological reductions in gray matter partially recovered once pain (peripheral nociceptive stimuli) was eliminated.

It is also possible that organic reorganization is not the cause of the pain experience but rather represents CNS adaptation to aberrant peripheral input. Some studies suggest that alterations in peripheral input may induce neuroplastic changes in the brain. More

recent results indicate that as little as 8 days of painful thermal stimulation can induce regional gray matter increases in the human brain [25].

3.2 Structural brain changes in TMJ PDS with myotonic syndrome

Similar changes have also been documented in patients with myofascial, painless TMJ PDS. Reductions in gray matter volume were observed in several regions of the trigemino-thalamo-cortical pathway, including the trigeminal sensory brainstem nuclei, thalamus, and primary somatosensory cortex, as well as increases in gray matter volume in certain limbic regions, such as the posterior putamen, globus pallidus, and anterior insular lobe, compared with healthy individuals [11]. Festa F. et al. [28], using fMRI, found changes in the pain sensitivity pathways of the trigeminal system in patients with myofascial pain in the masticatory muscles.

PET studies have shown that chronic facial pain (burning mouth syndrome) may be associated with reduced dopaminergic function in this region [29]. As in the thalamus, the gray matter increases observed in individuals with masticatory muscle dysfunction in TMJ PDS may represent somatotopic reorganization.

Younger J.W. et al. [11] found that a group of patients with masticatory muscle dysfunction in TMJ PDS had smaller rGMV than the control group in the primary somatosensory cortex.

Lin C.S. [30] conducted a meta-analysis of group studies of patients with painful masticatory dysfunction in TMJ PDS: consistent functional/structural alterations were observed in the thalamus and primary somatosensory cortex, pointing to the thalamo-cortical pathway as the primary site of brain plasticity in this population.

At present, interpretation of the results is complicated by uncertainty regarding which physiological substrates underlie the observed volumetric changes. Voxel-based morphometry technology does not allow us to differentiate between changes in neuropil, dendritic and axonal branching, cortical folding, gray matter band thickness, or glial density [31, 32]. Despite these limitations, our results indicate the presence of significant CNS abnormalities in individuals with masticatory muscle dysfunction in TMJ PDS.

The pattern of gray matter abnormalities suggests the involvement of trigeminal and limbic system dysregulation, as well as potential somatotopic or structural reorganization in the putamen, thalamus, and somatosensory cortex in myofascial TMJ PDS. Finally, this study also demonstrated that pain intensity was associated with gray matter increases in the rostral anterior cingulate cortex and posterior cingulate gyrus, supporting the role of trigeminal nociceptive signals in brain alterations [33].

Individuals with myofascial pain in the masticatory muscles frequently meet diagnostic criteria for fibromyalgia [34], a condition that may involve CNS sensitization. It was found that people with TMJ PDS had larger gray matter volume than controls in the anterior insular lobe, a limbic structure receiving inputs from the ventral posterolateral (VPL) nucleus of the thalamus (the main relay in the trigeminal sensory pathway) [35] and involved in integrating emotional and bodily states. This region appears to be crucial for interoception or emotional awareness of internal states [36, 37], as well as the emotional aspects of pain experience [38] and sensory anticipation [39].

3.3 Structural brain changes in TMJ PDS comorbid with anxiety and depression

Chronic pain affects not only sensory but also affective systems. Thus, alterations are observed in the affective system: increases in gray matter volume were found in the right putamen and right globus pallidus, in the anterior insular lobe, the right inferior frontal gyrus, and the posterior cingulate gyrus. A reduction in gray matter volume was found in the left anterior cingulate gyrus.

Increases in GMV were observed in two basal ganglia nuclei: the right putamen and right globus pallidus. Both regions contain neurons responsive to nociceptive input and serve to prepare behavioral responses to painful stimuli [40]. The putamen, in particular,

has been identified as an important structure in pain processing and is somatotopically organized for nociceptive information [41, 42, 43].

In patients with somatoform disorders with chronic pain—fibromyalgia [44], irritable bowel syndrome [45]—morphological alterations of brain structures have been identified. Common overlapping areas include the cingulate gyrus, thalamus, basal ganglia, insula, orbitofrontal cortex, and brainstem [15].

In patients with TMJ PDS, larger rGMV was found compared to controls in the anterior insular lobe. The anterior insula is a limbic structure that receives inputs from the ventral posterior (VP) nucleus of the thalamus [35] and participates in integrating emotional and bodily states. This region appears to be crucial for interoception or emotional awareness of internal states [36, 38], as well as the emotional aspects of pain experience and sensory anticipation. A greater rGMV in the right anterior insula was found to predict subjective ratings of visceral awareness [46].

