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Temporomandibular joint innervation: Anatomical study and clinical implications

Arda Kucukguven^a, Mehmet Deniz Demiryurek^b, Ibrahim Vargel^{a,*}

^a Department of Plastic, Reconstructive and Aesthetic Surgery, Hacettepe University Faculty of Medicine, 06080 Sihhiye, Ankara, Turkey ^b Department of Anatomy, Hacettepe University Faculty of Medicine, 06080 Sihhiye, Ankara, Turkey

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ABSTRACT

Background: Temporomandibular disorders and related pain are commonly seen in clinical practice. Due to its recurrent nature, they adversely affect a patient's social life. Current knowledge on the temporomandibular joint (TMJ) innervation is debatable and insufficient to ensure optimal treatment for the underlying pathology. This study aimed to elucidate the pathophysiology of temporomandibular pain by revealing the TMJ innervation topography, its variations, and its relationships with the surrounding anatomical structures. This will aid in creating a guide for temporomandibular, infratemporal, and preauricular interventions.

Methods: A total of 20 cadaver half heads, 10 fresh frozen and 10 embalmed, were used. The TMJ nerves were dissected together with the surrounding anatomical structures.

Results: We showed that the TMJ is mainly innervated by the auriculotemporal nerve posteriorly, the masseteric nerve anteriorly, the posterior deep temporal nerve anteromedially, and the TMJ branch originating directly from the mandibular nerve medially, and that there are variations in these innervation pathways. Additionally, we emphasized how these nerves might be affected in certain clinical conditions based on their anatomical relationships and pathophysiological mechanisms. To our knowledge, this is the first study showing the existence of a branch of the mandibular nerve directly innervating the TMJ.

Conclusion: In light of our findings, elucidating TMJ pain based on the anatomical characteristics of the region will allow precise treatment algorithms and better clinical outcomes in these patients. Based on this study, new clinical studies and interventions can be designed to reduce healthcare costs and alleviate the burden of temporomandibular disorders.

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1. Introduction

Temporomandibular disorders and related orofacial pain are conditions that are seen in 40–60% of the population. Due to its recurrent nature, they seriously impact a patient's social life (Agerberg and Carlsson, 1972; Grosfeld and Czarnecka, 1977; Hansson and Nilner, 1975; Helkimo, 1974; Ingervall and Hedegard, 1974; Molin et al., 1976; Posselt, 1971). Pain is the most common temporomandibular symptom, the most resistant to treatment, and the major symptom that affects a patient's quality of life (Okeson, 2020b). The treatment varies according to the underlying primary pathology, and it is important to reveal the relationship between the related temporomandibular joint (TMJ) innervation pathway and underlying pathology in detail for complete clinical recovery

* Corresponding author. E-mail addresses: arda.kucukguven@hacettepe.edu.tr (A. Kucukguven), mdeniz@hacettepe.edu.tr (M.D. Demiryurek), ivargel@hacettepe.edu.tr (I. Vargel). (Okeson, 2020b). Otherwise, recurrent pain and repetitive interventions increase patient morbidity and create a financial and moral burden on patients.

Several interventions have been described for the diagnosis and treatment of temporomandibular pain through possible innervation pathways of the TMJ. Nerve blockade with local anesthetic drugs for the diagnosis and treatment of pain (Donlon et al., 1984; DuPont, 2004; Klineberg and Lillie, 1980), iatrogenic TMJ neuroma excision (Granquist et al., 2011; Kodama et al., 2012), nerve decompression surgery (Cascone et al., 2010), and TMJ denervation in recurrent cases (Bradley, 1987; Dellon and Maloney, 2006) are some of these interventions. In addition, for the success of other temporomandibular and infratemporal region interventions such as arthroscopy and open surgeries, a comprehensive knowledge of the TMJ innervation topography is of great importance.

