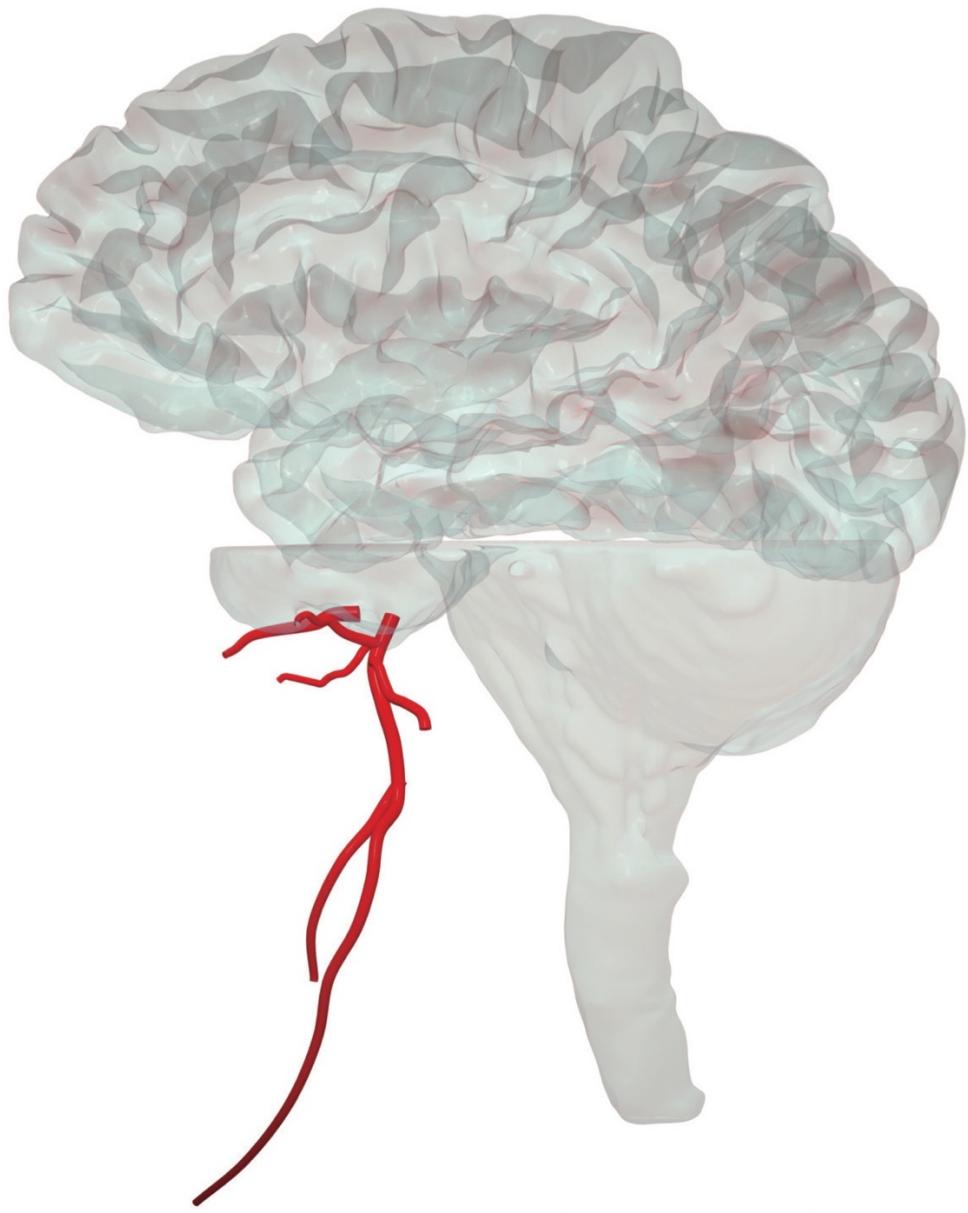


# TRIGEMINAL NERVE INJURIES

Frédéric Van der Cruyssen



evaluation and optimization  
of diagnostic methods



# NERVUS TRIGEMINUS LETSELS

EVALUATIE EN OPTIMALISATIE VAN DIAGNOSTISCHE  
METHODEN

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Proefschrift voorgedragen  
tot het behalen van de  
graad van Doctor in de  
Biomedische  
Wetenschappen



KU Leuven  
Biomedical Sciences Group  
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# TRIGEMINAL NERVE INJURIES

## EVALUATION AND OPTIMIZATION OF DIAGNOSTIC METHODS

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Dissertation presented in  
partial fulfilment of the  
requirements for the  
degree of Doctor in  
Biomedical Sciences



# PREFACE

This doctoral thesis consists of ten research chapters, two intermezzos and a concluding chapter. The chapters were based on the following peer-reviewed publications and manuscripts:

- CHAPTER 1      Van der Cruyssen F, Verhelst PJ, Stevens O, Casselman J, Renton T, Piagkou M, Bonte B, Politis C. Severe progressive post-traumatic trigeminal neuropathic pain after total temporomandibular joint replacement - A case report. *Oral and Maxillofacial Surgery Cases.* 2020;6(July):100175.
- Van der Cruyssen F, Politis C. Neurophysiological aspects of the trigeminal sensory system: an update. *Reviews in the Neurosciences.* 2018;29(2):115-123.
- Klazen Y, Van der Cruyssen F, Vranckx M, Van Vlierberghe M, Politis C, Renton T, Jacobs R. Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study. *International Journal of Oral and Maxillofacial Surgery.* 2018;47(6):789-793.
- Renton T, Van der Cruyssen F. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. *Oral Surgery.* 2019;13(4):389-403.
- Van der Cruyssen F, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, Renton T. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. *Journal of Oral Rehabilitation.* 2020;47(10):1212-1221.
- CHAPTER 2      Van der Cruyssen F, Nys M, Renton T, Vandeleene G, Callens M, Vanhaecht K, Jacobs R, Politis C, Luyten J. Healthcare costs of post-traumatic trigeminal neuropathy in Belgium - A retrospective analysis. *J Craniomaxillofac Surg.* 2022;50(8):627-636.
- INTERMEZZO 1    Van der Cruyssen F, Van Tieghem L, Croonenborghs TM, Baad-Hansen L, Svensson P, Renton T, Reinhilde J, Politis C, De Laat A. Orofacial quantitative sensory testing: Current evidence and future perspectives. *European Journal of Pain.* 2020;(June):1-15.
- CHAPTER 3      Meewis J, Renton T, Jacobs R, Politis C, Van der Cruyssen F. Post-traumatic trigeminal neuropathy: correlation between objective and subjective assessments and a prediction model for neurosensory recovery. *J Headache Pain.* 2021;22(1):44.

- CHAPTER 4 Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T. Prognostic factors, symptom evolution, and quality of life of post-traumatic trigeminal neuropathy. *Pain*. 2022;163(4):e557-e571.
- CHAPTER 5 Van der Cruyssen F, Peeters F, Croonenborghs TM, Fransen J, Renton T, Politis C, Casselman J, Jacobs R. A systematic review on diagnostic test accuracy of magnetic resonance neurography versus clinical neurosensory assessment for post-traumatic trigeminal neuropathy in patients reporting neurosensory disturbance. *Dentomaxillofacial Radiology*. 2020;50(1):20200103.
- INTERMEZZO 2 Peeters F, Van der Cruyssen F, Casselman J, Hermans R, Renton T, Jacobs R, Politis C. The Diagnostic Value of Magnetic Resonance Imaging in Post-traumatic Trigeminal Neuropathic Pain. *J Oral Facial Pain Headache*. 2021;35(1):35-40.
- CHAPTER 6 Van der Cruyssen F, Croonenborghs TM, Hermans R, Jacobs R, Casselman J. 3D Cranial Nerve Imaging, a Novel MR Neurography Technique Using Black-Blood STIR TSE with a Pseudo Steady-State Sweep and Motion-Sensitized Driven Equilibrium Pulse for the Visualization of the Extraforaminal Cranial Nerve Branches. *American Journal of Neuroradiology*. 2020;42(3):578-580.
- CHAPTER 7 Van der Cruyssen F, Croonenborghs TM, Renton T, Hermans R, Politis C, Jacobs R, Casselman J. Magnetic resonance neurography of the head and neck: state of the art, anatomy, pathology and future perspectives. *The British Journal of Radiology*. 2021;94(October):20200798.
- CHAPTER 8 Casselman J\*, Van der Cruyssen F\*, Vanhove F, Peeters R, Hermans R, Politis C, Jacobs R. 3D CRANI, a novel MR neurography sequence, can reliably visualise the extraforaminal cranial and occipital nerves. *Eur Radiol*. Published online November 26, 2022. \*Shared first authorship
- CHAPTER 9 Bangia M, Ahmadzai I, Casselman J, Politis C, Jacobs R, Van der Cruyssen F. Accuracy of MR neurography as a diagnostic tool in detecting injuries to the lingual- and inferior alveolar nerve in patients with iatrogenic post-traumatic trigeminal neuropathy. Submitted to European Radiology.
- CHAPTER 10 Van der Cruyssen F, Palla B, Van der Tas J, Jacobs R, Politis C, Zuniga J, Renton T. Consensus guidelines on training, diagnosis, treatment and follow-up care of trigeminal nerve injuries. Submitted to the International Journal of Oral and Maxillofacial Surgery.

## ACKNOWLEDGEMENTS

Een PhD komt niet tot stand zonder de hulp van anderen. Dit project begon met een persoonlijke overtuiging om een wetenschappelijk en klinisch vraagstuk aan te pakken en meer duidelijkheid te scheppen in een ondergewaardeerd onderzoeksgebied. Al snel merkte ik dat dit werk niet tot stand zou komen zonder samenwerking, doorzettingsvermogen en ondersteuning. Ik wil dan ook graag mijn oprechte dank uitspreken aan jullie allen voor jullie onschatbare steun tijdens mijn PhD-reis.

Mams, je was er bij van het begin maar mocht het einde niet meemaken. Wat doet het pijn dat ik je niet op de eerste rij kan zien zitten. Maar jouw steun verdwijnt nooit. De vele herinneringen aan jou, de talloze foto's die je achterliet en jouw bovenmenselijk doorzettingsvermogen gaven me de courage om dit neer te schrijven. Jouw voorbeeld zal ik altijd blijven volgen.

Papa en Katrien dank jullie voor het creëren van een warme thuis voor ieder van ons. Dankzij jullie opvoeding en continue ondersteuning is dit uitdagend project tot een goed eind gekomen. Als ondernemers hebben jullie altijd een creatieve oplossing klaar voor kleine tot grote problemen. Jullie *solution mindset* is om naar op te kijken en stel ik als voorbeeld voor mezelf. Dank jullie om ons te vormen tot wie we zijn.

Mijn zus Julie, schoonbroer Robert, en petekindjes Leonore en Helena bedankt voor alle leuke familiemomenten samen. Deze momenten zorgen steeds voor de nodige humor, gezelligheid en opgeladen batterijen. Dank je zus voor de vele peptalks over de afgelopen jaren en om er altijd te zijn voor mij. Dank je Robert voor je enthousiasme, BBQ-kunsten en fotografisch talent waar we dagelijks van mogen genieten.

Aan mijn tweede thuis, Lieve, Filip, Louise en Karen. Ik zag ooit een optreden van het cabaretduo de “Frivole Framboos” in de theaterzaal in Waregem. Een prachtige naam en optreden die me vaak aan jullie doet denken. Alleen moeten we er dan wel een gans bakske frambozen van maken. Met heel veel energie gaan jullie door het leven. Maar, jullie weten ook de familiemomenten te koesteren. De rust, die vinden we samen op zee, waar ook ter wereld. Dank om mij zo hartelijk op te nemen in jullie gezin, er steeds voor ons te zijn en ons te steunen in al onze projecten. Filip, mede dankzij jou begon ik aan mijn PhD traject. Je hielp me op weg

met mijn eerste publicatie tijdens mijn stages in Oostende. Je bent een bron van inspiratie en bewijst nog maar eens dat een goede clinicus ook een goede onderzoeker kan en mag zijn.

Mijn vrienden, jullie hebben me steeds gesteund in woord en daad. Op leuke momenten, vriendenweekends of reisjes, tijdens nachtelijke escapades, maar ook wanneer het moeilijk was. Dank voor al deze momenten samen, ze zetten de gedachten even op nul en brengen de zaken terug in perspectief. Op nog vele hoogtestages en gezellige avonden samen.

Pieter-Jan Verhelst, eerst en vooral mijn oprechte dank voor alle steun tijdens onze tandheelkunde opleiding. Zonder jou stond ik hier niet. Zowel persoonlijk als professioneel vonden we elkaar. Je hebt een waar talent om de zaken helder voor te stellen. Een talent die tijdens een PhD traject de nodige rust in het hoofd brengt. Met een glaasje wijn erbij of telefonisch wanneer we beiden in de auto zaten op weg naar huis. Ik mocht altijd beroep doen op jouw persoonlijk en professioneel advies. Ik kan je hier niet genoeg voor bedanken.

Tomas-Marijn Croonenborghs, dank om je herberg in Leuven een jaar voor mij open te stellen en dat jaar zo aangenaam te maken. Je positivisme en rechtvaardigheidsgevoel is hartverwarmend en om naar op te kijken.

Prof. dr. Constantinus Politis, mijn mentor. Uw werkethos en passie voor het vak is onevenaarbaar. In 2016 wakkerde u ook mijn passie aan om onderzoek te doen naar zenuwschade. U wakkerde ook mijn passie voor boeken aan, wat ondertussen tot een plaatsgebrek heeft geleid. U steunde mij in alle geslaagde, maar ook enkele niet-geslaagde projecten. Uw aanmoediging en coaching hielp me telkens die lat te verleggen en niet op te geven bij een tegenslag. Dank u om steeds tijd te maken, dag én nacht, te luisteren, bij te sturen, te ondersteunen, en mijn horizon te verbreden.

Prof. Tara Renton, already at our first meeting in Leuven, I was attracted to your enthusiasm and commitment to the difficult topic of trigeminal nerve injuries and orofacial pain. You helped me take my first steps in scientific writing and soon involved me in many of your projects. I am therefore sincerely grateful for all the opportunities you gave me. Thank you for allowing me to lean on your shoulders. I look forward to the joint ambitious projects ahead of us and further improve the care of these patients.

Prof. dr. Reinhilde Jacobs dank u voor alle ondersteuning doorheen dit traject. Zonder u was deze PhD nooit tot stand gekomen. Dank voor alle inhoudelijke en praktische ondersteuning. Uw netwerk is impressionant en strekt ver buiten België. Dankzij u kwam ik in contact met onder meer prof. Renton en prof. Casselman. Ik voel me nederig dat ik hiervan “gebruik” mocht maken. Dank je voor de vele babbels samen en verheldering wanneer ik even de draad kwijt was. Ook wil ik je bedanken om mij op te nemen in de OMFS-IMPATH groep. Een prachtige onderzoeksgroep waar u iedereen een thuis in geeft. De cultuur die er heerst is opmerkelijk en zorgt altijd voor boeiende projecten en collaboraties. Ik hoop dat ik hier in de toekomst verder mag toe bijdragen.

Prof. em. dr. Antoon De Laat. Ik heb het gevoel dat ik te weinig heb mogen leren van u. Uw toewijding naar de patiënt is uniek en hartverwarmend. Uw positivisme is al even opmerkelijk en uw fluitgezang 's ochtends in de gangen van Sint-Rafaël deden mijn dag altijd met een glimlach starten. Dank voor al het overleg samen. Dank u om mij te inspireren.

Prof. dr. Jan Casselman, zonder u kwam dit proefschrift nooit tot stand. Onze eerste ontmoeting zal ik nooit vergeten. Na reeds enkele maanden MRI sequenties testen, sprak ik u hierover aan. Uw antwoord was duidelijk: MRI voor perifere craniale zenuwen werkt niet, doe geen moeite. Ik ging met de moed in de schoenen naar huis en focuste op andere projecten. Maar enkele maanden later mocht ik u opnieuw ontmoeten en nodigde u me uit om langs te komen in Brugge. Uw enthousiasme was aanstekelijk en we waren iets op het spoor. Na veel testen, teleurstelling, verder optimaliseren en een toevalstreffer met contrast was de 3D CRANI sequentie geboren. Ik ben u dan ook oprecht dankbaar voor uw vertrouwen, onze samenwerking en de voorbeeldfunctie die u stelt.

Prof. dr. Robert Hermans, Ron en Frederik. Dank jullie om te geloven in ons MRI project en ons preklinisch en klinisch op weg te helpen. Dankzij jullie mocht ik tal van experimenten uitvoeren en konden we finaal ook de sequentie implementeren in de kliniek. Hartelijk dank om dit proces mee te begeleiden en jullie tijd in mij te investeren.

Aan de stafleden en het MKA team in UZ Leuven. Ik waardeer jullie tijd en expertise en ben dankbaar elke dag van jullie te leren. Leuven is en zal altijd mijn bakermat blijven. Dank aan ieder van jullie voor alle fijne momenten samen, jullie feedback, formele en informele babbels en het traditionele vrijdagavondpintje in het assistentenlokaal.

Aan de collega's uit het ETZ in Tilburg. Wat een fantastische tijd de afgelopen twee jaar... Jullie verwelkomden mij in het team als een gelijke en er ging geen dag voorbij zonder een moment van hilariteit. De open cultuur en het opleidingsklimaat zijn ongezien, de groepsuitjes en borrels legendarisch. Een team en periode in mijn leven die ik nooit zal vergeten.

Aan alle juryleden, bedankt voor jullie tijd om dit lijvig document na te lezen en kritisch te evalueren.

Liefste Laure, bedankt voor het ondersteunen en aanmoedigen van mijn dromen. Jouw liefde en steun zijn mijn belangrijkste bronnen van motivatie. Bovendien mocht ik ook beroep doen op jouw creatieve skills om mijn PhD boekje vorm te geven. Je bent een vat vol talent en bruist steeds van de energie. Waar ik soms te voorzichtig zou zijn, moedig jij mij aan om de *bold* keuze te maken en ervoor te gaan. Dankjewel voor de ruimte die je me geeft om mijn dromen te realiseren. Dankjewel voor je onvoorwaardelijke steun van elke dag.