Although neuroimaging research on somatoform disorders is growing, little is currently known about the neural correlates of these conditions. Therefore, in this systematic review Rossetti M.G. et al. (2020) summarized existing evidence of structural brain changes in SFD according to DSM-IV and DSM-5 criteria. Compared with controls, subjects with SFD showed morphological changes spanning motor, limbic, and somatosensory neuronal pathways. Although results remain inconclusive, they suggest that SFD is characterized by selective alterations of brain networks involved in cognitive control, regulation and processing of emotions, stress, and somato-visceral perception [47].

The main features of somatoform disorders are health anxiety and impaired affective processing. We used relative frontal alpha asymmetry, a method of measuring functional lateralization of affective processing, to investigate psychobiological correlates of SFD [48, 49].

In the study by Lin J. et al. [50], reduced mean thickness of the caudal portion of the left middle frontal gyrus was associated with more acute sensations in the TMJ region. The middle frontal gyrus plays a key role in regulating attentional networks, which may shift focus toward pain. A reduction in left orbitofrontal cortex thickness in TMJ PDS was also observed, which may be related to disturbances in the emotional domain.

In the work by Yin Y. et al. [9], morphometric and functional MRI (fMRI) studies revealed changes in brain regions involved in sensorimotor and emotional functions, including reduced cortical thickness in the right sensorimotor cortex, decreased volume in the left putamen and associated reduced functional connectivity with the anterior cingulate cortex, decreased volume/surface area in the left posterior superior temporal gyrus and associated increased connectivity with the precuneus.

4. DISCUSSION

This systematic review integrated data from 60 studies dedicated to neuroimaging findings of brain structure and function in patients with TMJ PDS and comorbid anxiety-depressive disorders. The results demonstrate a complex pattern of neuroplasticity affecting both sensory and affective pathways, revealing characteristic patterns of CNS reorganization.

4.1 Neuroplasticity in the trigeminal pain processing system

Key changes are concentrated along the trigemino-thalamo-cortical pathway, which is characteristic of all TMJ PDS phenotypes. Bilateral increases in gray matter volume in the pons (the principal sensory nucleus of the trigeminal nerve) and alterations in the spinal trigeminal tract indicate that peripheral sensitization serves as a trigger for neuroplastic remodeling. Of particular importance is the observed reduction in fractional anisotropy in the ventral trigemino-thalamic tract, reflecting microstructural damage to white matter. This may contribute to the chronification of pain. These structural changes are mirrored in clinical observations of trigeminal nerve asymmetry on MRI (Figure 2), where neurovascular conflicts or demyelination may potentially alter signal conduction.

4.2 Interaction of pain and emotion in comorbidity

In patients with TMJ PDS and comorbid anxiety-depressive disorders, specific reorganization of limbic-striatal structures has been identified. Increases in rGMV in the anterior insula and putamen correlate with the affective component of pain. At the same time, reductions in cortical thickness in the orbitofrontal cortex and middle frontal gyrus mirror findings in primary affective disorders. This points to shared neural substrates of emotional processing impairments. The dual role of the anterior insula—integration of interoceptive signals and prediction of visceral perception—may explain the pronounced somatic sensitivity in this category of patients.

4.3 Directionality of neural changes: Cause or consequence?

The results of the review support a bidirectional model of pain-related neuroplasticity:

- peripheral drivers: pain of short duration is associated with increases in rGMV in sensory nuclei (this may reflect an acute compensatory response);
- central adaptation: in long-term pain syndromes, reductions in rGMV are observed in prefrontal regulatory areas (this may indicate possible neurodegenerative processes resulting from chronic stress);
- reversibility of changes: existing evidence of partial rGMV recovery after pain elimination is a key argument in favor of trigger-dependent plasticity rather than primary pathology.

5. CONCLUSION

The rapid development of imaging in recent decades has led to an increase in the number of identified causes of trigeminal nerve dysfunction, which are amenable to specific treatment and functional recovery. A clinically oriented segmental approach to trigeminal nerve pathology is important for performing specialized high-resolution imaging studies, which represent a powerful tool in the examination of patients with trigeminal nerve dysfunction. Magnetic resonance imaging makes a significant contribution to the topical and nosological diagnosis of cranial nerve lesions due to its high tissue contrast, the ability to obtain images in various planes, and its capacity to accurately and reliably identify cranial nerves and surrounding anatomical structures without exposing the patient to radiation.

Author Contributions: Concept and design of the study, data analysis and interpretation, review of critical intellectual content, development of the study concept and design, approval of the final version of the manuscript, responsibility for the integrity of the manuscript content —Y.V.K.; preparation and initial analysis of factual material: E.V.E., I.K.S., Y.V.K.; concept and design of the study, final approval for manuscript publication — Y.V.K.; review of critical intellectual content— Y.V.K., R.V.G.

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