Although the literature mainly focuses on the auriculotemporal nerve (ATN) in the pathophysiology of temporomandibular nociceptive pain and TMJ innervation, a few studies have indicated that



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the sensory branches of the masseteric nerve and posterior deep temporal nerve (PDTN) before terminating in the masseter and temporal muscles, respectively, may also play a role in TMJ innervation (Davidson et al., 2003; Johansson et al., 1990; Schmid, 1969). Current knowledge on TMJ innervation is insufficient for proper treatment of the underlying temporomandibular pathology because of the fact that these TMJ innervation studies are old and insufficient in terms of demonstration, include a limited number of TMJ dissections, and provide insufficient data to explain TMJ innervation and its variations in detail. By clarifying this complicated innervation map, pain, which is the most recalcitrant symptom of temporomandibular disorders despite conservative approaches and minimally invasive and invasive interventions, may be treated adequately in the future. Therefore, this study aimed to elucidate the pathophysiology of orofacial pain of temporomandibular origin by revealing the TMJ innervation topography, its variations, and its relationship with surrounding anatomical structures. In light of these data, we aim to create a guide for treatment interventions, temporomandibular and infratemporal surgeries to be planned in the future. Thus, the treatment of patients seeking a solution because of recurrent temporomandibular pain can reach the desired point by completing this deficiency in the literature.

2. Material and methods

Twenty cadaver half heads, 10 embalmed and 10 fresh frozen cadavers, were dissected under 3.5× loupe magnification between September 2020 and December 2020. The present study was approved by the Institutional Non-Interventional Clinical Research Ethics Board (GO 20/571). Our study was compliant with the principles of the Declaration of Helsinki. All dissections were performed by the same surgeon (A.K.) in the head and neck dissection unit of the institutional anatomy laboratory.

2.1. Elevation of flaps and exposure of the infratemporal fossa

Skin and superficial musculoaponeurotic system flaps were raised by making a preauricular incision extending from the temporal region to the mentum along the mandibular border. The zygomatic arch, parotid gland, temporalis, and masseter muscles were exposed. The parotidomasseteric fascia was incised at the anterior border of the masseter muscle, and the muscle was elevated from the mandible in the subperiosteal plane, avoiding injury to the neurovascular structures of the sigmoid notch. The masseter muscle was also elevated from the zygomatic arch in the subperiosteal plane. At that point, the masseteric nerve, the only structure connecting the masseter muscle to the head, was dissected. Next, the ATN, which wraps around the condylar neck and runs superiorly in the superficial plane, and its superficial TMJ branches were dissected.

The temporalis muscle was fully exposed after removal of the zygomatic arch after osteotomies. Next, mandibular osteotomies were performed at the level of the condylar neck, just below the pterygoid fovea where the lateral pterygoid muscle inserts, and at the midpoint of the ipsilateral corpus (Fig. 1). Then, the temporalis muscle was transected at the site of its attachment to the coronoid process and the attachment of the medial pterygoid muscle to the angulus was released. The osteotomized mandible was then removed to expose the infratemporal fossa.

The temporalis muscle was elevated from the skull, taking care not to injure the PDTN coming from the infratemporal fossa. The small parts of the temporal and masseter muscles where the PDTN and masseteric nerve enter, respectively, were protected to make the muscle manipulations easier during the nerve dissections, and the remaining muscles were removed.



Fig. 1. Osteotomy lines.

2.2. Nerve dissections

Following the release of the lateral pterygoid muscle from the sphenoid bone, the two terminal branches of the mandibular nerve, namely the inferior alveolar nerve and the lingual nerve, were exposed and dissected proximally up to the foramen ovale. The TMJ capsule was elevated 360° over the temporal bone without damaging any nerves, thus releasing the TMJ and making its manipulation easier during the nerve dissection.

Subsequently, the mandibular nerve emerging from the foramen ovale was identified, and its branches were dissected distally to investigate the TMJ innervation topography and variations (Supplementary video content 1). The ATN, which runs posteriorly, wraps around the condylar neck, and continues cranially, was dissected along with its TMJ branches. The entrance points, number, and variations of the TMJ branches of the ATN were recorded.

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Subsequent to the ATN dissection, the posterior and anterior deep temporal nerves travelling to the temporal muscle anterolaterally, nerve branches innervating the lateral and medial pterygoids, buccal nerve, masseteric nerve, and all nerve branches innervating the TMJ were dissected and demonstrated. The ATN and masseteric nerve, which were isolated distally in the early stages of the dissection, were completely dissected starting from the foramen ovale. The topographic variations, number, entry points, and branching patterns of all the TMJ nerves were recorded, and their relationships with the surrounding anatomical structures were demonstrated.

3. Results

In our study, a total of 20 Caucasian half heads, 11 (55%) females and nine (45%) males, were used. The age at death of the subjects ranged from 55 to 78 years (mean, 67.2 ± 9.5 years) (Table 1).