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# LIST OF ABBREVIATIONS

3D	Three dimensional		MRCS	Medical Research Council Scale
3D CRANI	3D Cranial Nerve Imaging		MRI	Magnetic resonance imaging
ADC	Apparent diffusion coefficient		MRN	Magnetic resonance neurography
aNMCNR	Apparent nerve-muscle contrast-to-noise ratio		MSDE	Motion-sensitized driven equilibrium
aSNR	Apparent signal-to-noise		NA or N/A	Not applicable
ATP	Adenosine triphosphate		NCS	Nerve conduction studies
AUC	Area under the receiver operating characteristic curve		NeuPSIG	Neuropathic Pain Special Interest Group by IASP
BB	Blackblood		NK1	Neurokinin 1
BFFE	Balanced fast-field echo sequences		NPV	Negative predictive value
BPI	Brief Pain Inventory		NRS	Numerical rating scale
BSSO	Bilateral sagittal split osteotomy		NS	Not specified
CBCT	Cone beam computed tomography		NSAIDs	Nonsteroidal anti-inflammatory drugs
CDT	Cold detection threshold		NSD	Neurosensory disturbance
CE-MRA	Contrast-enhanced magnetic resonance angiograph		NST	Neurosensory testing
CGRP	Calcitonin gene-related peptide		OR	Odds ratio
CH	Channel		ORIF	Open reduction internal fixation
CI	Confidence interval		PHQ	Patient Health Questionnaires
CISS	Constructive interference in steady-state		PHS	Paradoxical heat sensation
CNR	Contrast-to-noise ratio		PNS	Peripheral nervous system
CNS	Central nervous system		PPT	Pressure pain threshold
CPM	Conditioned pain modulation		PPV	Positive predictive value
CPSP	Chronic post-surgical pain		PROSPERO	Prospective Register of Ongoing Systematic Reviews
CPT	Cold pain threshold		PSIF	Diffusion-weighted reversed fast imaging with steady state free precession
CT	Computed tomography		PSS	Pseudo-steady state
DDD	Defined daily dose		PTN	Post-traumatic trigeminal neuropathy (this can be non-painful and painful PTN), if painful this can also be referred to as PTNP
DESS-WE	Double-echo steady state with water excitation		PTNP	Post-traumatic trigeminal neuropathic pain
DFNS	German Research Network on Neuropathic Pain		QoL	Quality of life
DMA	Dynamic mechanical allodynia		QST	Quantitative sensory testing
DN4	Douleur Neuropathique 4 questionnaire		QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
DTA	Diagnostic test accuracy		QualST	Qualitative sensory testing
DTI	Diffusion tensor imaging		ROI	Region of interest
DTT	Diffusion tensor tractography		RSI	Relative signal intensity
EQ5D	EuroQoL 5 dimensions questionnaire		SCM	Sternocleidomastoid muscle
EQUATOR	Enhancing the Quality and Transparency of Health Research	SD		Standard deviation
FA	Flip angle		SI	Signal intensity
FA	Fractional anisotropy		SNR	Signal-to-noise ratio
FFE	Fast field echo		SPGR	Spoiled gradient recalled echo
FIESTA	Fast spoiled gradient recalled echo		STIR TSE	Short Tau Inversion Recovery Turbo Spin Echo
FLAIR	Fluid attenuated inversion recovery		STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
fMRI	Functional MRI		T	Tesla
FOV	Field of view		T2SIR	Signal intensity on T2 image

FS	Fat saturated	T2WI	T2 Weighted imaging
GAD-7	General Anxiety Disorder 7 questionnaire	TE	Time to echo
GON	Greater occipital nerve	TMJ	Temporomandibular joint
GP	General practitioner	TMJR	Temporomandibular joint replacement
GRASS	Guidelines for Reporting Reliability and Agreement Studies	TN	Trigeminal nerve
HPT	Heat pain threshold	TNI	Trigeminal nerve injury
HRQoL	Health-related quality-of-life	TNVBUK	TrigNerveBeUK registry
IAN	Inferior alveolar nerve	TON	Third occipital nerve
IASP	International Association for the Study of Pain	TR	Repetition time
ICHD-3	International Classification of Headache Disorders, 3rd edition	TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
ICOP	International Classification of Orofacial Pain	TRPM8	Transient Receptor Potential Cation Channel Subfamily M member 8
IHS	International Headache Society	TSE	Turbo spin echo
IQR	Interquartile range	TSL	Thermal sensory limen
LA	Local anesthesia	V1	Area of distribution of the ophthalmic nerve
LLLT	Low-level laser therapy	V2	Area of distribution of the maxillary nerve
LN	Lingual nerve	V3	Area of distribution of the mandibular nerve
LON	Lesser occipital nerve	VAS	Visual analogue scale
MDT	Mechanical detection threshold	VDT	Vibration detection threshold
MIP	Maximum intensity projection	VPL	Ventral posterolateral
MN	Maxillary nerve	VPM	Ventral posteromedial
MPR	Multiplanar reformatting	WDT	Warm detection threshold
MPS	Mechanical pain sensitivity	WUR	Wind-up ratio
MPT	Mechanical pain threshold		

# SECTION 1



introduction and burden of disease



# CHAPTER 1

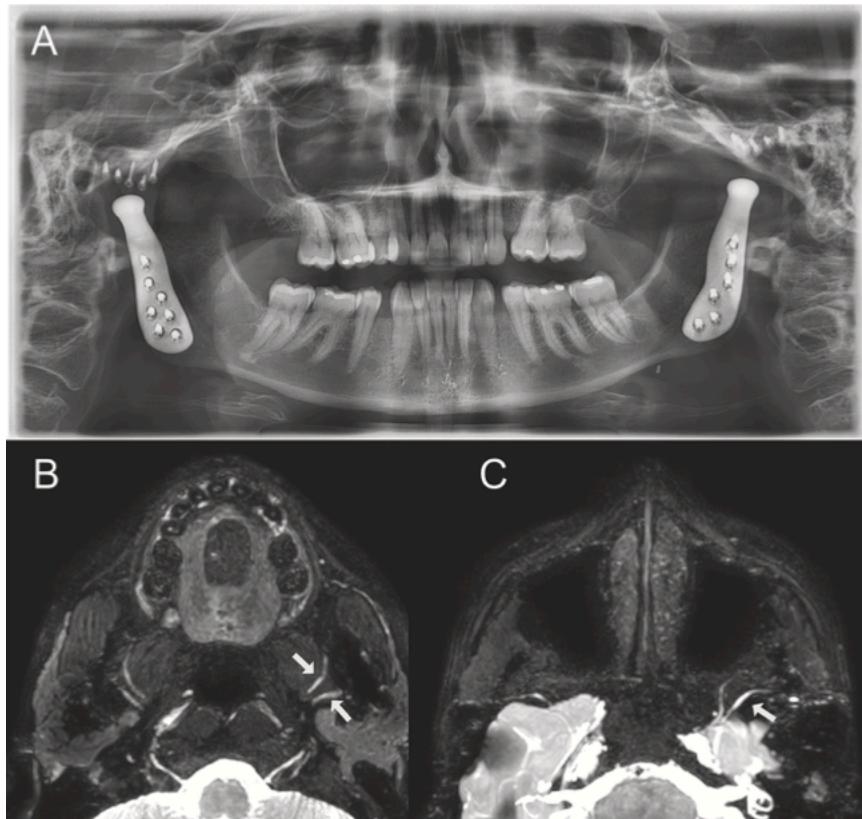
## General introduction

This chapter is partly based on the following manuscripts:

1. **Van der Cruyssen F**, Verhelst PJ, Stevens O, Casselman J, Renton T, Piagkou M, Bonte B, Politis C. Severe progressive post-traumatic trigeminal neuropathic pain after total temporomandibular joint replacement - A case report. *Oral and Maxillofacial Surgery Cases*. 2020;6(July):100175.
2. **Van der Cruyssen F**, Politis C. Neurophysiological aspects of the trigeminal sensory system: an update. *Reviews in the Neurosciences*. 2018;29(2):115-123.
3. Klazen Y, **Van der Cruyssen F**, Vranckx M, Van Vlierberghe M, Politis C, Renton T, Jacobs R. Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study. *International Journal of Oral and Maxillofacial Surgery*. 2018;47(6):789-793.
4. Renton T, **Van der Cruyssen F**. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. *Oral Surgery*. 2019;13(4):389-403.
5. **Van der Cruyssen F**, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, Renton T. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. *Journal of Oral Rehabilitation*. 2020;47(10):1212-1221.

## Introduction

A 43-year-old female with an unremarkable medical history was referred in February 2019 to the Department of Oral & Maxillofacial Surgery, University Hospitals Leuven, to evaluate her trigeminal nerve sensory function after undergoing a custom-made temporomandibular joint replacement (TMJR) of both joints in November 2018. The initial indication for TMJR was bilateral internal derangement of the TMJ (Wilkes classification V) with pain and limited mouth opening of 18 mm, unresponsive to conservative treatment (education, physiotherapy and splint therapy). Immediately after TMJR surgery, the patient reported left-sided hypoesthesia in the area of distribution of the lingual and mental nerves. Interincisal maximal mouth opening improved to 25 mm postoperative. A couple of days later, the patient developed shooting electric-like sensations in both the chin and tongue area for which she received pregabalin 75 mg three times daily. On a follow-up, four months after the TMJR procedure, she complained of mild shooting pains in the left mental region. Psychological and pain questionnaires showed moderate pain scores of 5 out of 10 on a visual analogue scale (VAS), without severe psychological impact (**Table 1**). Bedside neurosensory testing (NST) and quantitative sensory testing (QST) confirmed hypoesthesia of both lingual and mental areas with thermal allodynia. In the next two months during follow-up consultations, the patient reported progressive hypoesthesia with mechanical and thermal allodynia of V2 (area of distribution of the infraorbital nerve) and V1 (area of distribution of the supraorbital nerve) trigeminal division, which was again confirmed on QST. Corneal reflex was absent on the left side. Additionally, the patient developed left hemifacial untenable neuropathic pain, scoring ten out of ten on a visual analogue scale (VAS), in V3 and V2. Due to the severity of her complaints and progressiveness, further investigations were performed. Electromyography revealed severe motor axonal loss of the left masseter muscle. Conduction studies between the mental and oval foramina showed no response, arguing for a severe traumatic injury at the level or just below the oval foramen. Infra-orbital (V2) and supra-orbital (V1) stem reflexes were unremarkable, indicating intact V1-V2 branches. Cone beam computed tomography (CBCT) and the panoramic radiograph showed well-positioned bilateral TMJ prostheses (**Figure 1**). Magnetic resonance neurography revealed hypertrophy of the left masseteric nerve and increased signal intensities of the inferior alveolar and lingual nerve (**Figure 1**).



*Figure 1. Postoperative imaging studies after bilateral custom-made temporomandibular joint (TMJ) prosthesis. A; panoramic radiographic. B; Magnetic resonance neurography (MRN) after placement of bilateral custom made TMJ prostheses. The increased signal intensity of the left inferior alveolar and lingual nerve (arrows) is noted. C; MRN showing a left hypertrophic masseteric nerve with increased signal intensity (arrow). Figures and caption from: Van der Cruyssen F, Verhelst PJ, Stevens O, et al. Severe progressive post-traumatic trigeminal neuropathic pain after total temporomandibular joint replacement - A case report. Oral and Maxillofacial Surgery Cases. 2020;6(July):100175.*

No intracranial abnormalities were noted. The diagnosis was made of progressive post-traumatic trigeminal neuropathic pain. After a multidisciplinary discussion and due to the risk of prosthesis surinfection, a conservative approach was advised, and the patient was referred back to her treating physician. Medications included amitriptyline, pregabalin and tramadol with limited pain control. In the following year, she was treated with radiofrequency ablation of V2, V3, cervical branches and the trigeminal ganglion during multiple sessions with neuropathic pain improvement in V2 but not in V3. Twenty sessions of repetitive transcranial magnetic stimulation had no impact on the pain complaints. The patient eventually underwent implantation of a deep brain stimulator with partial pain alleviation. Follow-up questionnaires

a year after the initial joint surgery showed a deterioration of her quality of life and psychosocial measures (Table 1).

*Table 1. Quality of life (QoL), pain and psychosocial questionnaires at the initial presentation in our center, three months after total joint replacement and one year later. Major deterioration in overall QoL and psychosocial measures is seen. Table and caption from: Van der Cruyssen F, Verhelst PJ, Stevens O, et al. Severe progressive post-traumatic trigeminal neuropathic pain after total temporomandibular joint replacement - A case report. Oral and Maxillofacial Surgery Cases. 2020;6(July):100175.*

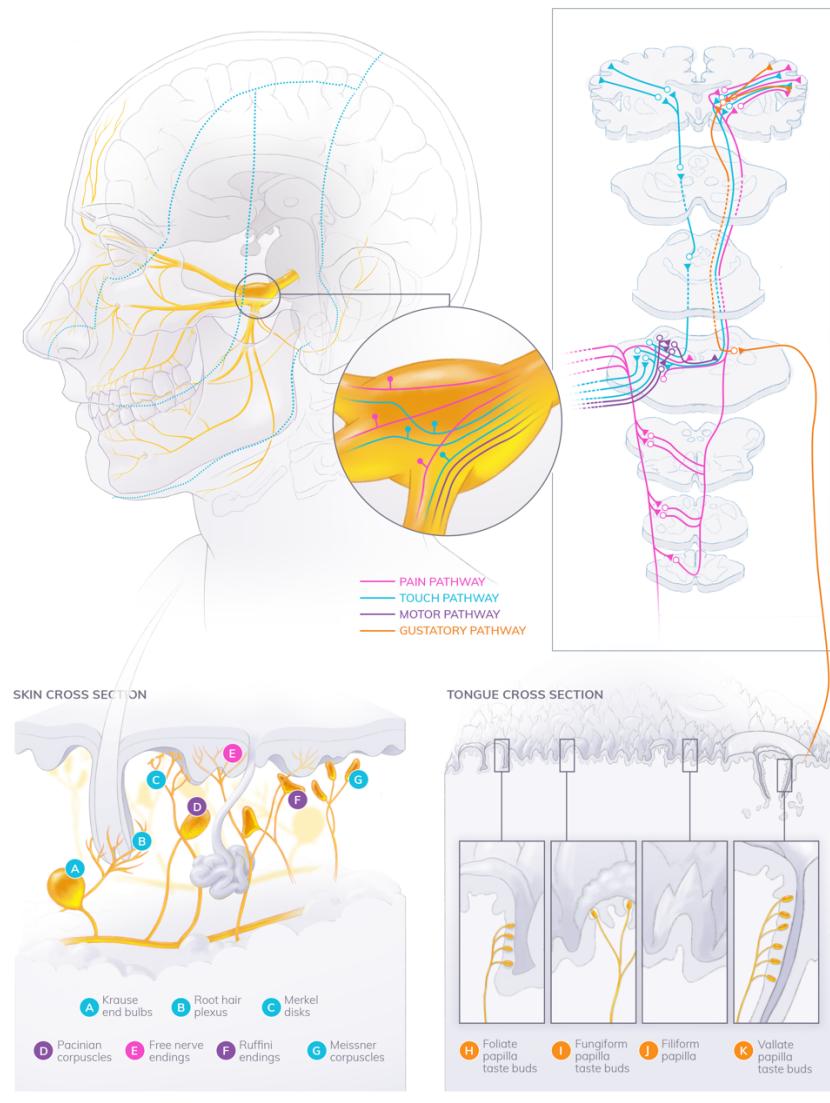
Questionnaire	Reference/scoring	Range	2019-02	2020-03
EuroQoL-5	Lower value indicates better QoL for subdomains			
Mobility		0-4	0	0
Self-care		0-4	0	0
Usual activities		0-4	0	3
Pain – Discomfort		0-4	3	3
Anxiety – Depression		0-4	0	1
Overall health	Higher value indicates better QoL	0-100	72	40
Central sensitization inventory	< 40 means unlikely for centralization phenomenon	0-100	39	39
Brief Pain Inventory	Lower values indicate better QoL and lower pain			
Maximum pain score		0-10	6	8
Minimum pain score		0-10	2	1
Mean pain score		0-10	4	5
Pain score now		0-10	5	6
Relieve		0-10	/	/
Activity		0-10	3	4
Mood		0-10	5	5
Running		0-10	0	0
Work		0-10	5	4
Relations		0-10	5	5
Sleep		0-10	8	9
Joy		0-10	5	3
Pain catastrophizing scale	< 20	0-52	15	26
Pain vigilance and awareness questionnaire	< 40	0-80	23	39

This case presentation illustrates a severe example of progressive hemifacial post-traumatic trigeminal neuropathic pain reflecting the dangers involved with orofacial surgical procedures. The peripheral trigeminal branches are at risk of mechanical, thermal or chemical damage with numerous other dental and maxillofacial procedures: endodontics (root canal treatment), dental extractions, removal of wisdom teeth, placement of implants, use of local anesthesia, orthognathic surgery, etc.<sup>1</sup> If damage to these nerve branches occurs, there is a risk of

developing a post-traumatic trigeminal neuropathy (PTN) that is considered very invalidating for patients while interfering with daily activities (eating, drinking, speaking, kissing, etc.).

### Anatomy, physiology and general considerations

The trigeminal nerve is an important cranial nerve in the human body and is responsible for the sense of touch, temperature, vibration and proprioception in the face, pain perception, taste sensation and motor innervation of the chewing muscles.<sup>2</sup> This nerve has a very extensive course, function and representation in the cerebral cortex (**Figure 2**).



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*Figure 2. Overview of the trigeminal system indicating the trigeminal ganglion, sensory nerve endings, gustatory and motor pathways.*

The three divisions emerging from the trigeminal ganglion are involved in the somatosensory functions that inform the body about the external environment. In describing the microscopic anatomical features of the sensory nerve endings, it is important to know about the various types of receptors that help in responding to various stimuli. Mainly there are three types of receptors in mammals in the areas being covered by the trigeminal system.<sup>3–6</sup>

1. Exteroceptors: providing information from the environment,
2. Enteroceptors: providing information from internal organs,
3. Proprioceptors: providing information from the musculoskeletal system (position sense).

A recent study has summarized the types of mechanoreceptors, afferent types and their morphologies.<sup>6</sup> Based on morphological characterization, the mechanoreceptors of soft tissues in the oral cavity and mucosal surfaces are Merkel cells (slow adapting type I), Ruffini endings (slowly adapting type II), Meissner corpuscles mainly perioral (rapidly adapting type I) and Pacinian corpuscles (rapidly adapting type II). Other receptors are Krause cold sensing receptors and free nerve endings that perceive superficial pain and tactile sensations.

Of importance the periodontal ligament, tongue, and mucosa have mainly Ruffini ending receptors.<sup>7</sup> The periodontal afferents exhibit high sensitivity when exposed to the low forces of the jaws. In parallel with true proprioceptors, they function as proprioceptors during the first contact of teeth, grinding food and speech. These receptors code force load and direction. When biting through food with high forces, less information is encoded, reducing the proprioception in these circumstances.<sup>5</sup> The importance of these periodontal afferents becomes apparent after tooth extraction or in edentulous patients where their function is lost. However, after implant placement, we can see a mechanism of ‘osseoperception’ where sensory-motor control partially recovers.<sup>8</sup> This can be explained by the presence of intraosseous and periosteal receptors near the implant sites. Other factors such as cortical plasticity and adaptation from different receptors, are likely to participate in regaining sensory input. True proprioceptors have been reported in the sensory trigeminal transmission process: muscle spindles and Golgi tendon organs are found in several muscles of the trigeminal system and temporomandibular joint capsule; however, research on this matter is limited.<sup>9–11</sup>

The signals originating from the trigeminally innervated area are varied based on the tissue of origin and receptor type. Particularly, the tongue has a different distribution and types of mechanoreceptors compared with other regions. The response threshold varies; for example:

mechanoreceptors of the deep tongue area are slowly adapting. Their activity persists during tongue movement when it is not in contact with anything.<sup>7</sup>

Based on the available scientific data, the oral somatosensory awareness theoretical model consists of three stages in sensory processing, including somatosensation, somatoperception and somatorepresentation.

After a sensory input triggers an action potential, the information is conveyed to the trigeminal ganglion (also known as Gasserian ganglion, semilunar ganglion, or Gasser's ganglion) residing in a pouch-like structure known as cavum trigeminale (Meckel's cave). The three sensory divisions of the trigeminal system enter into the ganglion at the convex margin and are somatotopic organized. The sensory root emerges from the ganglion at the concave margin and attaches to the anterior pons surface through the middle cerebellar peduncle.

The transmission and processing of sensory signals by the three divisions having a joint gateway, the trigeminal ganglion, is an active area of investigation. Histometric studies showed large differences in neuronal count between individuals ranging from 20.159 up to 156.702 nerve cells; the clinical relevance is yet not known.<sup>12</sup> Sensory fibers coming from three divisions have their cell bodies in the ganglion. After that, the sensory and motor root enter the central nervous system through the middle cerebellar peduncle of the pons. At this position, there is segregation of all sensory fibers.<sup>13</sup> The proprioceptive fibers pass through the ganglion without having their cell bodies there but continue to the mesencephalic nucleus where their neurons are located; touch, pressure, and vibration conveying fibers move toward the principal sensory nucleus. Nerve fibers involved with temperature and pain sensation have a relatively smaller diameter than the other fibers and make their way to the spinal nucleus, usually designated as the spinal tract of the trigeminal nerve.