TMJ innervation topography was demonstrated, and it was observed that there were many variations in the branching and innervation patterns of the nerves. It was shown that the nerves hia data

Table 1

Cadaver No	Туре	Side	Sex	Age
1	FF	Left	F	78
2	FF	Right	F	78
3	Е	Left	М	57
4	FF	Right	F	68
5	Е	Left	F	68
6	FF	Left	F	70
7	FF	Left	М	69
8	FF	Right	М	69
9	FF	Left	М	46
10	FF	Right	М	46
11	E	Right	F	71
12	Е	Left	F	71
13	Е	Right	F	69
14	Е	Right	F	78
15	Е	Left	F	78
16	Е	Right	М	67
17	FF	Right	М	71
18	FF	Left	М	71
19	E	Right	F	64
20	E	Right	М	55
Mean		-		67.2
SD				9.5

FF: Fresh frozen, E: Embalmed, SD: Standard deviation, M: Male, F: Female.

Table 2				
Temporomandibular	ioint	innervation	and	variations.

Cadaver No	Auriculotemporal nerve	Masseteric nerve	Posterior deep temporal nerve	TMJ branch of the mandibular nerve
1	3	2	-	1
2	1	2	-	1
3	2	1	1	-
4	2	1	-	1
5	2	_*	_*	1
6	3	1	2	-
7	3	1*	_*	1
8	1	1*	_*	1
9	2	1	-	1
10	3	1*	_*	-
11	2	1	-	-
12	2	1**	-	-
13	2	1	-	1
14	1	-	1	1
15	2	1	-	1
16	2	1	-	1
17	1	1	-	-
18	1	1	-	1
19	2	1	-	-
20	1	1	-	1
Mean	1.9	1.0	0.2	0.65

TMJ: Temporomandibular joint.

(*): The two marked nerves in the same row originate from a common trunk. (**): The branch to the TMJ (deemed as the masseteric branch) branches from the common trunk of the masseter and posterior deep temporal nerves proximal to the bifurcation.

involved in the innervation differed according to the entry surface of the TMJ capsule. Some nerves involved in innervation were absent in some cadavers, while some nerves innervated the TMJ from different surfaces with several different branches. In particular, it was shown that the ATN played a major role in TMJ innervation, with an average of 1.9 branches. In addition to the ATN, in the dissections, the masseteric nerve, the TMJ branch of the mandibular nerve, and the PDTN played a role in TMJ innervation, from the most common to the rarer presentation, respectively. All nerves innervating the TMJ and their variations are shown in Table 2. The innervation variations and the topographical relationships of the nerves involved in TMJ innervation with the surrounding anatomical structures, TMJ capsule, and retrodiscal bilaminar tissue are explained in detail below.



Fig. 2. Branches of the ATN to the TMJ capsule and retrodiscal tissue before it turns around the condylar neck and continues superiorly. The condyle is dislocated from the glenoid fossa anterolaterally for demonstration purpose. ATN: Auriculotemporal nerve, SCM: Sternocleidomastoid, TMJ: Temporomandibular joint.

3.1. Auriculotemporal nerve

In the dissections, it was observed that the ATN branched from the posterior of the mandibular nerve as soon as it exited the foramen ovale, moved posteriorly at the medial aspect of the condylar neck, and then ascended in the preauricular region. The branches of the posterior TMJ capsule and retrodiscal tissue were dissected as they turned around the condylar neck (Figs. 2 and 3).

On average, the ATN gave off 1.9 branches to the TMJ. These branches mostly entered the joint capsule posteromedially and posterolaterally (Fig. 4). We found that, with an average of 1.9



Fig. 3. Branches of the ATN entering the TMJ capsule from the lateral aspect before it runs superiorly to innervate the temple. ATN: Auriculotemporal nerve, TMJ: Temporomandibular joint.

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Fig. 4. Branches of the ATN entering the posteromedial and posterolateral surfaces of the TMJ. Note that the ATN makes a ring as soon as it branches from the mandibular nerve. ATN: Auriculotemporal nerve, TMJ: Temporomandibular joint.

branches, the ATN played a major role in TMJ innervation, especially in the retrodiscal tissue, compared to the other nerves contributing to the joint capsule innervation.