The trigeminal motor root has its distribution with the mandibular division. It has its own separate motor nucleus where the primary neuron synapses. Several studies have focused on the functional and physiological aspects of the trigeminal nuclei. Notably, the motor nucleus received relatively more attention due to its role in ferrying the poliomyelitis virus.<sup>14</sup> The polarity and projections of sensory and motor nerve fibres of the trigeminal system were initially defined through animal studies but can now be studied through magnetic resonance imaging (MRI) and diffusion tensor imaging.<sup>15,16</sup>

The trigeminal sensory nuclear complex comprises four nuclei: the main sensory nucleus (principal nucleus), oralis nucleus, interpolaris nucleus and caudalis nucleus (**Figure 2**). As in the ganglion, there is a somatotopic distribution of the fibers.<sup>17</sup> The principal nucleus receives tactile fibers with small receptive fields after synapsing secondary fibers mainly project to the ventral posteromedial (VPM) nucleus of the thalamus. In contrast, the nerve fibers arriving at the oralis nucleus have large receptive fields and convey intra-oral sensory information. Cross-innervations with other nuclei and the spinal cord were observed in rat studies. The interpolaris nucleus has projections from intra-oral and skin tissue. Pathways to the central nervous system are diverse and broad; several cerebellum and superior colliculus projections are still under debate. The caudalis nucleus receives myelinated and unmyelinated afferents from all trigeminal divisions and projects mainly to the VPM; however, broader connections have been discovered. It receives most of the nociceptor inputs. The mesencephalic nucleus plays an important role in masticatory control and reflex arches. It projects to the VPM of the thalamus but has cross-connections with the principal nucleus which could assist in proprioception.

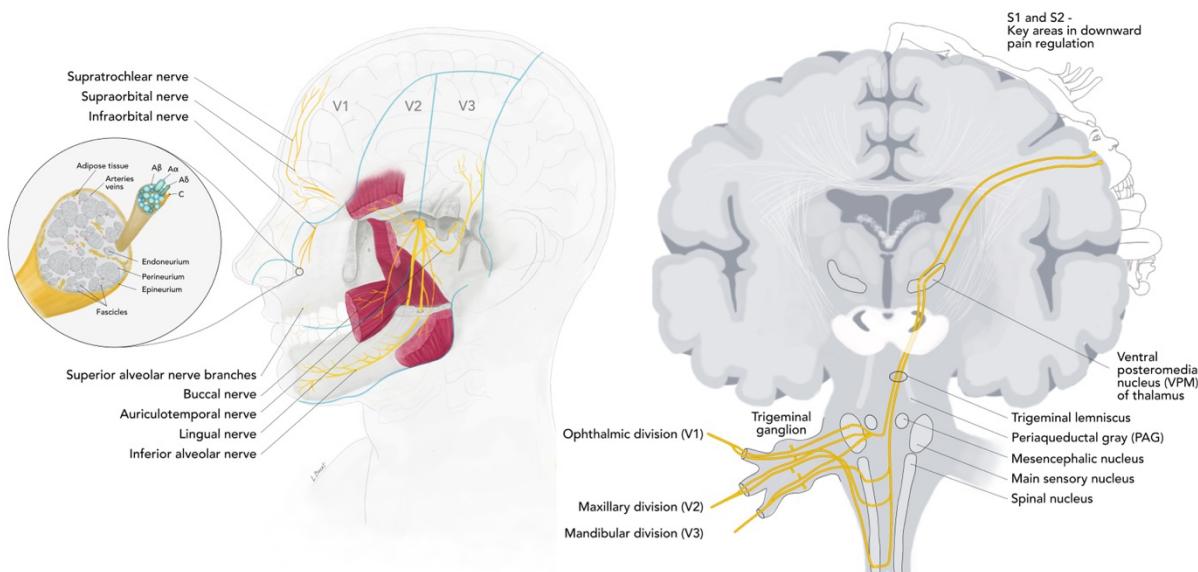
Trigeminal nuclei utilize a secondary ascending system also known as the ascending tract of the trigeminal nerve towards the thalamus and enter at the nucleus VPM of the thalamus.<sup>18–20</sup> The somatosensory information transmitted to the thalamic region travels in a bifurcated manner. The pain and temperature including deep pressure sensory messages are transmitted to ventral posterior lateral (VPL) and ventral posterior inferior intralaminar nuclei of the thalamus, whereas the tactile, vibratory, muscle tensile and joint position somatosensory messages only end up in the VPL nucleus. From here they project onward towards the somatosensory cortex.

## Pathophysiology

Recognizing that the trigeminal neural pathways have important differences compared to the spinal nerves is pertinent. The proprioceptive trigeminal afferents are the only first neuron fibers to have their cell bodies in the central nervous system (CNS). This is not the only basic morphological difference where the fifth cranial nerve differs from other sensory nerves. The nuclei for the TN including motor, sensory and special sensory nuclei, are all embedded in the midbrain and not the spinal system. The trigeminocervical complex converging input from C2 and C3 likely explains the often comorbid head and neck pains or autonomic signs and symptoms seen in chronic trigeminal pain, including post-traumatic trigeminal neuropathic pain.<sup>21</sup> In addition, these interactions as well as the close anatomical relationship between the

trigeminal sensory nuclei and other cranial nerves (7th, 8th and 9th) may relate to referred pain and symptoms in these nerve distributions as well. A well-known interconnection between the fifth and seventh cranial nerve is tested by performing the corneal reflex. Despite structural differences between the trigeminal somatosensory system and other spinal sensory nerves, there are many similarities with the somatosensory system of the rest of the body, for example using a common channel, the Transient Receptor Potential Cation Channel Subfamily M member 8 (TRPM8), for recognizing cold sensations.<sup>22</sup>

A normally functioning sensory system depends on maintaining equilibrium between the neurons and their environment.<sup>23</sup> Sequence of events after nerve injury are described below and illustrated in **Figure 3**. Commonly used terminology is explained in **Table 2**.



#### Peripheral

- Wallerian degeneration may favour the development of abnormal activity, including neurochemical abnormalities in the contiguous intact root ganglion, with overexpression of transient receptor potential vanilloid receptor 1 (TRPV1), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and mRNA for nociceptive neurotransmitters such as CGRP, in fibers spared by the lesion.
- Ectopic discharges in lesioned fibers and their corresponding ganglia. Within sites of axonal demyelination owing to altered distribution of voltage-dependent sodium channels in the demyelinated segments of the membrane.
- High frequency stimulation of small myelinated fibers (A<sub>B</sub>) generates pain, and a great deal of data favour the implication of large A<sub>B</sub> fibers in touch allodynia and secondary hyperalgesia. In addition, the temporal dynamics of tactile allodynia after nerve section closely follow those of ectopic discharges in myelinated A fibers, while such discharges are not observed in non myelinated C axons
- Abnormal activity in axons undamaged by the lesion due to newly inserted sodium channels include; Nav 1.7, 1.3, 1.8 and 1.9
- Alterations in the expression and regulation of intracellular calcium ions and modulatory receptors on primary afferent terminals.
- Neuroimmune interactions resulting in enhanced and/or altered production of inflammatory signalling molecules.
- Sensory-sympathetic coupling and other alterations in receptor signalling.

#### Central

**Ectopic neural activity** After a peripheral nerve lesion, spontaneous activity is evident in both injured and neighbouring uninjured nociceptive afferents. Increasing levels of mRNA for voltage-gated sodium channels seem to correlate with ectopic activity, and increased expression of sodium channels in lesioned and intact fibers might lower action potential threshold until ectopic activity takes place. Similar changes within second-order nociceptive neurons are thought to occur after central lesions, leading to central neuropathic pain.

**Central sensitisation** Secondary allodynia and hyperalgesia (ie, evoked pain, in particular dynamic mechanical allodynia) in the area adjacent to the innervation territory of the lesioned nerves requires involvement of the CNS. Central sensitisation might develop as a consequence of ectopic activity in primary nociceptive afferent fibers and structural damage within the CNS itself might not be necessarily involved. Ongoing discharges of peripheral afferent fibers that release excitatory aminoacids and neuropeptides within the dorsal horn of the spinal cord lead to postsynaptic changes of second-order nociceptive neurons, such as phosphorylation of NMDA and AMPA receptors or expression of voltage-gated sodium channels. These changes induce neuronal hyperexcitability that enables low-threshold mechanosensitive A<sub>B</sub> and A<sub>C</sub> afferent fibers to activate second-order nociceptive neurons. This means that normally innocuous tactile stimuli such as light brushing or pricking the skin become painful. Similar mechanisms might take place not only within the spinal cord, but also at supraspinal levels, as has been reported in patients with central pain.

*Figure 3. Diagram illustrating the peripheral and central changes after peripheral sensory nerve injury. Figure and caption from: Renton T, Van der Cruyssen F. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. Oral Surgery. 2019;13(4):389-403.*

*Table 2. Commonly used terminology in nerve injuries as defined by the International Association for the Study of Pain.*

Term	Definition
Allodynia	Pain due to a stimulus that does not normally provoke pain
Analgesia	Absence of pain in response to stimulation which would normally be painful
Dermatome	An area of the skin supplied by nerves from a single nerve root
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperalgesia	Increased pain from a stimulus that normally provokes pain
Hyperesthesia	Increased sensitivity to stimulation, excluding the special senses
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system
Neuropathy	A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy
Nociceptor	A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli
Pain	An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage
Paresthesia	An abnormal sensation that is not unpleasant, whether spontaneous or evoked
Sensitisation	Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs
Sensory profile	A cluster of similar pain and neurosensory characteristics based on neurosensory testing responses and patient-reported measures
Wallerian degeneration	Wallerian degeneration is an active process of retrograde degeneration of the distal end of an axon that is a result of a nerve lesion

### *Peripheral changes*

Changes in the equilibrium, as caused by nerve damage, leads to a cascade of events progressing from the periphery to the central nervous system.<sup>24</sup> During this stage, the presence of inflammatory mediators released during the tissue injury and from the recruited immune cells leads to increased sodium and calcium channel currents, which reduce the thresholds of the nociceptors in the peripheral nervous system (PNS).<sup>25</sup> This increased sensitivity at the site of injury is called peripheral sensitization (primary hyperalgesia and allodynia).<sup>24</sup> After peripheral injury adenosine triphosphate (ATP) signal transduction induces activation of both cell types

further contributing to an inflammatory cascade.<sup>26</sup> The vesicular nucleotide transporter regulates ATP release and could be a potential pharmacological target. Another channel, the subunit a2/d-1 of the L-type channel of the dihydropyridine receptor, has shown to be highly selective for gabapentin and is abundantly present in the trigeminal neurons. Other key molecules in pain transmission are calcitonin gene-related peptide (CGRP) and nitric oxide that are released after inflammation occurs, causing upregulation of neurokinin 1 (NK1) receptors. This upregulation causes higher excitability of the trigeminal neurons. The NK1 receptors are also present in the glial cells.

An extensive review by Holland reports the morphological structural and electrophysiological postinjury changes after peripheral sensory nerve of the ganglion in cats.<sup>27</sup> In experimental animal studies, crush injuries recovered faster with less central disruption than transection injury, chemical nerve injuries were not evaluated. All nerve injuries resulted in lower conduction velocities and sensory impairment. When immediate re-apposition of cut ends is performed no cell death occurred; however, proximal degeneration and distal Wallerian degeneration were seen as well as axonal sprouting. Associated degenerative changes of brainstem nuclei were observed. If neural gaps were needed to be covered, stretching the nerve after release from its connective tissues resulted in better functional results compared to neural grafting.

Traumatic injury to a peripheral nerve, at the distal stump of the nerve fiber, causes Wallerian degeneration at the distal ends of the damaged nerve.<sup>28,29</sup> Schwann cells, responsible for providing trophic support to the nerve fibers, begin to degenerate and lose their myelin or encapsulation in cases of unmyelinated nerves.<sup>30</sup> Schwann cells and their recruited immune cells, clear the debris and release (neuro)-trophic factors that facilitate axonal growth.

#### *Central consequences — trigeminal ganglion, secondary and tertiary neurons*

The understanding of the structural and molecular changes causing central sensitization is limited.<sup>31</sup> Membrane excitability changes with lower resting membrane potentials causing lower thresholds for transduction. Altered synaptic transmission and plasticity lead to increased responsiveness to input from nociceptors. Pain-related neurotransmitters and growth factors are upregulated. Changes in the descending tracts facilitate further in the release of postsynaptic potentials. Axonal sprouting starts enhancing excitatory synapses further. Polysynaptic pathways start to form, causing epileptiform activity with burst-like discharges and

synchronization. Increased excitability and synaptic plasticity lead to central sensitization causing hyperalgesia, allodynia, hyperpathia and aftersensations.

### **Diagnostic criteria**

PTN can be defined as an injury to the trigeminal nervous tissues. After injury has been inflicted, a painful or non-painful trigeminal neuropathy may develop. When pain arises as a consequence of this nerve injury and certain criteria are met (see below), then one may speak of a neuropathic pain. Currently, the International Association for the Study of Pain (IASP) defines neuropathic pain as ‘pain caused by a lesion or disease of the somatosensory nervous system.’ A grading system to aid in diagnosing neuropathic pain has been proposed as well.<sup>32</sup> A *probable* diagnosis of neuropathic pain is made when patients complain of pain and sensory signs in a neuroanatomically plausible area. When a confirmatory test is present, the diagnosis of *definite* neuropathic pain can be made. This diagnostic test may include computed tomography, MRI, skin biopsy, electrophysiological tests, blink reflexes, microneurography, verification of intraoperative nerve damage and genetic testing for hereditary neuropathy.

The diagnostic criteria for pain due to trigeminal nerve damage, presently termed as post-traumatic trigeminal neuropathic pain (PTNP) in the latest International Classification of Headache Disorders, 3rd edition (ICHD-3)<sup>33</sup> are:

- A. Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C
- B. History of an identifiable traumatic event to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypoesthesia, hypoalgesia) signs of trigeminal nerve dysfunction
- C. Evidence of causation demonstrated by both of the following: a. pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event, b. pain has developed within six months after the traumatic event (up to six months to allow for development of neuropathy after chemotherapy and radiation. Many surgical injuries have immediate onset, but it is possible that the pain only comes on after a few days or weeks.)
- D. Not better accounted for by another ICHD-3 diagnosis.

These criteria are very similar to newly suggested criteria proposed by an international collaborative group of orofacial pain and headache researchers under the name of International

Classification of Orofacial Pain (ICOP) version 1.0.<sup>34</sup> Both the ICHD-3 and ICOP present diagnostic criteria for PTNP. Criteria B and D from above can be used for non-painful post-traumatic trigeminal neuropathy for patients with trigeminal nerve damage without any associated neuropathic pain.

### Risk factors, incidence, etiology

Risk factors for chronic postsurgical pain (not limited to PTN) are many (**Table 3-4**), highlighting, the complexity of predisposition to persistent pain due to sensory nerve injury. Risk assessment involves the patient selection, preoperative planning, both clinical and radiographic and suitable treatment protocol and follow-up. It is important that the clinician is familiar with the nerve injury risk factors, specific for each of type of invasive procedure.

*Table 3. Risk factors for chronic postsurgical pain. Table and caption from: Renton T, Van der Cruyssen F. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. Oral Surgery. 2019;13(4):389-403.*

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Preoperative factors
Pain, moderate to severe, lasting more than one month
Repeated surgery
Psychological vulnerability (e.g. catastrophizing)
Preoperative anxiety
Female gender
Older age
Workers' compensation
Genetic predisposition
Inefficient diffuse noxious inhibitory control (DNIC)
Intraoperative factors
Surgical approach with risk of nerve damage
Postoperative factors
High pain experience (severe)
Radiation therapy to area
Neurotoxic chemotherapy
Depression
Psychological vulnerability
Neuroticism
Anxiety

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*Table 4. Common surgical risk factors in oral surgery. Table and caption from: Renton T, Van der Cruyssen F. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. Oral Surgery. 2019;13(4):389-403.*

Dental local anesthesia (LA)	Block anesthesia Lingual nerve > inferior alveolar nerve Concentration and type of LA agent Multiple block injections Severe pain on injection
Third molar surgery	Increased patient age Increased duration of surgery Lingual access surgery Inexperience of surgeon Depth of impaction of mandibular wisdom tooth Proximity to inferior alveolar nerve
Dental implants	Proximity to inferior alveolar nerve Longer implants > 10 mm Not using drill stops or guides
Endodontic treatment	Proximity of tooth apex to inferior alveolar canal Root and bone defects that allow chemicals to leak from root tip to local bone area

### **Incidence and etiology**

Many patients with PTN make a spontaneous recovery but a small proportion of patients end up with lifelong complaints.<sup>35</sup> Exact figures are difficult to obtain but it is estimated that around 0.5-5% of patients undergoing oral and maxillofacial procedures suffer from persistent complaints attributed to PTN beyond three months after injury.<sup>1,35,36</sup> These numbers can widely vary and mainly depend on the etiology of the injury. However, other risk factors are increasingly being identified in developing chronic neuropathic complaints.<sup>37</sup>

During a two-year study period (2013-2014), a total of 8845 patients were seen at the department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Belgium. Among these patients, 53 (0.6%) were consulted due to PTN of the trigeminal nerve caused by an iatrogenic injury. These patients were more commonly female ( $n = 36$ , 68%) than male ( $n = 17$ , 32%). Their average age was 42.9 years (range 15–80 years) for female patients and 40.4 years (range 23–69 years) for male patients (overall average age 42.1 years).

Among the 53 patients included, the average referral delay was 323 days, with a range of one day to 2383 days (6.5 years). Overall, 29% of patients presented within three months, 49% within six months, and 63% within one year of injury. Among internal referrals, the average delay was fourteen days, and all were seen within three months after the injury.

The recorded injuries included 28 cases of inferior alveolar nerve (IAN) damage (53% of patients), 21 lingual nerve (LN) injuries (40% of patients), three cases of buccal nerve (BN) damage (6% of patients), and six cases of damage to the maxillary division (V2) of the trigeminal nerve or branches (11% of patients).

The most common cause of PTN was the extraction of third molars (24 cases, 45%), followed by local anesthesia injuries (nine cases, 17%) and implant-related injuries (nine cases, 17%). Among the nine cases of local anesthesia injury, five involved the use of articaine 4% and one was due to intra-osseous anesthesia; the anesthetic product utilized was not mentioned for the remaining three cases. PTN was related to non-third molar extraction in nine cases (9%) and to endodontic treatment in eight cases (6%).

### **Signs, symptoms and Quality of Life**

In a multicenter study of two tertiary centers in two countries (Belgium and the United Kingdom) 1331 patients with PTN were retrospectively reviewed.<sup>38</sup> Pain was the most reported symptom in 837 (63%) patients, followed by numbness in 672 (50%) (**Table 5**).

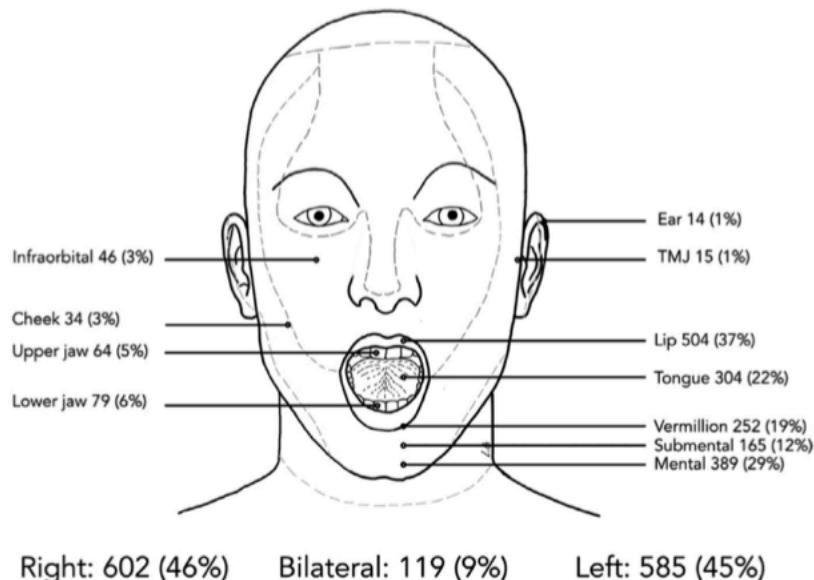
*Table 5. Most frequently reported symptoms by patients suffering from post-traumatic trigeminal neuropathy and results of basic neurosensory testing. Table and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

Reported signs and symptoms	N	%		
Pain	837	63		
Numbness	672	50		
Paresthesia	491	37		
Burning sensations	156	12		
Neurosensory test results	n/N	%	Mean (%)	SD

Affected dermatome extra-oral	454	-	56	35
Affected dermatome intra-oral	371	-	57	39
Light touch test				
No sensation	65/200	33		
Little/reduced sensation	59/200	30		
Normal sensation	29/200	15		
Elevated sensation	19/200	10		
Extra-oral sharp-blunt discrimination				
No sensation	39/187	21		
Little/reduced sensation	42/187	23		
Normal sensation	60/187	32		
Elevated sensation	15/187	8		
Intra-oral sharp-blunt discrimination				
No sensation	18/81	22		
Little/reduced sensation	24/81	30		
Normal sensation	15/81	19		
Elevated sensation	7/81	9		
Moving-point discrimination				
No sensation	40/177	23		
Little/reduced sensation	25/177	14		
Normal sensation	22/177	12		
Elevated sensation	1/177	1		
Thermal discrimination				
No sensation	12/174	7		
Little/reduced sensation	14/174	8		
Normal sensation	22/174	13		
Elevated sensation	16/174	9		

Paresthesia was reported in 491 (37%) patients, and burning sensations were present in 156 (12%). Forty per cent of patients with pain also complained of numbness. 43% reported both pain and paresthesia. Two hundred and seven patients (15.6%) described a combination of pain, paresthesia and numbness. VAS pain scores ranging from 0 to 100 increased with age ( $P < .0001$ ) with a mean of 38 (SD: 35.1). Females reported higher VAS scores with a mean of 46 (SD: 14.81 [13.00-91.00]) compared to males with a mean of 45 (SD: 14.81 [19.00-85.00]) ( $P = .0005$ ). Forty-one per cent of all patients reported a score of 50 or higher. Patients with persistent injury had significantly higher VAS scores than those with transient injury (4.35 [SD: 3.51] vs 0.85 [SD: 2.23], respectively,  $P < .001$ ).

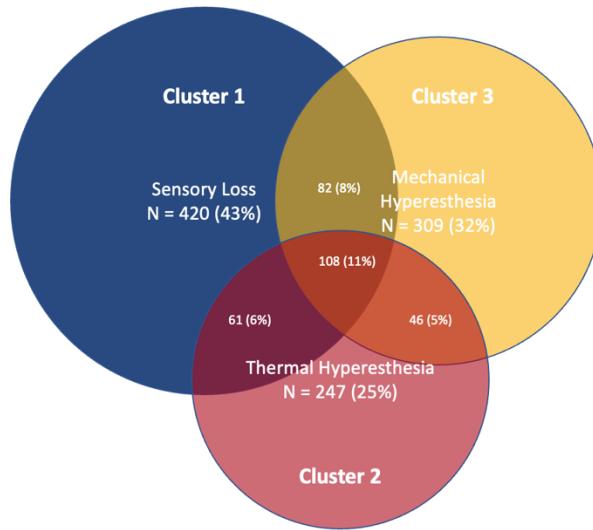
Symptoms were most frequently reported in the lower lip and chin region. Some patients had complaints at the level of the temporomandibular joint or ear (**Figure 4**). The tongue was affected in 304 (22%) patients, and bilateral symptoms were noted in 119 (9%). Most patients complained of constant symptoms (87%), whereas 13% had intermittent symptoms. Reported symptoms were comparable between the two institutes.



*Figure 4. Symptom distribution. Most frequently involved area is situated in the mental area.*  
*Figure and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

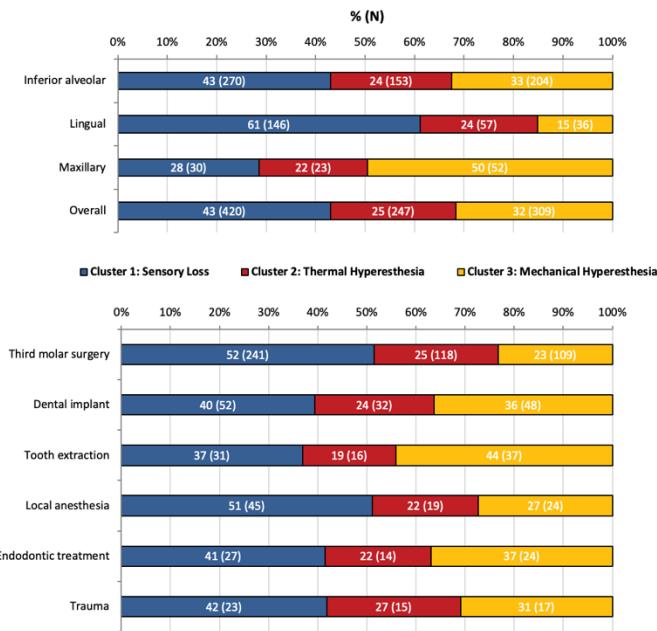
The mean percentage of the affected extra-oral dermatome was 56% (SD: 35) and was comparable between the two centers. Intra-oral, a mean affected dermatome was noted of 57% (SD: 39). Mapping of the affected percentage of the dermatome showed a significantly larger affected area when persistent injury was present (mean: 59.61%, SD: 34.183) comparing to a transient injury (29.45%, SD: 34.179;  $P < .001$ ). The same was true regarding involvement of the intra-oral dermatome (59.81%, SD: 33.018% vs 23.93%, SD: 32.236;  $P < .001$ ). Neurosensory test (NST) results are summarized in **Table 4**. More patients showed an abnormal response to NST when the injury was considered persistent compared to transient ( $P < .05$ ). When comparing painful to non-painful PTN, no significant differences in NST outcomes were identified.

After clustering patients, 420 (43.03%) patients were assigned to cluster one (sensory loss with pain), 247 (25.31%) to cluster two (thermal hyperesthesia) and 309 (31.66%) to cluster three (mechanical hyperesthesia). A total of 82 (8.40%) patients were assigned to both clusters one and three, 61 (6.25%) to clusters one and two and 46 (4.71%) to clusters two and three, and 108 (11.07%) patients were assigned to all three clusters (**Figure 5**).



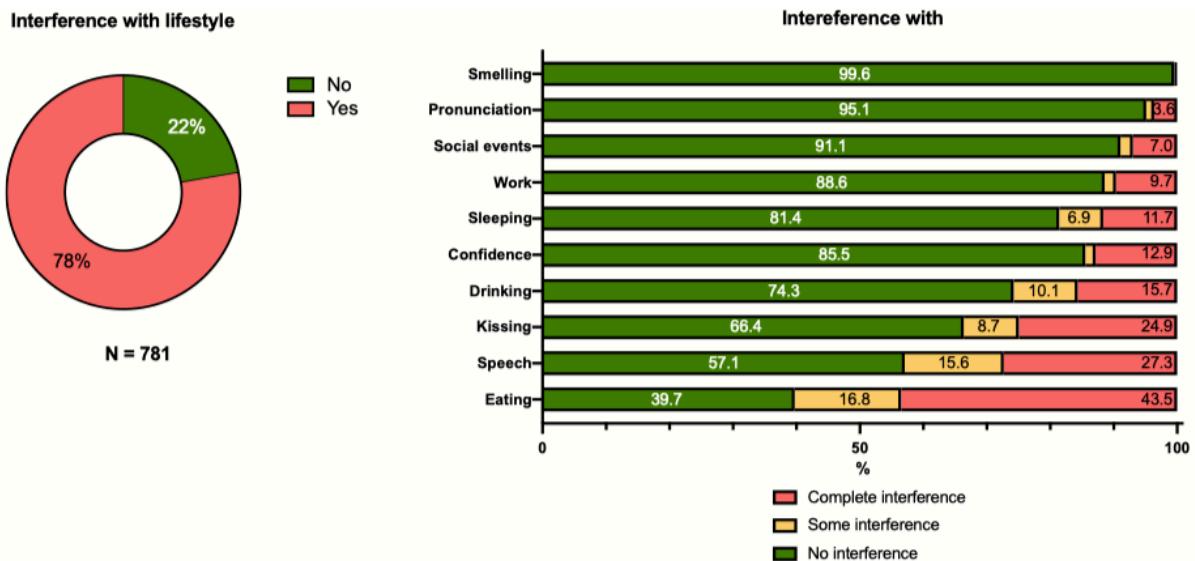
*Figure 5. Clusters of sensory phenotype frequency and overlap for post-traumatic trigeminal neuropathic pain. Sizes of circles are to scale; overlaps are not to scale. Figure and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

Following significant differences ( $P < .05$ ) were observed when examining the distribution of sensory profiles between the different affected nerve branches and etiologies. We observed a higher representation of lingual nerve injuries in cluster one compared to inferior alveolar or maxillary nerve injuries (**Figure 6**). Maxillary nerve injuries were more prevalent in cluster three, and affected branches were more evenly distributed in cluster two. Among the different etiologies, there was a higher representation of patients suffering injury after third molar surgery or local anesthesia in cluster one. Extraction-induced injuries or those incurred after implant placement or endodontic treatment were most frequent in cluster three. An equal distribution among etiologies was seen in cluster two (**Figure 6**).



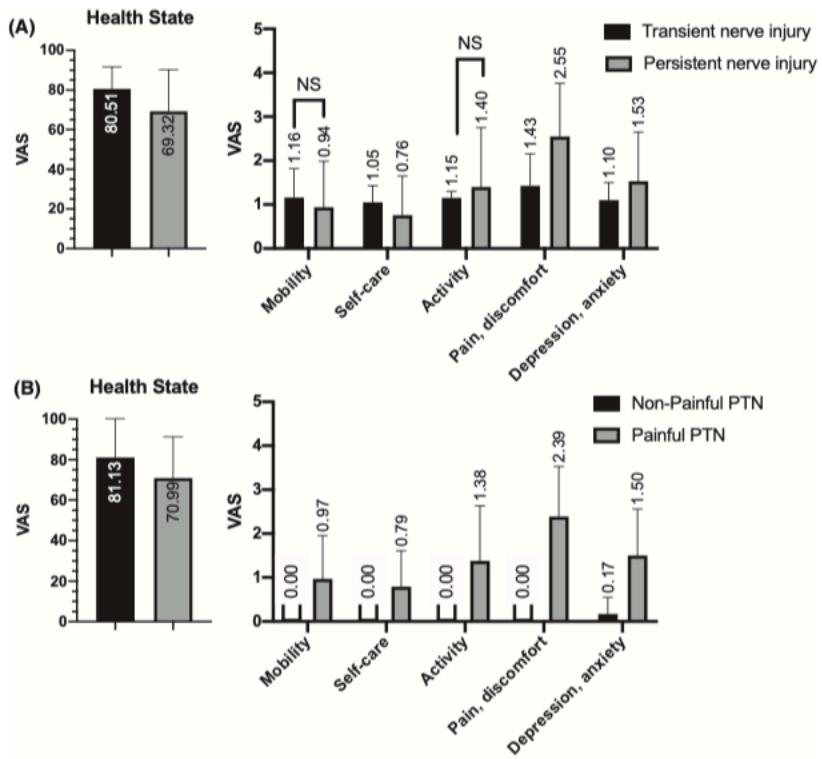
*Figure 6. Distribution of the three clusters within the injured nerve branch and within etiologies. Figure and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

In total, 607 patients reported interference with their lifestyle (77.7%), whereas 174 patients reported no interference. More detailed data on interference are reported in **Figure 7**. Most interference was reported for eating (420; 60.3%), speech (294; 42.9%), kissing (224; 33.6%), drinking (174; 25.7%) and sleeping (129; 18.5%). Clusters significantly differed for speech ( $P = .021$ ), eating ( $P = .024$ ), drinking ( $P < .001$ ), kissing ( $P < .001$ ) and sleeping ( $P = .006$ ). More interference was noted if the patient had mechanical hyperesthesia or was categorized in multiple clusters. In addition, compared to patients with transient injury, more patients with persistent injury complained of lifestyle interference (76.4% vs 7.6%;  $P < .05$ ).



*Figure 7. Self-reported interference of lifestyle of post-traumatic trigeminal neuropathy patients and stratified for subdomains indicating degree of interference. Figure and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

All quality-of-life (QoL) parameters were significantly different between painful and non-painful PTN, illustrating worse QoL measures if painful PTN is present (**Figure 8**). QoL measures between transient and persistent injury showed significantly worse outcomes for activity, pain, depression and health state in patients with a persistent injury. Interestingly, self-care was perceived to be worse in patients with a transient injury ( $P < .05$ ). Mobility and activity scores between patients with persistent or transient injury were not significantly different.



*Figure 8. Quality of life domains and self-perceived health state measured by the EQ5D-5L questionnaire. Comparison between transient and persistent nerve injuries (A) as well as non-painful versus painful post-traumatic trigeminal neuropathy (B). NS, not significant. Open-ended boxes indicate a value of zero with standard deviation of zero. Standard deviations are indicated. Figure and caption from: Van der Cruyssen F, Peeters F, Gill T, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

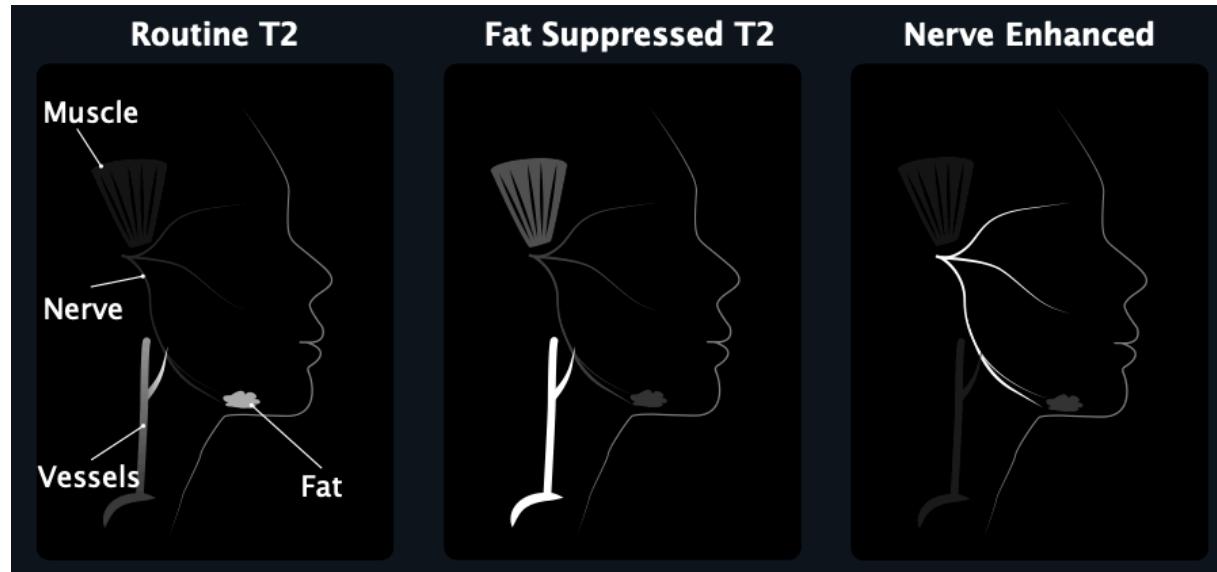
Patients with painful PTN had significantly higher scores for anxiety and depression with less perceived social support compared to those with non-painful PTN. Oral health-related QoL was considered worse in painful PTN with a mean score of 30 (SD: 14.9). No significant difference was found in the total score on pain acceptance between both groups. However, pain willingness was significantly lower for the painful PTN group.

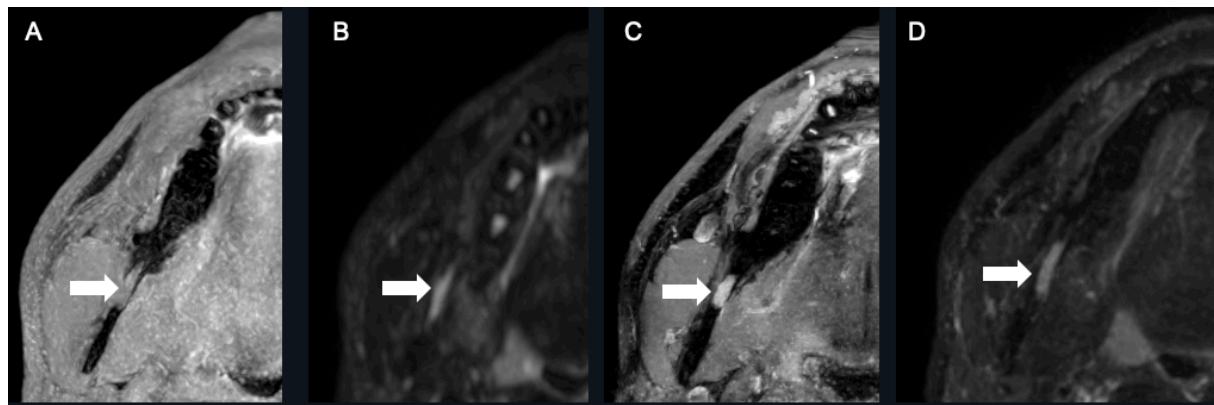
## Imaging

Many patients with PTN will eventually undergo a magnetic resonance imaging (MRI) scan to rule out underlying pathologies such as a tumor or multiple sclerosis as the cause of their pain.<sup>39</sup> MRI is a non-invasive imaging technique that provides detailed images of the brain and its

surrounding structures including the trigeminal nerve. It established its role in the management of trigeminal neuralgia, one of the many orofacial pain conditions.<sup>40</sup> However, its role in post-traumatic trigeminal neuropathies is debated. MRI scans are often used in a desperate hope to detect any damage of the peripheral nerve fibers, but often fail to do so. We suspect that current MRI sequences have a too low sensitivity and specificity as they are not nerve-specific, and therefore have little diagnostic value. New high-resolution MRI protocols could reveal the presence, location and severity of nerve damage in the maxillofacial region and allow increasing diagnostic accuracy.<sup>41</sup> Moreover, clear imaging of this traumatic damage could help in the treatment of these lesions. Studies already showed high success rates of neurosensory recovery after microsurgical repair of the peripheral branches of the trigeminal nerve.<sup>42,43</sup> However, timing seems a crucial factor in the outcome of these patients. The more time elapses, the lower the chances of successful neurosensory recovery.<sup>44</sup> Thus, prompt diagnosis is indispensable if we are to improve outcomes in these patients. Whereas previously a "watch and wait" policy was adhered to, new imaging techniques could allow a faster approach and finally improve the quality of life in some of these patients.

MR neurography (MRN) is a novel MRI technique specifically developed to visualize nerve fibers.<sup>45</sup> This technique makes it possible to adequately distinguish the fat-rich nerve trunks from their environment (**Figure 9**).





*Figure 9. Upper panel: schematic representation of current MRI (non-nerve selective) T2 imaging, fat-suppressed and nerve-selective imaging. Lower panel A: T1 thrive sequence illustrating the inferior alveolar nerve (white arrow) on an axial view. B: heavily T2 weighted imaging but low spatial resolution. C: Balanced fast-field echo sequence showing improved spatial resolution but without selectively enhancing the inferior alveolar nerve. D: True nerve-selective imaging using the 3D cranial-nerve imaging (CRANI) sequence.*

Recent progress in this technology has allowed the visualization of large nerve bundles with diameters above two millimeters.<sup>46</sup> Further developments in this field also demonstrated the use of MRN for visualization of the trigeminal nerve and its peripheral branches but further validation is warranted.<sup>41</sup>

## Hypotheses and aims

Currently, PTN diagnosis is primarily based on the patient's history and description of symptoms, together with results from physical and neurological examination.<sup>47</sup> Therefore, diagnosis remains largely limited to subjective and non-standardized evaluations. Considering overlapping symptoms and the large number of conditions that can cause orofacial pain, obtaining a correct diagnosis is difficult. However, finding the cause of pain is crucial for setting up an efficient therapy plan.<sup>48</sup> As these injury are mainly caused by relatively "minimally invasive" procedures, often preceded by a limited informed consent, meanwhile having a major impact on the patient's quality of life, medico-legal actions are relatively common.<sup>49–51</sup> The limited symptom control with current therapies of these post-traumatic neuropathies of the trigeminal nerve may lead to frustration and powerlessness of both patient and treating physician, potentially evolving in medical shopping. Considering the lack of guidelines, a central registry, and the absence of dedicated referral centers for iatrogenic trigeminal injuries, there is a gap in scientific evidence and thus also in clinical management. The social cost of this is particularly high.<sup>52,53</sup> Some patients end up with neurostimulators as illustrated in the case above, others languishing in social isolation or in psychiatric institutions confronted with persistent, inevitable pain complaints.<sup>54</sup>

We assumed the following hypotheses. Firstly, the impact of PTN is underestimated and causes a significant impact on QoL of patients with a substantial healthcare cost. Secondly, diagnostic features differ between PTN patients and may predict outcomes. Lastly, magnetic resonance neurography is feasible, valid and accurate in detecting trigeminal nerve injuries and has the potential to aid diagnosis and treatment.