3.2. Masseteric nerve

It was observed that the masseteric nerve proceeded laterally after it originated from the mandibular nerve as soon as it exited the foramen ovale, passed over the lateral pterygoid muscle and through the sigmoid notch, and innervated the masseter muscle. In most cases, it innervated the TMJ capsule anteriorly, with an average of one branch (Figs. 5 and 6). In 25% of the dissections, the masseteric nerve and PDTN emerged as a common branch from the mandibular nerve and then bifurcated into the masseteric nerve and PDTN.



Fig. 5. Anterior TMJ branches of the masseteric nerve before innervating the muscle and exiting the sigmoid notch, ATN: Auriculotemporal nerve, TMJ: Temporomandibular joint.

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Fig. 6. The branch of the masseteric nerve entering the TMJ capsule anteriorly before innervating the muscle. Note that the PDTN and the masseteric nerve initially originate from the mandibular nerve as a single trunk. The temporal and masseter muscles are released and reduced and only the nerve entry regions are left intact for ease of manipulation and dissection. The lateral pterygoid muscle is also released from its origin. The condyle is dislocated from the glenoid fossa anterolaterally for demonstration purpose. ATN: Auriculotemporal nerve, PDTN: Posterior deep temporal nerve, TMJ: Temporomandibular joint.

3.3. Posterior deep temporal nerve

It was observed that the PDTN proceeded anterolaterally as soon as it branched from the mandibular nerve after exiting the foramen ovale. It then passed from under the infratemporal crest of the sphenoid bone, moved anterosuperiorly, and innervated the temporal muscle. The TMJ branch of the PDTN, which was found in 15% of the dissections, was identified as the nerve playing the most minor role in TMJ innervation. It was determined that the PDTN innervated the anteromedial surface of the TMJ capsule (Fig. 7).

3.4. TMJ branch of the mandibular nerve

This nerve, which was seen in 65% of the dissections, was found to be a TMJ branch directly arising from the mandibular nerve. It was observed that it proceeded laterally after originating from the mandibular nerve, passed over the superior lateral pterygoid muscle, and innervated the TMJ capsule medially (Figs. 8 and 9).

4. Discussion

The prevalence of at least one sign of TMJ disorders has been reported to be 40–75% in the population (Scrivani et al., 2008). Moreover, 10–25% of the population present to clinics for professional help because of temporomandibular disorders (Bertoli et al., 2018; Pedroni et al., 2003; Schiffman et al., 1990; Schwartz and Freund, 2002; Scrivani et al., 2008). Among all temporomandibular symptoms, pain is the major factor that causes patients to seek professional help (Epker and Gatchel, 2000; Santana-Moraa et al., 2021). Clarifying the pathophysiology of temporomandibular pain and establishing a successful treatment plan for patients is possible only if the TMJ innervation topography is addressed in detail. In addition, a comprehensive knowledge of the innervation topography of this complex region is crucial for the success of temporomandibular and infratemporal region interventions, such as

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Fig. 7. Branches of the PDTN to the joint capsule anteromedially. In addition, anterior TMJ branch of the masseteric nerve and posterior TMJ branches of the ATN can be seen. Note that the ATN makes a ring as soon as it branches from the mandibular nerve. The temporal and masseter muscles are released and reduced and only the nerve entry regions are left intact for ease of manipulation and dissection. The condyle is dislocated from the glenoid fossa inferiorly for demonstration purpose. ATN: Auriculotemporal nerve, PDTN: Posterior deep temporal nerve, TMJ: Temporomandibular joint.

minimally invasive treatments, nerve blockages, percutaneous injections, arthroscopies, and open surgeries.

The cranial part of the lateral pterygoid plate on the roof of the infratemporal fossa, the foramen ovale where the mandibular nerve exits, and the TMJ are on the same plane horizontally and are anatomically very close (Fig. 9). Owing to the proximity of the mandibular nerve to the TMJ, variations in the TMJ innervation and their relationship with the surrounding anatomical structures are important.