## **Part 1. Costs of illness**

To date, no studies exist that assessed the healthcare costs of patients with PTN. We hypothesize that these costs, productivity loss and the use of services and medications are high and may differ among PTN subgroups.

The objectives were:

1. To estimate the healthcare cost of patients with PTN,
2. To determine average productivity loss,
3. To assess medication use, and;
4. To evaluate correlations between quality of life, healthcare costs, productivity loss or medication use.

The hypothesis was that:

*“PTN is associated with productivity loss, high healthcare costs and high medication use.”*

## **Part 2. Predicting the outcome**

In part two we aim to gain insights in the “burden of disease” of post-traumatic trigeminal neuropathy by performing a retrospective study analyzing patient records of all cases of post-traumatic, including iatrogenic, injury to branches of the trigeminal nerve and to predict the outcome. Subsequently we will gather prospective data in a similar way to assess these endpoints longitudinally.

The primary objectives were:

1. To predict temporary or persistent nerve injuries using symptoms and or clinical exam parameters, and;
2. To assess the correlation between clinical parameters such as the cause of injury, neurosensory profiles, persistency and quality of life

The hypothesis was that:

*“PTN outcomes can be predicted and differ between subgroups of patients. Certain clinical parameters are more predictive and correlate better with persistency and patient-reported outcome measures.”*

### **Part 3. Magnetic resonance neurography**

MRI is often used in the diagnostic workup of patients with cranial neuropathies, however, the diagnostic value to date is unclear. Also, current MRI techniques are plagued by non-nerve-selective imaging of the head-neck region which complicates interpretation. New MR neurography techniques may be able to improve visualization and diagnosis of cranial neuropathies.

The objectives were:

1. To gain insights into the role of current MRI protocols in the diagnosis of PTN
2. To assess the available evidence on previously published MRN sequences and more specifically evaluate the diagnostic accuracy in diagnosing PTN patients
3. To develop, validate and assess the diagnostic accuracy of a new MRN sequence in non-pathological and pathological trigeminal nerve states.

The hypotheses were that:

*“Current magnetic resonance imaging protocols have little value in diagnosing post-traumatic trigeminal neuropathies. Nerve-selective MRI, MR neurography, can improve the visualization of the extraforaminal cranial nerves and aid in diagnosing post-traumatic trigeminal neuropathies.”*

### **Part 4. Consensus guideline on PTN management**

To date, no guidelines exist on the management of PTN patients. Our specialty urgently needs such guidelines given the issues surrounding these patients. A first step in the development of such guidelines could be a Delphi study of PTN experts. A Delphi study is a group-decision-making method in having experts complete a questionnaire in multiple rounds. After the first round, a summary of the results is compiled and fed back to the experts until they reach a consensus on the provided statements. We aimed to obtain more information on how patients with PTN should be cared for, what services are needed, what training should be provided, what diagnostic methods are recommended and what are the preferred treatment options by means of a modified Delphi method amongst PTN experts.

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# **CHAPTER 2**

## **Healthcare costs**

*This chapter is based on the following manuscript:*

**Van der Cruyssen F**, Nys M, Renton T, Vandeleene G, Callens M, Vanhaecht K, Jacobs R, Politis C, Luyten J. Healthcare costs of post-traumatic trigeminal neuropathy in Belgium - A retrospective analysis. *J Craniomaxillofac Surg.* 2022;50(8):627-636.

## **Abstract**

### **Aim**

The present aim was to estimate direct healthcare costs of patients suffering from post-traumatic trigeminal neuropathy (PTN) and to compare the use of healthcare services, medications, and costs between temporary and persistent ( $> 3$  months) PTN cohorts.

### **Methods**

A pre-existing clinical dataset of PTN patients visiting a tertiary orofacial pain clinic in Belgium was utilized, including symptoms and quality of life measurements. Cost and resource utilization data were obtained by Belgium's largest health insurance provider for a period of 5 years after onset.

### **Results**

Data from 158 patients was analyzed. The average cost per patient in the first year after injury was €2353 (IQR 1426-4499) with an out-of-pocket expense of 25% of the total cost. Hospitalization and technical interventions were the main drivers of cumulative costs, followed by consultation costs. For each cost category, expenditure was significantly higher in patients with persistent PTN than in those with temporary PTN (median 5-year total costs in persistent PTN patients yielded €8866 (IQR 4368-18191) versus €4432 (IQR 2156-9032) in temporary PTN,  $p <0.001$ ) PTN patients received repeated and frequent head and neck imaging (mean number of imaging investigations per patient was  $10 \pm 12$ ). Medication consumption was high, with an unwarranted higher use of opioids and antibiotics in persistent PTN patients.

### **Conclusion**

Within the limitations of this study, it seems there is a need for informing patients in detail on the inherent risks of nerve damage after dental and oromaxillofacial procedures. Every surgery should be preceded by a risk-benefit assessment in order to avoid unnecessary nerve damage.

## Introduction

Post-traumatic trigeminal neuropathy (PTN) is defined by a painful or non-painful lesion of the trigeminal nerve, caused by trauma with symptoms and/or clinical signs of trigeminal nerve dysfunction. In the case of painful PTN, the term post-traumatic trigeminal neuropathic pain is currently used as defined by the recently introduced International Classification of Orofacial Pain (ICOP).<sup>1</sup>

PTN is a well-known complication in the field of oral and maxillofacial surgery and dentistry. A previous study, on which this one builds, has already shown that about half of the cases are caused by dentists, and the other half by oral and maxillofacial surgeons.<sup>2</sup> Because the trigeminal nerve supplies most of the face and mouth with sensory and partly motor innervation, damage can occur during numerous procedures in this region. The most common cause of PTN is the removal of wisdom teeth, a frequently performed procedure. In the United States ten million third molars are removed each year.<sup>3</sup> Other causes of PTN may include tooth extractions, endodontic treatment, administration of local anesthetics, orthognathic surgery, placement of dental implants, and maxillofacial trauma.<sup>4,5</sup> The true incidence of PTN is not well known but it is estimated that 1% of dental, oral or maxillofacial procedures result in persistent PTN.<sup>6,7</sup>

Symptoms of PTN are considered very disabling for the patient.<sup>2,8</sup> They range from numbness in one part of the face to severe electrical or burning pain radiating to various orofacial regions. When the symptoms persist for more than three months, the condition is known as persistent PTN.<sup>9</sup> Diagnosing and managing PTN can be challenging, and long referral delays to specialist centers, medical shopping, overtreatment, and legal claims are often a consequence of this.<sup>2,4,7</sup> Treatment of PTN remains cumbersome and may include surgical intervention or a pharmacological approach.<sup>10,11</sup> Recent animal studies show promise for the use of low-level laser or ozone treatment and more disease-specific treatments are on the way.<sup>12,13</sup>

To date, no data exist on the specific resource utilization pattern of patients with PTN as well as its estimated costs to patients, health systems and society. A single study from the UK by Durham et al. in patients with persistent orofacial pain, not limited to PTN, shows a per annum overall direct cost per patient of 362£ at 2012 prices (i.e. €478 in Belgian 2019 prices<sup>14</sup>).<sup>15</sup> However, no stratification according to the cause of orofacial pain was made. Another study shows the cost of neuropathic pain conditions in five European countries.<sup>16</sup> Annual direct costs per patient ranged from €1939 to €3131 (i.e. €2335–€4158 in Belgian 2019 prices<sup>14</sup>) and were highest for diabetic peripheral neuropathy, radiculopathy, and neuropathic back pain. Total

annual costs were mainly driven by indirect costs of productivity loss and varied from €9305 to €14446 per patient (€11207–€17168) in Belgian 2019 prices<sup>14</sup>.

The aim of the present study is to estimate direct healthcare costs of patients suffering from PTN and to compare the use of healthcare services, medications, and costs between temporary and persistent PTN cohorts over a 5-year period, starting from the onset of symptoms. These analyses are carried out from the point of view of the health insurer.

## Materials and Methods

### Source of data

Identifying PTN patients at a national level to allow for a similar study is difficult. There is no national registry, nomenclature number or International Classification of Disease coding to identify patients suffering from PTN. Therefore, a hybrid bottom-up and top-down method was used. A clinical dataset from the orofacial pain clinic at the university hospitals of Leuven with confirmed PTN patients was linked to financial and healthcare resource utilization data of Belgium's largest healthcare insurance provider, the Christian Health Insurance (CM). The latter also stores data on prescribed medications, dosages, medical-technical services performed and work incapacity. They also keep a registry of the patient's share of costs (out-of-pocket expenses) and amounts reimbursed by the provider.

The clinical data used in this study originated from the TrigNerveBeUK (TNVBUK) registry.<sup>2</sup> The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855). The study was conducted according to the STROBE guidelines. Data retrieved from the charts of patients visiting the Department of Oral and Maxillofacial Surgery and the orofacial pain clinic (University Hospitals Leuven, Leuven, Belgium) were collected between October 2018 and January 2019 after informing all patients. Next, a data team from CM retrieved financial and healthcare services data (resource use data) for each individual patient. Finally, clinical and resource use data were matched, pseudonymized and analyzed by the CM team. All data extractions and analyses that used or included CM data were performed under supervision of the Chief Medical Officer and Chief Scientific Officer of CM. The other research partners received no personally identifiable information (including small cells) from CM. The CM gathers all resource use information of its members.

## Patient selection

Patients were included in the TrigNerveBeUK registry if they presented with post-traumatic or iatrogenic injury of the trigeminal nerve or its branches (e.g., inferior alveolar nerve, lingual nerve) and met the recent ICOP criteria for PTN.<sup>1</sup> No restriction was made on age. Patients were excluded if the pain presented in a region other than the trigeminal nerve or the injury was not caused by an oromaxillofacial or dental procedure. Traumatic events that were considered were: facial trauma, local anesthesia administration, tooth extraction, wisdom tooth surgery, endodontic treatment, and dental implant placement.

After pseudonymization and selection of CM-affiliated patients, the dataframe was further completed by the CM data team. The study flow chart is summarized in **Figure 1**.

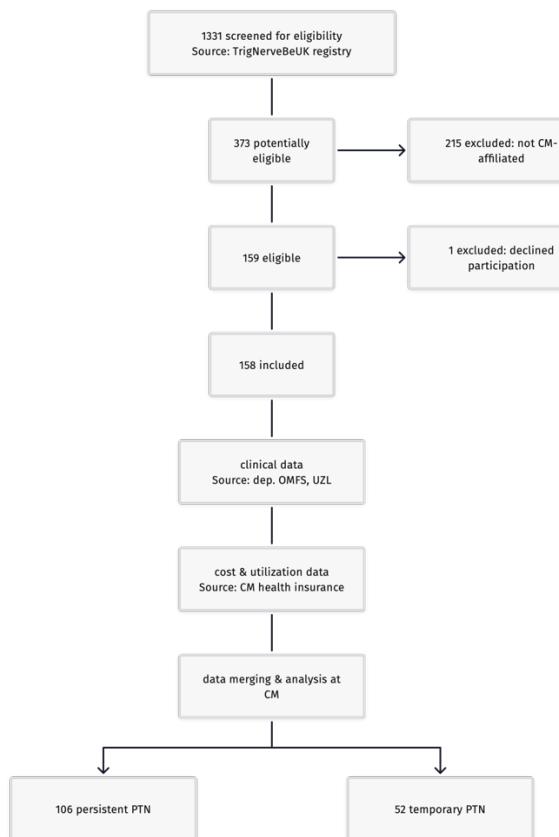


Figure 1. Study flowchart.

After grouping all data, two patient cohorts were constructed: temporary PTN and persistent PTN. Persistent PTN was defined if the symptoms persisted for more than three months after trauma. This is according to the definition put forward by the International Association for the Study of Pain for chronicity after trauma or surgery.<sup>9</sup>

## **Measures and instruments**

Initial data collection included demographic data, time and cause of trauma, location of complaints, persistence of symptoms, and health related quality-of-life (HRQoL) using the visual analog scale (VAS) of the EQ5D-5L questionnaire (Herdman et al., 2011). The EQ5D-5L assesses five domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on a five-point ordinal scale (0: no problems; 1: slight problems; 2: moderate problems; 3: severe problems; 4: extreme problems). Patients also indicated their self-rated health on a VAS, ranging from 0 (worst) to 100 (best imaginable health state). The EQ5D-5L scores from the last clinical report were used.

The resource and cost data were collected starting from the date of trauma up to the five consecutive years. The CM also added data on employment status, assigned preferential payer rate, and whether the patient had a registered chronic pain status. The preferential rate in Belgium exists for people with a lower income, orphans, or people with a disability, to keep healthcare costs affordable.

Direct total costs recorded at the CM were further stratified into consultation costs, technical costs, imaging costs, and medication-related costs. All healthcare utilization costs are shown in Euro and represent Belgian rates in 2019.

Total costs, out-of-pocket (patient) expenses, and healthcare provider expenses were identified. Consultations were reviewed and divided into primary medical care versus secondary (specialist) medical care visits. Dental visits were not listed separately as dental consultations in Belgium are coded in combination with technical interventions.

All head and neck or oral imaging modalities were reviewed and summarized. Technical interventions were checked and stratified according to the performing physician's specialty code. After consultation with all authors, it was decided to focus on the PTN-relevant specialties: primary care, dentistry, maxillofacial surgery, neurosurgery, neurology, and psychiatry. Finally, medication consumption was analyzed by summarizing costs and the defined daily dose (DDD). We applied the World Health Organization's anatomical therapeutic chemical (ATC)/DDD system to analyze consumption of paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, antiepileptics, antipsychotics, corticosteroids, and antibacterials per patient.

In Belgium, work incapacity is registered by health insurance providers as soon as it exceeds thirty days. Consequently, any episode of work incapacity lasting longer than 30 days was reviewed.

## **Data analysis and statistical procedures**

RStudio (version 1.4.1103, PBC, Boston, MA, USA) and SAS software (SAS Institute Inc 2013, Cary, NC, USA) were used for all analyses. Sample size was determined for a moderate effect ( $d = 0.4$ ) with alpha of 0.05 and beta of 0.80 at 114 patients. Standard descriptive statistics were calculated followed by non-parametric testing to compare group differences. Data are mean  $\pm$  standard deviation or median (interquartile range (IQR)) unless otherwise stated.

EQ5D-5L index values were calculated based on the Flemish index values for the EQ-5D-3L from Cleemput<sup>17</sup> and mapped for the EQ5D-5L according to the crosswalk function proposed by van Hout et al.<sup>18</sup>

Mean differences between temporary and persistent PTN were compared using a Mann-Whitney U test. Ratios between cohorts were calculated and compared using a Chi square or Fisher's exact test.

A time-series analysis was done comparing total direct healthcare costs between temporary and persistent PTN cohorts in the five years following the onset of PTN. A multiple linear regression with stepwise selection model was calculated to determine if age, EQ5D, gender, affected nerve and cause of trauma could predict total cost.

Finally, an outlier analysis was performed based on boxplot inspection and the Rosner test of total costs over a five-year period to identify and further characterize potential risk populations. The cumulative total costs of this subgroup were compared with the cumulative total cost of the overall sample. There were no missing data in the final sample.

# **Results**

## **Study sample**

The final study population consisted of 158 (or 43%) patients with a female predominance of 66% and mean age of 52 years. There were no statistical differences between the final study sample and the non-CM affiliated, excluded, patients (**Supplementary table**). The main cause of PTN in this sample was third molar surgery (21%), followed by non-third molar extraction (19%). Most patients reported symptoms in the lower jaw (51%) and 67% had persistent PTN. The average QoL index value was  $0.70 \pm 0.20$ . Patient characteristics are presented in **Table 1**.

*Table 1. Patient characteristics of the study sample.*

Characteristic (N)	N	Count (%)	Mean (SD)	Median (IQR)
Age	158		52 (17)	52 (36-64)
Gender	158			
Male		54 (34)		
Female		104 (66)		
Cause of injury - count (%)	158			
Local anesthesia		2 (1.3)		
Third molar surgery		33 (20.9)		
Tooth extraction		30 (19.0)		
Endodontic treatment		15 (9.5)		
Dental implant placement		20 (12.7)		
Maxillofacial trauma		21 (13.3)		
Other		37 (23.0)		
Location of complaints	158			
Lower jaw		80 (50.6)		
Tongue		22 (13.9)		
Upper jaw		56 (35.4)		
Persistency of symptoms	158			
Temporary (< 3 months after injury)		52 (32.9)		
Persistent (> 3 months after injury)		106 (67.1)		
Employment status	175			
Employee		131 (75)		
Self-employed		17 (10)		
Retired		27 (15)		
Work incapacity > 30 days				
Number of patients		52 (33)		
Days			264 (749)	0 (0-55)
Preferential rate	175	25 (14)		
Chronic pain status	158	21 (13)		
Quality of Life (EQ5D-5L)	100			
Dimensions				
No problems		21 (21)		
Any problem		79 (79)		
Index			0.70 (0.26)	0.76 (0.62-0.81)
Health state			71 (26)	75 (65-90)

Seventy-five percent of patients were employed at the time of data collection, 10% were self-employed, and 15% were retired. No patients in this sample were unemployed. However, 14% received a preferential rate and 13% had a registered chronic pain status. The mean QoL score

was  $71 \pm 26$  out of 100 (100 indicating best QoL). Twenty-one percent indicated no problems on EQ5D dimensions.

### **Overall costs and healthcare utilization**

**Table 2** summarizes average and median costs and healthcare use for the total study population since the complaint began.

Hospitalization and technical interventions were the main drivers of cumulative costs, followed by consultation costs. The total average cost per patient in the first year was €2353 (1426-4499). Of this, the patient paid an average of €587 (303-982) out-of-pocket (i.e., 25% of total costs). In a period of 5 years after PTN diagnosis, the average cumulative cost per patient was €6978 (3473-15338) with a mean out-of-pocket expense of €1802 (651-3658), i.e., 26%. The multiple regression model could not significantly predict total cost ( $F(18, 80) = 0.8385$ ,  $p < 0.6508$ , adj.  $R^2 = -0.03057$ ). None of the variables added significantly to the prediction.

The number of doctor visits in this population was high, with a mean of 27 primary care visits and 47 specialist visits over a 5-year period per patient amounting to a total annual mean cost of €133 and €211, respectively. When assessing median visiting numbers mainly primary care physicians were visited.

In the five-year period after the onset of PTN, 97% of patients received at least one imaging exam. The mean number of imaging investigations per patient was  $10 \pm 12$ , with one patient receiving up to 94 investigations (mainly intra-oral radiographs). On average, patients received one computed tomography (CT) head and several intraoral and panoramic radiographs in the five years following the occurrence of PTN. Thirty-seven percent of patients underwent magnetic resonance imaging (MRI) of the brain and 70% had cone-beam computed tomography (CBCT) or a CT of the head. Eleven percent of patients underwent at least two MRIs of the brain in the first five years and 36% of patients had two or more CTs or CBCTs of the head taken. Costs of technical interventions mainly cumulated in the dental and maxillofacial disciplines, but also a considerable share of interventions were registered by the primary caregiver. On an annual basis, maxillofacial surgery costs were the highest with a median cost of €183 (52-362), followed by dental procedures amounting to €158 (71-323).

We observed a high level of medication consumption in this population as illustrated in **Table 2**. The cumulative costs were the highest for antibacterials, NSAIDs and antidepressants after PTN was diagnosed

Table 2. Direct healthcare costs and resource utilization of the study sample.

Characteristic (N)	Year 1				5-year-average per annum				5-year-total			
	Mean frequency	Median frequency	Mean cost (SD)	Median cost (IQR)	Mean frequency	Median frequency	Mean cost (SD)	Median cost (IQR)	Mean frequency	Median frequency	Mean cost (SD)	Median cost (IQR)
	(SD)	(IQR)			(SD)	(IQR)			(SD)	(IQR)		
<b>Consultations</b>												
Primary medical care	7 (9)	6 (3-10)	179 (235)	147 (78-229)	5 (6)	4 (1-7)	133 (170)	87 (30-178)	27 (15)	18 (6-36)	663 (380)	436 (149-890)
Secondary medical care	17 (16)	14 (9-19)	352 (393)	296 (182-458)	9 (11)	0 (0-2)	211 (256)	0 (0-33)	47 (24)	0 (0-8)	1055 (573)	0 (0-167)
<b>Hospitalization</b>												
Duration (in days)	1.7 (5.6)	2 (1-4)	612 (779)	2418 (1537-3777)	2.0 (14.0)	0 (0.0-0.4)	508 (2273)	0 (0-315)	9.9 (31.4)	0 (0-2)	2542 (5095)	0 (0-1573)
<b>Imaging</b>												
Intra-oral	1.5 (3.7)	1 (0-2)	15 (30.8)	12 (0-26)	0.9 (2.7)	0.4 (0.0-1.0)	10.3 (38.1)	4 (0-11)	4.6 (6.0)	2.0 (0.0-5.0)	51.3 (85.5)	20 (0-57)
Panoramic	1.4 (2.3)	1 (0-2)	43.2 (63.3)	42 (0-111)	0.6 (1.3)	0.3 (0-0.8)	18.3 (36.4)	9 (0-24)	3.0 (3.0)	1.5 (0.2-4.0)	91.3 (81.5)	44 (0-119)
Lateral head	0.2 (0.4)	0 (0-0)	4.4 (10.0)	0 (0-0)	0.1 (0.3)	0 (0-0)	2.26 (10.2)	0 (0-0)	0.4 (0.7)	0 (0-0)	11.3 (22.8)	0 (0-0)
Conebeam CT	0.2 (0.2)	0 (0-0)	12.2 (12.3)	0 (0-0)	0.1 (0.1)	0 (0.0-0.2)	4.80 (7.48)	0 (0-12)	0.4 (0.3)	0 (0.0-1.0)	24.0 (16.8)	0 (0-60)
Head CT	0.4 (0.2)	0 (0-1)	26.2 (31.5)	0 (0-60)	0.2 (0.3)	0.2 (0.0-0.2)	12.2 (21.7)	0 (0-18)	1 (0.6)	1.0 (0.0-1.0)	60.9 (48.7)	0 (0-88)
MRI head-brain	0.3 (0.4)	0 (0-1)	20.7 (28.1)	0 (0-0)	0.1 (0.2)	0 (0.0-0.2)	8.22 (14.0)	0 (0-18)	0.5 (0.4)	0 (0-1)	41.1 (31.4)	0 (0-92)
<b>Technical interventions</b>												
Primary medical			226 (266)	160 (74-273)			169 (199)	126 (43-223)			846 (446)	630 (216-1117)
Dental			557 (1252)	228 (86-580)			1306 (1587)	158 (71-323)			261 (708)	790 (353-1616)
Maxillofacial surgery			1090 (1427)	573 (68-1369)			323 (852)	183 (52-362)			1613 (1909)	913 (260-1810)
Neurosurgery			22.8 (154)	0 (0-0)			15.6 (159)	0 (0-0)			78.2 (356)	0 (0-0)
Neurology			31.4 (58.7)	0 (0-0)			29.6 (74.3)	0 (0-23)			148 (167)	0 (0-113)
Psychiatry			48.3 (292)	0 (0-0)			31.9 (174)	0 (0-0)			160 (390)	0 (0-0)
<b>Medications</b>												
Paracetamol	34.7 (196)	0 (0-1)	2.30 (4.83)	0 (0-2.5)	45.1 (414)	0 (0-5)	1.85 (8.34)	0.5 (0-1.2)	226 (928)	1 (0-24)	9.26 (18.7)	2 (0-6)
NSAIDs	27.2 (32.8)	15 (0-35)	12.8 (17.2)	7 (0-16)	12.4 (23.3)	6 (3-16)	5.39 (9.86)	3 (1.3-6.6)	62.0 (52.2)	30 (15-80)	26.9 (22.1)	15 (7-33)

Opioids	22.2 (74.9)	0 (0-5)	29 (198)	0 (0-9)	26.4 (205)	3 (0-27)	24.4 (180)	0 (0-5)	132 (460)	1 (0-5)	122 (404)	1 (0-27)
Antidepressants	57.4 (105)	0 (0-42)	42.8 (103)	0 (0-28)	53.5 (98.2)	5 (0-54)	45.1 (125)	3 (0-28)	267 (220)	27 (0-272)	226 (280)	13 (0-140)
Antiepileptics	17.0 (53.0)	0 (0-0)	19.3 (52.6)	0 (0-0)	17.6 (46.8)	0 (0-5)	23.8 (104)	0 (0-3)	88.0 (105)	0 (0-24)	119 (233)	0 (0-17)
Antipsychotics	5.52 (30.2)	0 (0-0)	9.63 (58.2)	0 (0-0)	4.40 (20.2)	0 (0-1)	6.78 (41.8)	0 (0-0)	22.0 (45.3)	0 (0-5)	33.9 (93.7)	0 (0-0)
Corticosteroids	9.49 (16.5)	2 (0-6)	5.22 (6.77)	0 (0-8.6)	7.91 (35.3)	1 (0-6)	3.48 (13.2)	1.7 (0-3.46)	39.6 (79.1)	6 (0-30)	17.4 (29.5)	8 (0-17)
Antibacterials	30.0 (28.6)	19 (2-43)	43.9 (53.3)	22 (6-55)	16.4 (22.1)	10 (4-21)	22.5 (37.5)	11 (4-31)	82.2 (49.5)	48 (18-103)	112 (84.1)	57 (19-155)
Total			3577 (3457)	2353 (1426-4499)			2400 (4156)	1396 (695-3068)			12002 (9317)	6978 (3473-15338)

### **Comparing temporary versus persistent PTN cohorts**

When comparing temporary and persistent PTN cohorts, the persistent PTN cohort comprised relatively more women than the temporary PTN cohort (72% versus 54%,  $p = 0.026$ ). The median age was significantly higher in the persistent PTN group (54 versus 46 years,  $p = 0.003$ ). We observed a disproportionate localization of nerve damage: persistent nerve damage was more commonly associated with localization in the upper jaw (**Table 3**). No significant differences were noted in the cause of injury between both cohorts. Quality of life was significantly lower in patients with persistent PTN ( $0.60 \pm 0.24$  versus  $0.92 \pm 0.15$ ,  $p < 0.001$ ).

*Table 3. Comparison of patient characteristics and healthcare expenditure between persistent and temporary PTN. Prices are given in 2019 € for Belgium. SD: standard deviation.*

Characteristic	Persistent PTN (N = 106)	Temporary PTN (N = 52)	p-value
Age - mean (SD)	55 (15)	46 (18)	0.003
Gender - count (%)			0.026
Female	76 (72)	28 (54)	
Male	30 (28)	24 (46)	
Cause of injury - count (%)			> 0.05
Local anesthesia	1 (0.9)	1 (0.9)	
Third molar surgery	15 (14.0)	18 (35.0)	
Tooth extraction	19 (18.0)	11 (21.0)	
Endodontic treatment	11 (10.0)	4 (7.7)	
Dental implant placement	15 (14.0)	5 (9.6)	
Maxillofacial trauma	14 (13.0)	7 (13.0)	
Other	31 (29.0)	6 (12.0)	
Location of complaints - count (%)			
Lower jaw	49 (46)	31 (60)	0.034
Tongue	14 (13)	8 (15)	
Upper jaw	43 (41)	13 (25)	
Employment status - count (%)			0.064
Employee	85 (71)	45 (82)	
Self-employed	24 (20)	3 (5.5)	
Retired	10 (8.4)	7 (13)	
Work incapacity > 30 days			
Patients - count (%)	40 (38)	12 (23)	0.065
Days - mean (SD)	304 (800)	175 (619)	0.2
Preferential rate - count (%)	19 (16)	6 (11)	0.6
Chronic pain status - count (%)	20 (19)	1 (1.9)	0.003

## Quality of Life (EQ5D-5L)

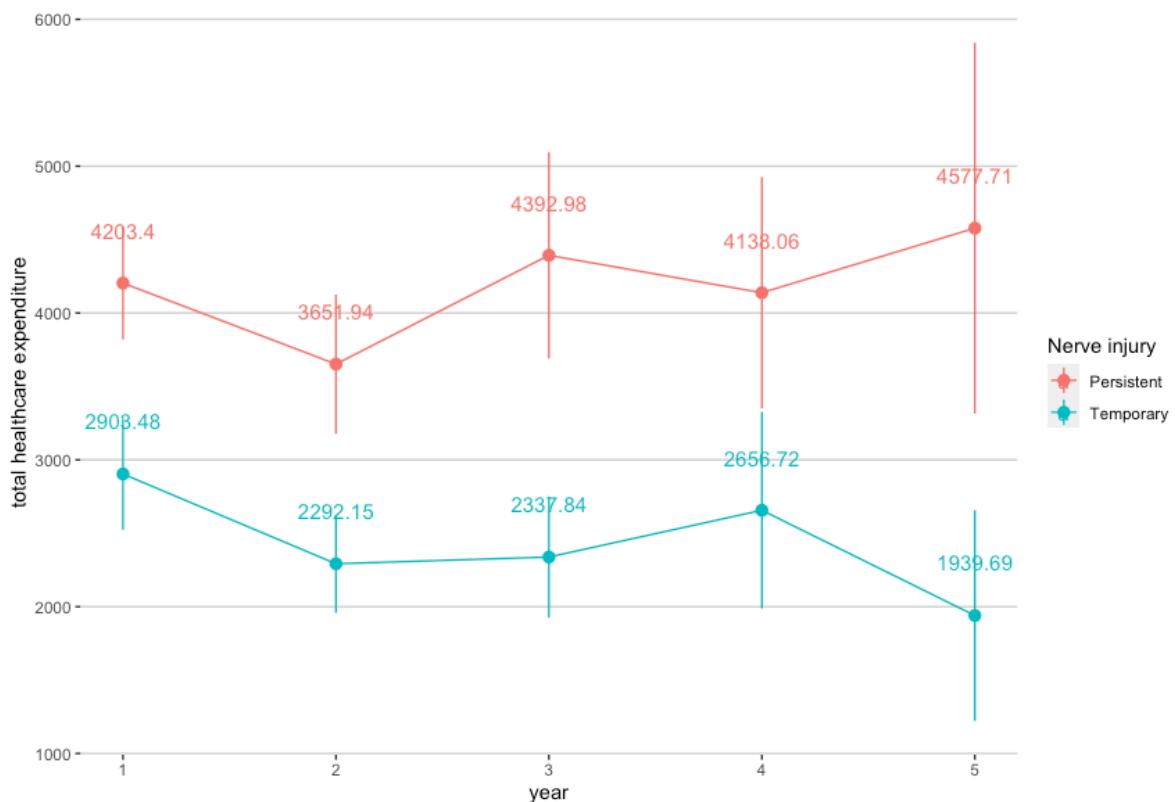
Dimensions - count (%)			<0.001
No problems	1 (1)	20 (20)	
Any problems	71 (71)	8 (8)	
Index	0.61 (0.24)	0.92 (0.15)	<0.001
Health state - mean (SD)	66 (29)	82 (9)	0.002
Health care expenditure in € - median (IQR)			
Patient expenditure (out-of-pocket) year 1	618 (398-1130)	441 (198-793)	0.029
Health insurance provider expenditure year 1	1912 (946-4273)	1393 (1043-2040)	0.017
Total healthcare expenditure year 1	2535 (1584-5478)	1946 (1299-3228)	0.021
Patient expenditure (out-of-pocket) first five years	2084 (1088-3989)	1294 (446-2754)	0.005
Health insurance provider expenditure first five years	6716 (2713-13569)	3202 (1665-5876)	<0.001
Total healthcare expenditure first five years	8866 (4368-18191)	4432 (2156-9032)	<0.001
Patient expenditure (out-of-pocket) 5-year-average per annum	417 (218-798)	259 (89-551)	0.005
Health insurance provider expenditure 5-year-average per annum	1343 (543-2714)	640 (333-1175)	<0.001
Total expenditure 5-year-average per annum	1773 (874-3638)	886 (431-1806)	<0.001

Healthcare expenditure was highest in the persistent PTN cohort with a median 5-year total expense of €8866 (4368-18191) versus €4432 (2156-9032) in patients suffering from temporary PTN ( $p < 0.001$ ). This corresponds to a ratio of two. Furthermore, the median 5-year out-of-pocket expense for a patient with persistent PTN was €2084 (1088-3989) (i.e., 24% of the total healthcare expenditure) versus €1294 (446-2754) (i.e., 29% of the total healthcare expenditure) with a ratio of 1.6. Hospitalization and technical interventions yielded the highest costs for both cohorts. For each cost category, the expenditure of patients with persistent PTN was statistically significantly higher than that of patients with temporary PTN.

Medication consumption measured by the defined daily dose (DDD) was high in both cohorts. The amount of prescribed NSAIDs, opioids, antibiotics, and corticosteroids was significantly higher in patients with persistent PTN. The DDD of typical pain medications (paracetamol, NSAIDs, opioids) and atypical pain medications (antidepressants, antiepileptics, antipsychotics) was particularly high for both cohorts. For instance, the maximum DDDs reported for paracetamol and opioids per annum were 2203 and 3543, respectively.

There were no statistically significant differences in work incapacity between the two cohorts. A significantly higher proportion of persistent PTN patients had a registered chronic pain status (19% versus 1.9%,  $p = 0.003$ ) and their QoL scores were lower ( $66 \pm 29$  versus  $82 \pm 9$ ,  $p = 0.002$ ).

We performed a longitudinal analysis of annual mean costs in the first five years after occurrence of PTN between the two cohorts. Total costs were higher for persistent PTN versus temporary PTN at every time point. Furthermore, a steady increase in costs was seen in patients with persistent PTN versus a decrease in the temporary PTN group (**Figure 2**). This translated into a cost ratio of 1.4 at the start of symptoms, increasing to 2.4 after five years.



*Figure 2. Time series analysis of total healthcare expenditure between temporary and persistent PTN cohorts in the first five years after onset of PTN. Mean prices ± standard deviations are given. Prices are given in 2019 € for Belgium.*

### Outlier analysis

Outlier analysis revealed that eight patients (5% of the study population) had particularly high direct healthcare costs. The cumulative cost of these eight patients was €533526 with an average of €66691 per patient, over the 5-year period following the onset of PTN. Together this represented 28% of the overall direct costs of the entire study population. Further exploratory analysis showed that these were seven women and one man with a mean age of  $70 \pm 13$  years. These patients all belonged to the persistent PTN cohort. The mean QoL index value was  $0.40 \pm 0.40$  with a self-perceived HRQoL score of  $48 \pm 17$ .

## **Discussion**

This study demonstrates that PTN patients represent a high economic burden, with a median annual direct cost of €1396 per patient. Patients with persistent PTN incurred significantly higher direct costs (annual median cost of €1773 versus €886 in temporary PTN) which further increased in the years after the onset of PTN. The identified direct costs incurred by PTN patients are considerably higher than the previously reported annual direct costs of 362£ at 2012 prices (i.e., €478 in Belgian 2019 prices<sup>14</sup>) in persistent orofacial pain patients, published by Dubner et al.<sup>15</sup> The annual direct total costs reported in this study are comparable to the costs of postsurgical neuropathy reported by Liedgens et al.<sup>16</sup> To put this further into perspective, other analyses of national health insurance data, which applied a methodology similar to that of this study, show that the average annual healthcare expenditure of dental patients without a chronic condition in Belgium is €980 versus €5076 when a chronic condition is present.<sup>19</sup> For reference, we mention that OECD figures of 2019 state an average overall healthcare expenditure of €3679 per capita in Belgium.<sup>20</sup> However, the methodology behind these figures is different and does not allow for an unequivocal comparison.

The present study suggests high out-of-pocket rates nearly of up to 30% for patients suffering from PTN compared with national numbers. Other studies have already shown that inequality occurs in chronic conditions.<sup>21,22</sup> Out-of-pocket spending generally increases with increasing age, multimorbidity, and chronicity.<sup>22</sup> The persistent PTN cohort in this study consisted of significantly older people, which may explain why the out-of-pocket expenses are higher in this group. This study adds to the evidence base that those out-of-pocket costs are relatively high in the presence of a neuropathic condition.

Healthcare resource utilization was significantly higher in patients with persistent PTN. A high frequency of primary care visits was seen in this cohort. On average, there were five general practitioner (GP) visits per year and nine visits to specialists. Figures from Liedgens' study show that here too, the economic impact of PTN is higher than the mean of three GP visits and five specialist consultations reported in their study on a large population of neuropathic pain patients in Europe.<sup>16</sup> The annual average number of hospitalization days in this study of two days per patient is lower than reported figures for patients with chronic conditions in Belgium, which is estimated to be 13 days per year<sup>19</sup> and the reported OECD average length of stay of 7.2 days.<sup>20</sup>

From a 2018 Belgian population-wide study we learn that the overall HRQoL was 0.79 for Belgians with age of 15 years or more.<sup>23</sup> The HRQoL for men in age group 45-54 was 0.81 and

for women 0.75. This suggest a lower HRQoL in patients with PTN and even more so when patients suffer from persistent PTN.

It is striking in this study that the average number of examinations and repetitive imaging per patient is very high. This might indicate that both practitioners and patients refuse to accept or recognize the diagnosis, therapy, and prognosis of a PTN-condition. This hypothesis is strengthened since costs seem to decrease over time for patients with temporary PTN.

Technical services proved to be one of the main drivers of total costs. Of the disciplines investigated, the cumulative intervention cost was highest in the fields of maxillofacial surgery, primary care, and dentistry. However, there was a slight but significant difference in cumulative costs between the persistent and temporary PTN cohorts. Contrary to expectations, there thus appears to be no imbalance in the costs of delivered technical services between these cohorts.

Medications were prescribed more often for patients with persistent PTN, who recorded significantly higher use of NSAIDs, opioids, and corticosteroids. There was a wide range in the DDDs with some extremely high outliers (**Table 4**). This is a disturbing finding, especially because we also found these extreme values for opioids and antibiotics. Both have no or only a limited place in the treatment of PTN. This indicates that this population may be at particular risk of wrongful prescribing and overprescribing.<sup>24</sup> Currently and to the best of our knowledge, no data are available on the DDD for the investigated medication classes in comparable populations. Additionally, care should be taken when using the DDD metric because the actual DDD of different opioid derivatives and the WHO-reported DDD can differ significantly.<sup>25</sup>

A small number of patients (5%) contributed to almost 30% of total costs in this study population. This suggests a subpopulation with particularly high economic and psychosocial impact. Early identification and adequate support of these patients should therefore be high on the agenda.