After the mandibular nerve enters the infratemporal fossa by passing through the foramen ovale, it gives off several branches, such as the meningeal branch, auriculotemporal nerve, lingual nerve, inferior alveolar nerve, masseteric nerve, deep temporal nerves (anterior and posterior), buccal nerve, and lateral and medial pterygoid nerves (Somayaji et al., 2012; Iwanaga et al., 2020). According to the literature, the TMJ is mostly innervated by the ATN and may rarely be innervated by the masseteric and deep temporal nerves. Limited studies have reported innervation pathways other than the auriculotemporal nerve. These studies are old and inadequate in terms of demonstration of TMJ innervation and its variations in detail. Moreover, a limited number of TMJ dissections were performed in these studies (Davidson et al., 2003; Schmid, 1969). In a cadaver study conducted by Davidson et al. (2003), the ATN innervated the TMJ in all joints. In addition, the masseteric nerve, originating from the maxillary nerve in 75% of the joints, gave off branches to the TMJ. However, it is now known that the masseteric nerve is a branch of the mandibular nerve. Further, in the study by Davidson et al. (2003), it was reported that a branch coming through the mandibular notch innervated the joint capsule anteromedially in 33% of the dissections. Moreover, they emphasized that this branch most likely originated from the maxillary nerve, came from the lateral pterygoid muscle, and innervated the TMJ. Considering the current anatomical knowledge and findings of our study, it can be concluded that contradictory findings have been reported in those studies.

In addition to the fact that the TMJ is primarily innervated by the ATN posteriorly, we have demonstrated that it is innervated by the masseteric nerve anteriorly, by the PDTN anteromedially, and by the TMJ branch of the mandibular nerve medially, and that there are variations in these

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Fig. 8. The branch coming directly from the mandibular nerve medially to the TMJ capsule. In addition, posterior TMJ branches of the ATN can be seen. The temporal and masseter muscles are released and reduced and only the nerve entry regions are left intact for ease of manipulation and dissection. The condyle is dislocated from the glenoid fossa anterolaterally for demonstration purpose. ATN: Auriculotemporal nerve, PDTN: Posterior deep temporal nerve, TMJ: Temporomandibular joint.

innervation pathways (Fig. 10 and Supplementary video content 2). In 55% of the dissections, the TMJ was innervated by the ATN together with the masseteric nerve and a TMJ branch directly originating from the mandibular nerve. In 25% of the dissections, the combination of masseteric and auriculotemporal nerves played a role in TMJ innervation in 25% of the dissections, and in 10% of the dissections, in addition to the masseteric and auriculotemporal nerves, the PDTN contributed to TMJ innervation.

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To the best of our knowledge, this is the first study in the literature showing the existence of a branch of the mandibular nerve directly innervating the TMJ. It was found that among the four nerves involved in the TMJ innervation (the ATN, masseteric nerve, TMJ branch of the mandibular nerve, and PDTN), the ATN innervated the TMJ, especially the retrodiscal tissue, with an average of two branches from the posteromedial, posterior, and posterolateral surfaces. The ATN approaches the condyle neck medially, turns around it, and continues superiorly. Its proximity to the condylar neck during its course puts this nerve at high risk for injury in subcondylar fractures or TMJ surgeries (Johansson et al., 1990; Kodama et al., 2012; Schmidt et al., 1998; Garcia-Guerreroa et al., 2018). In addition, compression or irritation of the ATN branches innervating the retrodiscal tissue that attaches posteriorly to the articular disc plays a major role in the pathophysiology of pain in TMJ dysfunction (Okeson, 2020a).

The masseteric nerve, which branches from the mandibular nerve after exiting the foramen ovale, runs over the lateral pterygoid muscle laterally and passes in close proximity to the anterior of the TMJ capsule before passing through the sigmoid notch. In our study,



Fig. 9. The branch coming directly from the mandibular nerve medially to the TMJ capsule. In addition, the branches of the ATN to the posterior joint capsule, left behind after the dislocation of the condyle, are seen. Note that the PDTN and masseteric nerves originate from the mandibular nerve as a single trunk and then bifurcate, and the TMJ branch of the masseteric nerve enters the joint capsule anteriorly. The temporal and masseter muscles are released and reduced and only the nerve entry regions are left intact for ease of manipulation and dissection. The lateral pterygoid muscle is also released from its origin. The condyle is dislocated from the glenoid fossa anterolaterally for demonstration purpose. ATN: Auriculotemporal nerve, PDTN: Posterior deep temporal nerve, TMJ: Temporomandibular joint.

the TMJ branch of the masseteric nerve innervated the joint anteriorly. In TMJ hypermobility, anterior dislocations of the TMJ, or interventions affecting the anterior region of the joint, this nerve may be injured, resulting in temporomandibular dysfunction causing painful symptoms (Johansson et al., 1990). The TMJ branch of the mandibular nerve, which innervates the TMJ medially, branches from the mandibular nerve laterally as soon as it exits the foramen ovale and enters the infratemporal fossa. This branch travels in a narrow space while approaching the TMJ. It is prone to stretching or compression when the TMJ proceeds horizontally to the contralateral or ipsilateral side. There is a possibility of compression, especially in traumatic medial dislocations. In TMJ open surgeries, the possibility of injury is high because it is medial to the capsule, which makes its identification and dissection difficult.