*Table 4. Comparison of medication use between persistent and temporary PTN patients. Per annum and per day defined daily dose (DDD) of frequently used medication classes.*

DDD per annum per patient during first five years	Persistent PTN				Temporary PTN				p-value
	Mean (SD)	Median (IQR)	Min	Max	Mean (SD)	Median (IQR)	Min	Max	
Paracetamol	94 (378)	4 (1-16)	0	2203	12 (25)	2 (1-11)	0	140	0.2
NSAIDs	25 (34)	14 (7-30)	0	240	15 (16)	9 (6-19)	3	97	0.023
Antidepressants	158 (226)	41 (11-219)	2	964	78 (86)	40 (7-108)	3	286	0.4
Antiepileptics	129 (207)	25 (5-162)	1	993	36 (37)	28 (15-36)	4	106	0.9
Antipsychotics	40 (71)	5 (2-45)	0	257	36 (37)	28 (15-36)	4	106	0.7
Opioids	98 (452)	10 (3-28)	0	3543	10 (27)	3 (0-6)	0	140	< 0.001
Antibacterials	52 (59)	38 (14-71)	1	418	19 (17)	14 (8-27)	0	72	< 0.001
Corticosteroids	21 (51)	7 (3-15)	0	322	6 (7)	4 (3-8)	1	30	0.010

DDD per day per patient during first five years	Persistent PTN				Temporary PTN				p-value
	Mean (SD)	Median (IQR)	Min	Max	Mean (SD)	Median (IQR)	Min	Max	
Paracetamol	0.26 (1.04)	0.01 (0.00-0.04)	0.00	6.03	0.03 (0.07)	0.01 (0.00-0.03)	0.00	0.38	0.2
NSAIDs	0.07 (0.09)	0.04 (0.02-0.08)	0.00	0.66	0.04 (0.04)	0.02 (0.02-0.05)	0.01	0.26	0.023
Antidepressants	0.43 (0.62)	0.11 (0.03-0.60)	0.01	2.64	0.21 (0.24)	0.11 (0.02-0.30)	0.01	0.78	0.4
Antiepileptics	0.35 (0.57)	0.07 (0.01-0.44)	0.00	2.71	0.10 (0.10)	0.08 (0.04-0.10)	0.01	0.29	0.9
Antipsychotics	0.11 (0.19)	0.01 (0.01-0.12)	0.00	0.71	0.11 (0.24)	0.01 (0.01-0.08)	0.01	0.27	0.7
Opioids	0.27 (1.24)	0.03 (0.01-0.08)	0.00	9.71	0.03 (0.07)	0.01 (0.00-0.02)	0.00	0.38	< 0.001
Antibacterials	0.14 (0.16)	0.10 (0.04-0.19)	0.00	1.15	0.05 (0.05)	0.04 (0.02-0.07)	0.00	0.20	< 0.001
Corticosteroids	0.06 (0.14)	0.02 (0.01-0.04)	0.00	0.88	0.02 (0.02)	0.01 (0.01-0.02)	0.00	0.08	0.010

The strengths of this study are that the analysis was based on real-world data and could be traced back to the individual level to identify clinically relevant subpopulations. Without a national registry or universal coding of these patients, it would not be possible to obtain these data.

Study limitations include a potential selection bias as all patients were drawn from a tertiary center clinical dataset. No detailed information was available as to who caused the injuries, their experience or training. Also, compared to other health insurance companies, within the

CM membership, there is a slight bias towards older age groups (mean age CM members = 44, versus mean age Belgian population = 41) and the unemployed are slightly underrepresented (40.6% of the unemployed are members vs. an expected 43.7%).<sup>26</sup> Only, direct costs were investigated, and all financial data were taken into account—not only those attributable to PTN. However, we did prove that e.g. age and gender did not explain the total cost. This indicates that these populations do indeed differ in terms of disease phenotype and thus total cost. A future study that also identifies the indirect costs of these patients based on structured interviews could be a logical next step. Finally, we note that the current dataset did not allow us to map all out-of-pocket expenses. Particularly in the ambulant care setting in Belgium, additional supplements as well as the system of an out-of-pocket maximum can influence the patient contribution, which was not accounted for here.

## Implications and future opportunities

The presented results highlight the importance of first and foremost preventing nerve injuries from happening. Trigeminal nerve injuries are largely preventable by careful patient selection and treatment planning. 3D virtual planning is routinely applied in both dental and maxillofacial surgery specialties. These new tools already implement nerve tracing tools to avoid these structures being injured during surgery.<sup>27</sup>

But, even in the best hands and with the most minimal invasive techniques, nerve injuries can still occur. This is where current evidence stops. Both patients and specialists languish into ignorance. There is a risk misdiagnosing and mistreating the nerve injury patient. Patients may steer towards medical shopping or medicolegal action. Some will end up with lifelong neuropathic pain resulting in a detrimental QoL. Secondary prevention is currently lacking. This is illustrated by studies showing large variation in referral delays, diagnostic measures and treatment options. Unfortunately, no gold standard or internationally accepted guidelines exist.<sup>4,11</sup>

Future studies should focus on developing diagnostic and treatment guidelines. In parallel, both patients and clinicians should be made aware of the risk of trigeminal nerve injuries, how they can be avoided and treated. Expert talks at conferences and in patient support groups could be a good starting point to increase this awareness.

Finally, we hypothesize that centralization of these patients may aid in a faster and more cost-effective approach. This could be evaluated in a future cost-effectiveness study.

## **Conclusion**

PTN is a debilitating condition that is costly to both society and patient. Repeated and frequent use of head and neck imaging was observed in this study population. Patients with persistent PTN showed an unwarranted higher use of opioids and antibiotics. Subpopulations were identified with significantly worse QoL and higher expenses. Within the limitations of this study, it seems there is a need for informing patients in detail on the inherent risks of nerve damage after dental and oromaxillofacial procedures. Every surgery should be preceded by a risk-benefit assessment in order to avoid unnecessary nerve damage.

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## Supplemental data

*Supplementary table. Chi square and Mann-Whitney U test comparing the final study sample with the excluded non-CM affiliated patients. No statistically significant differences were present.*

Characteristic (N)	CM-Affiliated (N=158)	Non-CM (N=215)	P-value
Age	51 (35-63)	52 (36-62)	0.3
Gender			>0.9
Male	54 (34)	72 (33)	
Female	104 (66)	143 (67)	
Cause of injury - count (%)			0.065
Local anesthesia	2 (1.3)	13 (5.9)	
Third molar surgery	33 (21)	53 (24)	
Tooth extraction	30 (19)	44 (20)	
Endodontic treatment	15 (9.5)	15 (6.8)	
Dental implant placement	21 (13)	26 (12)	
Maxillofacial trauma	20 (13)	23 (10)	
Other	37 (23.4)	41 (19.1)	
Location of complaints			0.7
Lower jaw	80 (50.6)	112 (50)	
Tongue	22 (13.9)	35 (15.6)	
Upper jaw	56 (35.4)	70 (31.2)	
Persistency of symptoms			>0.9
Temporary (< 3 months after injury)	52 (32.9)	64 (28.6)	
Persistent (> 3 months after injury)	106 (67.1)	131 (58.5)	
Quality of Life (EQ5D-5L)			
All domains			>0.2
Health state	75 (65-90)	75(60-80)	0.6



# **INTERMEZZO**

## **Orofacial sensory testing**

*This chapter is based on the following manuscript:*

**Van der Cruyssen F, Van Tieghem L, Croonenborghs TM, Baad-Hansen L, Svensson P, Renton T, Reinhilde J, Politis C, De Laat A.** Orofacial quantitative sensory testing: Current evidence and future perspectives. *European Journal of Pain.* 2020;(June):1-15.

# **Abstract**

## **Background and objective**

Orofacial quantitative sensory testing (QST) is an increasingly valuable psychophysical tool for evaluating neurosensory disorders of the orofacial region. Here, we aimed to evaluate the current evidence regarding this testing method and to discuss its future clinical potential.

## **Data treatment**

We conducted a literature search in Medline, Embase and Scopus for English-language articles published between 1990 and 2019. The utilized search terms included QST, quantitative, sensory testing and neurosensory, which were combined using the AND operator with the terms facial, orofacial, trigeminal, intraoral and oral.

## **Results**

Our findings highlighted many methods for conducting QST—including method of levels, method of limits and mapping. Potential stimuli also vary, and can include mechanical or thermal stimulation, vibration or pinprick stimuli. Orofacial QST may be helpful in revealing disease pathways and can be used for patient stratification to validate the use of neurosensory profile-specific treatment options. QST is reportedly reliable in longitudinal studies and is thus a candidate for measuring changes over time. One disadvantage of QST is the substantial time required; however, further methodological refinements and the combination of partial aspects of the full QST battery with other tests and imaging methods should result in improvement.

## **Conclusions**

Overall, orofacial QST is a reliable testing method for diagnosing pathological neurosensory conditions and assessing normal neurosensory function. Despite the remaining challenges that hinder the use of QST for everyday clinical decisions and clinical trials, we expect that future improvements will allow its implementation in routine practice.

## **Introduction**

For patients with sensory neuropathy, qualitative sensory testing (QualST) is the most commonly used method in clinical consultations, and quantitative sensory testing (QST) is purported to be useful for phenotyping.<sup>1</sup> Notably, both QST and QualST are considered to be subjective, and many authors recommend objective sensory tests for neuropathy assessment.<sup>2</sup> Nerve conduction tests such as somatic sensory evoked potentials, blink reflex, sudomotor and other reflex tests provide the most objective and repeatable measures as they exclusively assess the integrity of a few neural pathways.<sup>3</sup> However, they are not able to assess patients' symptoms and experience of their neuropathy, which is arguably the most important aspect to evaluate when the goal is treatment.<sup>3</sup> Thus, increasing attention has been focused on QST, and an ever-growing body of published evidence supports its value. Orofacial QST has lifted off in the last 30 years and since the task force report on orofacial QST by Svensson et al. in 2011, many new insights have emerged.<sup>4</sup> We hope to bring an update of the literature in orofacial QST as this is lacking from the current literature.

In the present narrative review, we aimed to critically review existing evidence about QST in the orofacial area, to reflect on shortcomings and to elucidate future perspectives. Readers should be able to understand the fundamentals, strengths and pitfalls of orofacial QST after reading this paper. In addition, several pertinent questions have been raised. Does QST add to our clinical decision making? Does it correlate with specific diseases or pain syndromes and their severity? Does it influence our treatments? And what is its diagnostic value? To answer these questions, we first must establish basic information about QST. We will address the following questions. What is QST? How is it performed? Are the measurements and parameters for the orofacial area reliable and relevant? Can we diagnose and differentiate different pathologies? What factors influence outcomes? And does QST offer added value compared with other diagnostic aids? These questions will be answered using the most recent literature wherever possible.

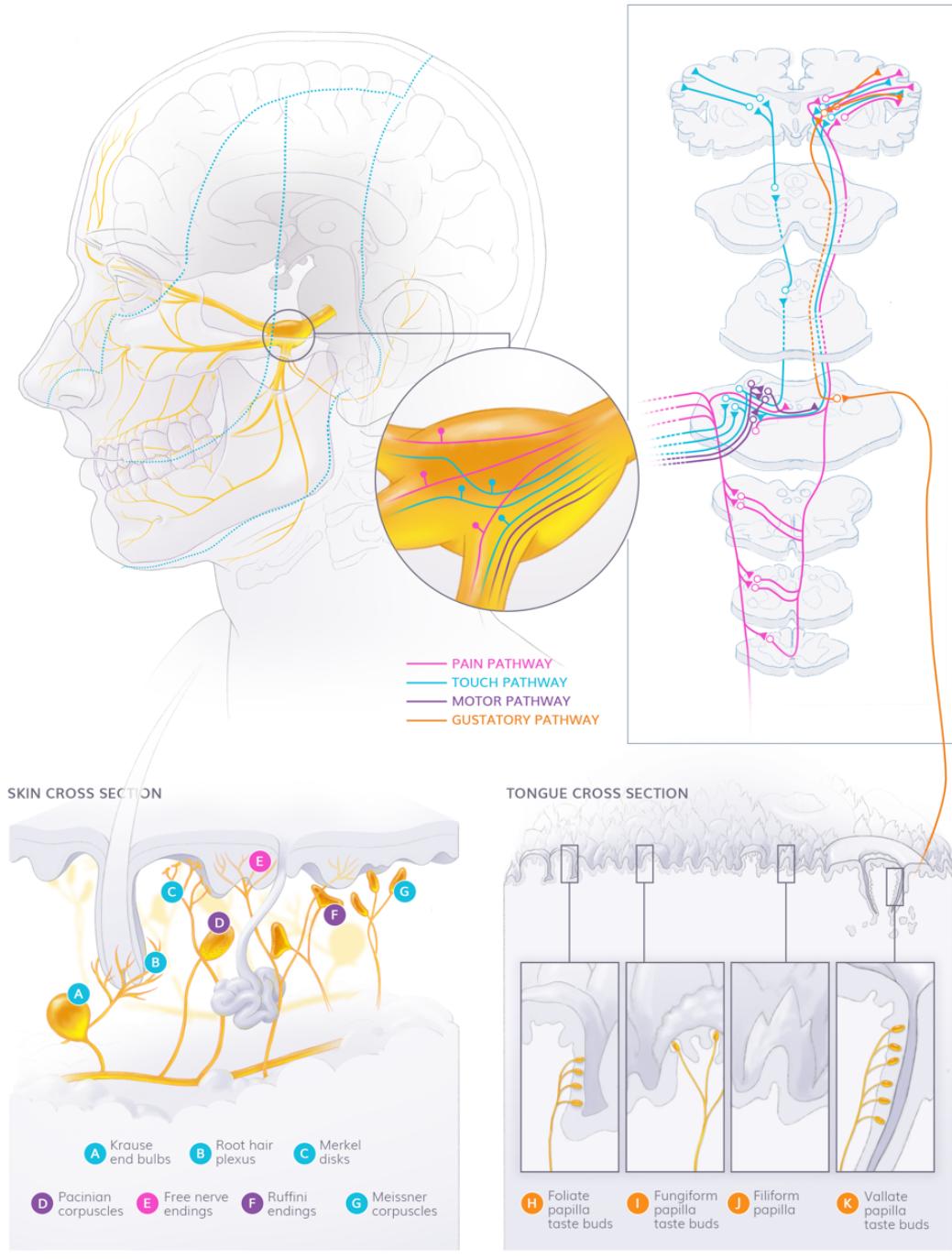
## **Methods**

We performed a scoping literature search in Medline, Embase, Web of Science and Scopus using the following search terms: QST, quantitative, sensory testing and neurosensory. These terms were combined using the AND operator with: facial, orofacial, trigeminal, intraoral and oral. We included all English-language articles published between January 1990 and January

2018. Articles were selected based on title and abstract screening, followed by full-text analysis. We also performed manual screening of reference lists and the grey literature to identify other relevant articles.

## Discussion

Before discussing diagnostic tools for detecting neurological disorders in the orofacial region, a thorough understanding of normal functioning and trigeminal neurophysiology is required. Multiple books provide an overview of this broad topic; however, our understanding of complex trigeminal neurophysiology and the various orofacial functions is still at an early stage. Our group has previously reviewed trigeminal neurophysiology.<sup>4,5</sup> Trigeminal pathways carry information for tactile and thermal stimuli, taste and nociception, as well as motor fibers (**Figure 1**). Understanding these pathways and their functions is important for interpreting clinical pathology and QST findings.



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*Figure 1. Trigeminal sensory and motor pathways. Sensory input from the orofacial area is carried through the trigeminal ganglion toward the trigeminal nuclei. There, the peripheral afferent neurons synapse with their secondary neuron, and convey sensory information through the thalamus towards the somatosensory cortex. Specialized receptors are found in the orofacial skin, mucosa, gingiva, tongue, periodontal tissues, joints and muscles.*

## **What is QST?**

QST is performed with the goal of diagnosing and differentiating underlying pathophysiological somatosensory mechanisms based on subsets of responses. QST can differentiate multiple modalities of neurosensory disturbance—including mechanical or thermal allodynia, hyperalgesia, hypoesthesia, anesthesia and disturbances of touch and directional sense. The recognition of different patterns that correlate with specific underlying mechanisms can lead to phenotyping, which may, in turn, guide adjustments of therapy. Several instruments have been developed for measuring neurosensory disturbances, including von Frey monofilaments, pressure algometers and thermal probes. In this review, we will introduce these modalities and discuss their practical use in psychophysical experiments.

QST is the term used to describe the application of quantitative methods to conduct research on the somatosensory nerve system.<sup>6</sup> The characteristics of the applied stimuli are defined (the modality, location, size of the contact area, duration, frequency and intensity). But, in contrast with QualST, the patient's response is measured quantitatively. QST is considered a psychophysical test because responses are subjective to the patient's perception and can be verbal or nonverbal.<sup>7</sup> This is one advantage of QST over electrophysiological tests that do not consider the patient's perception of stimuli. Other advantages of QST include its non-invasive nature, and its potential to evaluate the smaller A-delta and C fibers, which cannot be tested using routine electrophysiological tests, such as somatosensory evoked potentials or electroneurography.

Disadvantages of QST include that it cannot be used to localize lesions in the neurological pathway towards the cortex, as well as the requirements that patients cooperate and understand the tasks and questions.<sup>8</sup> It remains unclear whether QST actually reflects the patient experience. Certain aspects are not assessed by QST such as the extent of the affected neuropathic area, paresthesia or spontaneous neuralgia.<sup>9</sup> These symptoms may hold equally important information in diagnosis and in determining a management strategy. Additionally, the researcher must be trained in QST, and the method requires an environment that allows for quiet and methodical evaluation.<sup>10</sup> The required equipment is expensive, especially if the researcher wishes to carry out thermal sensory testing.

## **Methods of performing QST**

Several methods can be used to vary the utilized stimuli, to assess the patient's responses to them. Some methods are better suited for use with specific stimuli, and methods can be

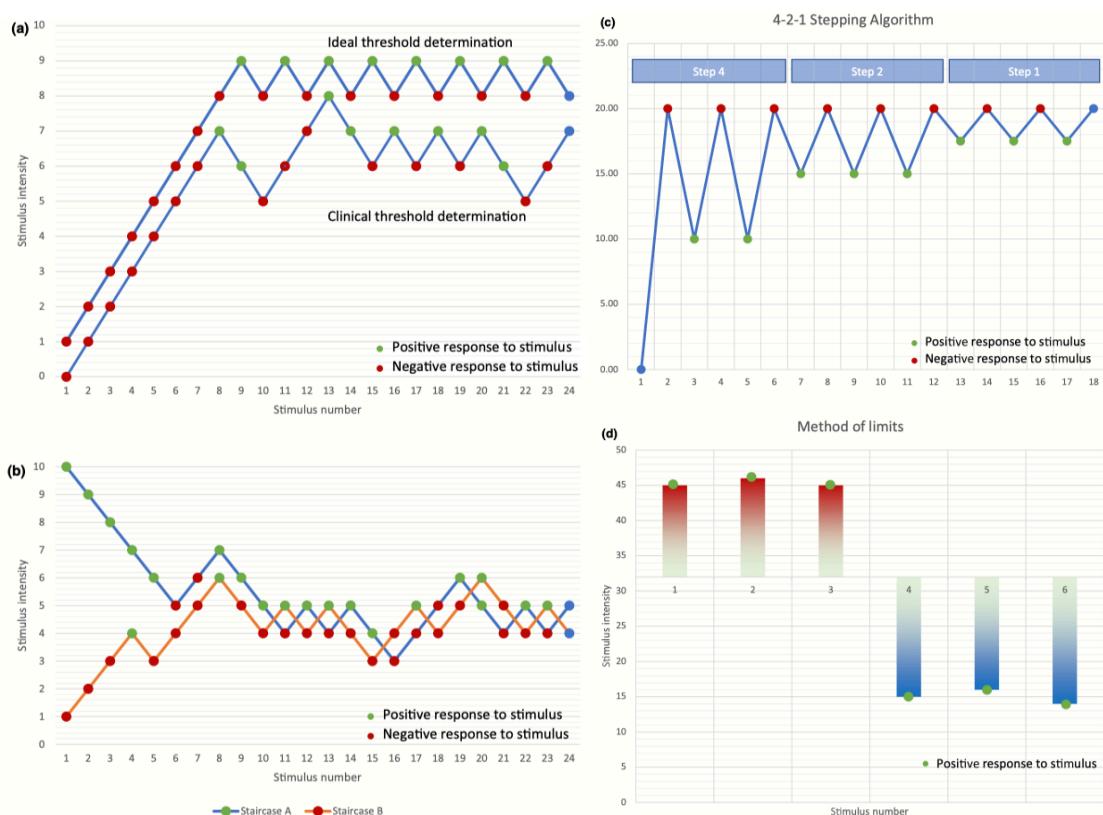
combined in a battery of testing, for example, in the German Research Network on Neuropathic Pain (DFNS) QST protocol.<sup>11</sup> A recently published taskforce report on somatosensory assessment of the orofacial area provides guidelines for orofacial QST and future directions.<sup>4</sup> Here, we describe several commonly used psychophysical paradigms.