It was observed that the PDTN had a relatively small role in TMJ innervation. It emerged from the mandibular nerve as a common branch with the masseteric nerve in 25% of the dissections. The PDTN innervated the TMJ in only 15% of the dissections. It initially proceeds anterolaterally toward the temporal muscle and gives off the TMJ branch before turning superiorly from the temporal crest, and this branch enters the TMJ capsule anteromedially. Any infratemporal mass, such as a tumor or collection, might compress this branch and cause symptoms. Especially in TMJ internal dearrangements seen in temporomandibular dysfunctions, irritation of this branch by the anteromedially dislocated articular disc may cause temporomandibular discomfort (Chang et al., 2018; Okeson, 2020a). In addition to the symptoms caused by the injured TMJ nerves, these injuries can also have indirect effects via their connections with other cranial nerves including the vagus nerve. The trigeminocardiac reflex is a possible mechanism which might occur following an injury to the TMJ nerves since they are all originated from the trigeminal nerve (Lang et al., 1991).

A study conducted by Johansson et al. reported two cases of articular disc dislocation; the ATN was almost in contact with the medial surface of the TMJ, which could cause irritation. Further, it was shown that in a joint with condylar hypermobility, the condyle compressed the TMJ branch of the masseteric nerve (1990). In the TMJ innervation dissections performed by Schmid during the autopsy of six infants (1969), the joint was innervated by branches from the ATN, masseteric nerve, PDTN, and facial nerve. However, the fact that the study was from several decades ago and the dissection images were of poor quality casts doubt on these findings (Schmid, 1969). Considering the erroneous findings in these



Fig. 10. Horizontal section view of the temporomandibular joint innervation topography and its variations (superior view). (Left) In this detailed illustration, the anatomical structures surrounding the TMJ, the branches that the TMJ receives from the ATN posteromedially and posterolaterally and from the masseteric nerve anteriorly, and the TMJ branch of the mandibular nerve coming from the medial aspect are demonstrated. This variation was found in 55% of the dissections. (Right above) In this simplified illustration, the TMJ branches of the ATN innervating the TMJ capsule posteromedially and posterolaterally and the anterior TMJ branch of the masseteric nerve are shown. This variation was found in 25% of the dissections. (Right below) The joint is innervated by the ATN posteromedially and posterolaterally, by the PDTN anteromedially, and by the masseteric nerve anteriorly. This variation was found in 10% of the dissections.

studies and the inadequacy of the anatomical demonstration in the photographs, it appears that these studies are not sufficient to explain the TMJ innervation today. The TMJ innervation studies published by Griffin and Harris (1975), in contrast, were histological studies, similar to the study performed by Asaki et al. (2006). They demonstrated the neural structures in the joint sections rather than the TMJ innervation pathways. In this respect, our study presents visual and numerical data that can fill this gap in the literature.

5. Conclusions

In this cadaver study, we demonstrated the TMJ innervation topography, its variations, and its relationships with the surrounding anatomical structures. Thus, we addressed the lacuna created by the fact that the studies in the literature are old and insufficient in terms of demonstration. We showed the three-dimensional course of the four nerves involved in TMJ innervation (the ATN, masseteric nerve, TMJ branch of the mandibular nerve, and PDTN) until they reached the capsule. To our knowledge, this is the first study that showed the existence of a branch of the mandibular nerve that directly innervates the TMJ. Considering the findings of our study and the pathophysiology of temporomandibular disorders, the treatment of these patients may yield favorable outcomes in the future. Our study can also be used as a guide for interventions involving the temporomandibular, infratemporal, and preauricular regions. Based on this study, new clinical studies and interventions can be designed to reduce healthcare costs and alleviate the burden of temporomandibular problems and TMJ pain in these patients.

Ethical statement

Our study was approved by the Institutional Non-Interventional Clinical Research Ethics Board (GO 20/571). The protocol of this study was compliant with the principles of the Declaration of Helsinki.

CRediT authorship contribution statement

Arda Kucukguven: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Project administration. **Mehmet Deniz Demiryurek:** Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision, Project administration. **Ibrahim Vargel:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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