### *Method of levels*

In “method of levels” testing, a repetitive static stimulus is applied with the intensity and duration adjusted based on the response to the previous stimulus.<sup>6</sup> The limit is defined as the stimulus intensity at which 50% of stimuli are detected, producing an S-like stimulus–response graph. The CASE IV system (WR Medical Electronics Co.) applies this testing method using the “just-noticeable difference” (JND). If the participant perceives the stimulus, less-intense stimuli are applied until the stimulus is no longer perceived, and vice versa. A participant who perceives level zero stimulus is considered hypersensitive, while one who does not perceive level 25 is considered insensitive. When small differences are used, this technique enables very precise level detection.<sup>12</sup> Additionally, this method has low interest variability and, thus, has relatively good reproducibility; however, it is time-consuming and can lead to sensitization.<sup>13</sup> Notably, heat pain thresholds cannot be determined using this method because tissue damage is possible, and respondents may anticipate the next stimulus by prematurely indicating a positive or negative response.<sup>12,14</sup>

Selection of the different levels can be performed in several ways. In the forced-choice method, the patient is given two or more response options, and must commit to an actual answer. Examples are the temporal forced-choice method where a stimulus is applied in a certain time window or not. The patient must then indicate the time window in which the stimulus was administered. Another example is the spatial forced-choice method. Here, the patient must choose between two presented probes and indicate which one was the predetermined stimulus.<sup>15</sup> This technique is time-consuming, and performance may decline because the participant becomes bored. To overcome this challenge, another method has been developed: the 4–2–1 stepping algorithm.<sup>16</sup> Unlike the forced-choice method, the 4–2–1 stepping algorithm begins with a middle-level stimulus and progresses via a stepwise approach based on the patient's responses. When the patient gives a consistent positive response to the applied stimulus, the stimulus is decreased in a stepwise fashion dividing its intensity or, for example, the inter-prong distance in case of two-point discrimination, narrowing the range in determining the final threshold level.<sup>16</sup> This method shows good inter-rater and intra-rater reliability when used for

tactile threshold determination and for two-point discrimination.<sup>16–18</sup> Lastly, the staircase method starts with a stimulus of high intensity (or low intensity), which is then lowered (or raised) until the patient no longer perceives the stimulus (or begins to perceive the stimulus). Then the staircase is reversed until a new positive (or negative) response is given, which then triggers another reversal. This method is used in the DFNS protocol for the determination of tactile and pain thresholds. A modification of this technique involves the use of two staircases: one starting with a high intensity and the other starting with a low intensity. The alternation between staircases can be randomized to reduce both participant and examiner bias.<sup>19</sup> An overview of these methods is provided in **Figure 2**.



**Figure 2.** (a) Staircase method for level determination. A low or high stimulus intensity is chosen and is raised or lowered depending on the patient's response, until a positive response is given. The sequence is then reversed until a negative response is provided, and so on. After a predetermined number of stimuli, the average threshold is calculated. An ideal threshold is illustrated where the variation around the level is minimal and the patient's response is unequivocal versus a clinical situation, which is more in line with reality (b) Randomized staircase method, in which two staircases are combined and the utilized staircase stimulus is randomly selected. (c) The 4–2–1 stepping algorithm, in which an ever-decreasing stimulus intensity is used to determine a threshold. (d) The method of limits determination, in which a

*continuously increasing or decreasing stimulus is applied until reaching a predetermined cue. For example, heat pain thresholds and cold pain thresholds are determined with this method.*

#### *Method of limits*

With the “method of limits,” stimulus intensity is raised or lowered until it is perceived or no longer perceived, respectively.<sup>6</sup> The threshold is marked by a button or a verbal cue stopping further stimulation. This can be repeated several times to determine an average threshold to the stimulus. The utilized stimuli are considered dynamic, and are less time-consuming to conduct than those applied in the method of levels.<sup>12</sup> The method of limits can be used to determine tactile detection thresholds, thermal heat and cold noxious and innocuous thresholds, vibration, and deep pain thresholds. Thresholds are determined using this method in the DFNS protocol.<sup>11</sup> Intensity must be slowly increased with a standardized ramp (e.g., 1°/second) or decreased to minimize the influence of reaction time. This method is subject to habituation.<sup>20</sup>

#### *Method of adjustment*

The method of adjustment allows patients to adjust the stimulus intensity themselves.<sup>21</sup> An example of orofacial QST could be the application of a thermode in the mental area. Next, the patient is given a control button and asked to raise the temperature until the heat pain threshold is reached. This limits the patient's loss of interest. However, this method is rarely used because, other than electrical stimuli, most stimulus modalities are difficult to apply in this manner. The authors could not identify any application of this method in orofacial QST.

#### *Suprathreshold intensity rating*

Suprathreshold intensity rating involves the application of several known stimuli with intensities above the detection threshold.<sup>22</sup> The participant scores the intensities on a numerical rating scale (NRS) or a visual analogue scale (VAS). The data can be used to draw a stimulus–response curve. It is important to define the lower and upper limits—for example, when measuring pain, zero would indicate no pain and 100 would indicate the worst imaginable pain. The magnitude estimation scale is constructed by defining a standard stimulus. The patient scores the next stimulus in relation to the standard modulus. One disadvantage of this scale is that calculation of the mean is influenced by the randomly determined first score. Previous studies demonstrated that pain sensitivity, which can be measured using this method, decreases with age.<sup>23,24</sup> This demonstrates the importance of having reliable reference tables stratified for sex and gender.

### *Mapping*

In mapping, a thermoroller or marching needle technique is used to identify areas having the same somatosensory properties. However, intraoral application remains challenging. Since it is easy to perform, the mapping technique is often used in QualST.<sup>25–27</sup> In a previous study, it was suggested that the affected surface percentage of the trigeminal dermatome may indicate whether nerve injury will be permanent.<sup>28</sup>

### **Different modalities and stimuli**

Orofacial receptors and their nerve fibers can be clinically tested to assess the integrity of different fiber types. Several stimuli have been designed to assess these different modalities.<sup>29</sup> Most stimuli trigger multiple receptors at once. The numbers and types of receptors that are recruited may influence the patient's perception, and thus response, to the stimuli.<sup>30–32</sup>

### *Mechanical stimulation*

Non-painful tactile stimuli are conveyed via A-beta fibers, which can be tested using monofilaments".<sup>33</sup> The filament is placed perpendicularly to the tested surface for 1–2 s until it bends and is then kept in place for two additional seconds before the stimulus is removed. The filaments bend with pressure forces ranging from 4 mg to 300 g. Von Frey originally used horse hairs, while Semmes and Weinstein used nylon and further standardized these hairs (e.g., the Weinstein Enhanced Sensory Test and Semmes–Weinstein Filaments).<sup>34</sup> Other hairs have been developed to further optimize these filament tests. Rather than nylon, OptiHair2 uses glass fibers with rounded tips that make them more durable (Somedic, Schriesheim, Germany). Most filaments are calibrated and express a logarithmic relation between filament diameter and force. Thus, a scale is often used to convert the coded filaments into grams and force per area or millinewtons (mN), which can then be translated into residual sensory function for clinical interpretation.

The traditional Semmes–Weinstein filaments are not useful for intraoral testing because their properties change in humid environments, and their design is not optimized for intraoral use.<sup>35</sup> However, reliable light touch thresholds of the anterior oral mucosa using these filaments have been reported.<sup>29</sup> In this study, thresholds measured using the staircase method did not differ significantly from the ascending and descending method. Preferred options for intraoral testing include optic glass fiber filaments with forces from 0.125 to 512 mN, with a rounded tip and a

0.5-mm cross-sectional diameter. Another option is Cheung–Bearelly monofilaments, which can be constructed by researchers themselves and are easily utilized. However, their stimulus intensity is not calibrated, making comparison with other QST research difficult.<sup>36</sup> In the future, the use of airflow stimulation could overcome some of the technical issues encountered with intraoral filament use.<sup>37</sup> Dynamic tactile stimulation can be tested using a cotton swab or toothbrush, and is helpful for the detection of allodynia and determining directional sense.<sup>4,38</sup>

### *Two-point discrimination*

Two-point discrimination is the minimum separation that a patient can detect between two simultaneously applied tactile stimuli, ideally having the same intensity.<sup>39</sup> This phenomenon depends on peripheral innervation density. In the orofacial area, the distance varies between two and 30 mm. Intraorally, this technique is frequently applied on the tongue tip and the vermillion. It can also easily be performed on the anterior oral mucosa. One study used self-constructed calibrated pressure probes and found an overall mean two-point discrimination of 9.2 mm for the oral buccal mucosa of anterior upper jaw but they did not assess other orofacial areas.<sup>29</sup> Another study reported normative data on several trigeminal areas, and included information regarding sex, site and stimulus-dependent values.<sup>39</sup> The results showed that women have a higher discriminative ability than men, and that the tongue tip and lower lip are more sensitive than the cheek and forehead. Gingival and mucosal surfaces were not analyzed in that study.<sup>39</sup> Flexible calibrated filaments can be used to overcome inaccuracies and variability caused by the application of different stimulus intensities when using a two-point discrimination device. Isobaric pressure meters have also been suggested as a means of overcoming these inaccuracies and variability.<sup>40</sup>

### *Vibration*

The Rydel–Seiffer tuning fork is the standard device currently used for testing vibration. This device works best when placed on thin skin–bone contact.<sup>41</sup> After the fork is snapped into motion, it is placed on the test area. The patient is asked to indicate when the vibration is no longer felt. The intersect between the apparent triangles indicated on the fork is recorded by using an arbitrary scale from 0 to 8.<sup>42</sup> Application on the tongue is difficult to standardize as it is not supported by a bony floor. Additionally, the tuning fork design cannot easily be used for intraoral testing of gingival areas due to the required angulation. Nevertheless, intra-oral vibration thresholds have been reported.<sup>43</sup> Vibration can be similarly tested by electronic vibrators that have adjustable frequency, amplitude and pressure.<sup>29</sup> Different amplitudes induce

the activation of different mechanoreceptors. A vibrating electric toothbrush is a viable alternative device that can be used for intra- and extra-oral vibro-tactile testing.<sup>44</sup> However, it remains unclear whether anything similar to allodynia exists with regards to vibration.

### *Pinprick*

To determine mechanical pain thresholds, researchers use pinprick stimulators, which are usually thicker (and sometimes electric) von Frey filaments, or force-calibrated pins or needles. Standardized blunt needles with a 0.25-mm diameter and a weight range from 8 to 512 mN are used, and the shape, size and angulation affect the pain threshold. Modified dental probes can also be used intraorally.

### *Deep pressure*

Both simple and more sophisticated pressure algometers are available, and several types have been described for intraoral use.<sup>45-47</sup> For deep pressure measurements, pain and tolerance thresholds are sought. For orofacial testing, the study by Pigg et al. applied probe diameters of 4.8 mm for intraoral use and 1.1 cm for extraoral use.<sup>43</sup> The pressure can be changed at different rates, with a recommended rate of 50 kPa/s, and three separate measurements should be performed at 1-min intervals.<sup>43</sup> A previous study determined intraoral pressure-pain thresholds, and reported high variability between different tested sites, as well as disproportionate modulation when pre-loading different sites.<sup>46,47</sup>

### *Thermal stimulation*

Devices for thermal stimulation, guided by A-delta and C fibers, are evolving. Early testing was performed using copper and aluminum rods with diameters of up to 1 cm, and a variant thereof, comprising four discs made of different materials (Minnesota Thermal Disks, WR Medical Electronics Co.). Investigations with these devices provided the first insights into thermal topographical variation. Tests were also performed using thermal rollers that are cooled or heated in a water bath.<sup>48</sup> These materials are still used today, but mainly for qualitative research. Drawbacks include difficulty controlling the temperature, and the fact that they exert mechanical stimuli in addition to thermal stimuli.<sup>48</sup>

The use of thermal bars and discs was replaced by thermodes. Thermal contact stimulators were designed that enabled the application of precise stimuli to the skin or mucosa. These stimulators comprise a thermoelectric heating and cooling element (according to the Peltier principle) and

have a contact surface of up to 10 cm<sup>2</sup> (Pathway, Medoc, Ramat Yishai, Israel). Investigation of the orofacial region requires smaller contact areas (1–4 cm<sup>2</sup>) to test the different dermatomes of the trigeminal nerve, which can be too small to test with regular probes or instruments.<sup>4</sup> However, the use of different contact areas will recruit different receptor fields such that the results of QST assessment may also change.<sup>32</sup> This was proven for orofacial thermal thresholds, where an increasing stimulus area was associated with spatial summation for warm and heat pain thresholds, but not cold detection thresholds.<sup>49</sup> Intraoral probes are now available for several commercial systems. These systems enable linear temperature changes, as required for the “method of limits,” as well as a rapid return to baseline temperature. However, the disruptive effect of mechanosensation is still present. Thermodes with a Peltier element and water-cooling system are still used, but are now computer-based, such as the Thermal Sensory Analyzer (TSA) II (Medoc, Israel), Pathway (Medoc, Israel) and Modular Sensory Analyzer (MSA, Somedic, Sösdala, Sweden).

The second important group of currently used equipment includes radiant heat or laser stimulators.<sup>50,51</sup> Light energy is absorbed by the tissue surface, causing a rise in temperature. This technique has the major advantage that no tactile afferent fibers are activated. The disadvantages are that the generated skin temperature is not monitored, only heat tests can be performed (not cold), there is a risk of tissue damage, and the system is expensive and requires technical maintenance.<sup>50</sup> Most lasers (including argon, CO<sub>2</sub>, Nd-YAG and thulium-YAG lasers) can be used intraorally, but sometimes they can only be applied in the anterior region because the rays have to pass through articulating arms. A recently launched new generation of laser stimulators, termed diode lasers, are more stable, smaller and cheaper, and are thus promising for QST.<sup>52</sup>

In addition to the above-described complex devices for thermal stimulation, there is also a simple test that estimates central sensitization. An ice cube is held in the mouth, and then removed, and examiners check for the presence of an “after-sensation”.<sup>53</sup> Alternatively, an ethyl chloride canister can be used to cool a dental probe, which can be applied extraorally or intraorally.<sup>54</sup>

Recent research has focused on dynamic QST, such as conditioned pain modulation (CPM) to assess endogenous pain inhibition.<sup>55</sup> One method of CPM assessment involves the use of a painful thermal stimulus (e.g., an ice-cold water bath) as a conditioning stimulus. Additional

research will be needed to improve standardization of CPM protocols, and to assess its clinical implications in orofacial pain.<sup>56</sup>

#### *Other variations*

There are several other variations of techniques. First, oral perceptual abilities can be assessed based on stereognostic recognition of form or shape.<sup>57</sup> Such assessment can be beneficial for both planning and predicting future outcomes of any treatment modality in the orodental region. One group has performed two studies to assess the use and reliability of grating domes (Stoelting, Wood Dale, USA).<sup>58,59</sup> They used several methods to investigate patients who underwent orthognathic surgery, and found that the grating orientation test was a better predictor of neurosensory deficit than the patient's subjective report.<sup>58,59</sup> However, another study group reported that postoperative grating dome testing did not correlate well with intraoperative nerve damage.<sup>60</sup> These tests require inputs and integration from multiple receptors, synapses, nuclei and (sub-)cortical areas, which may be more clinically meaningful than assessing a single receptor response.

Second, occlusal sensitivity can be transduced via mechanoreceptors embedded in the periodontal ligaments.<sup>61,62</sup> Notably, pulpal, muscular and articular receptors also contribute to occlusal sensitivity, and osseoperception has been described around implants lacking a periodontal ligament.<sup>63</sup>

Third, in dentistry, pulpal sensitivity and vitality testing are commonly used to assess pulp vitality in cases of periodontal disease and caries, which helps guide treatment decisions.<sup>64</sup> Pulp sensitivity is also conveyed via the trigeminal afferents, which can be evaluated by applying cold rods against the tooth (Odontotest, Fricar, Zurich, Switzerland) or using electric pulp-testing devices.<sup>65</sup> These tests have varying ranges of sensitivities and specificities, and are qualitative in nature because the patient simply indicates whether they perceive the stimulus.

Lastly, blink and muscle reflexes can be evaluated to assess the integrity of the neuromuscular pathways, and to thus partly assess central processing and integration with different cranial nerves.<sup>66–68</sup> One study assessed blink reflexes in atypical odontalgia patients compared to healthy individuals. They revealed that the patients showed a reduced late blink reflex signal.<sup>69</sup>

### *Extensive QST protocol*

In 2006, the German Research Network on Neuropathic Pain (DFNS) compiled a “QST battery” of seven tests, including 13 parameters: cold detection threshold (CDT), warm detection threshold (WDT), paradoxical heat sensation (PHS), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT) and pressure pain threshold (PPT).<sup>11,70</sup> These parameters can be measured intraorally and extraorally, and represent almost all sensory modalities. A z-transformation is performed to eliminate the different units used to describe the various parameters, allowing easy comparison. The DFNS protocol is currently used worldwide, and its reproducibility and reliability are considered sufficient for skin and intraoral measurements.<sup>43,71</sup> Some concerns have been raised regarding the different statistical methods used to assess test-retest reliability in QST research, and recommendations for future research have been suggested.<sup>72</sup>

### **Factors that influence QST**

Factors that influence the final QST results can be separated into intrinsic and extrinsic factors. The intrinsic factors are due to differences in somatosensory function. Extrinsic factors are those factors that influence the QST equipment and its application. Extrinsic factors and how they may influence QST results have been described above. In the next paragraphs, we will discuss intrinsic factors. The available QST data suggest that the face is the most sensitive region of the body.<sup>73</sup> Sensitivity decreases in the orofacial posterolateral direction, and gingival sensitivity is lower compared to the tongue and face.<sup>49,74,75</sup> Studies also report sex differences in various QST parameters, with women clearly having lower pain thresholds than men for most stimulus modalities.<sup>76,77</sup> QST seems to be influenced by age, but to only a limited degree in the face.<sup>23,78</sup> Ethnicity also plays a role in influencing QST.<sup>79</sup> Moreover, it is possible to modulate the trigeminal somatosensory function, such as in conditioned pain modulation.<sup>80</sup>

QST could be further influenced by treatments that our patients undergo. One randomized double-blinded controlled trial assessed the effect of low-level laser therapy (LLLT) on QST and pain ratings in patients undergoing orthodontic treatment. It was shown that patients treated with LLLT had lower pain ratings and higher CDT, WDT, CPT, HPT thresholds indicating a treatment effect that is measurable with QST.<sup>81</sup> In other fields, the effect of analgesics has

shown to affect QST results and vice versa QST may predict the analgesic response but more research will be needed to further substantiate these statements.<sup>82,83</sup>

Researchers have established normative reference values for the QST parameters assessed by the DFNS protocol, and have stratified the results according to age, sex and body region.<sup>73</sup> For the orofacial area, reference values are available for the second division of the trigeminal nerve (V2) and intraorally.<sup>43,73,74</sup> No normative datasets have been published for the ophthalmic and mandibular divisions of the trigeminal nerve, nor are there any normative intraoral datasets for the lingual, maxillary and inferior alveolar nerves, stratified according to age and sex. This lack of data limits the possibility of determining whether results deviate from the standard, and complicates clinical decision making, although some knowledge may be obtained by comparisons between an affected site and its mirror-image contralateral site. Moreover, only limited research has investigated other factors that may influence orofacial QST; therefore, conclusions must be extrapolated from data from other body regions. This could be problematic since the orofacial area has unique characteristics that must be considered when performing QST. Notably, the innervation density and fiber ratio shift from the forehead to the perioral tissues.<sup>84</sup> Intraoral QST can be difficult to obtain due to limited access, saliva may change stimulus transduction and complicate stimulus application, and tissue elasticities differ between test areas. For example, deep pressure pain thresholds are markedly lower at the tongue compared to a mucosal surface overlying the jaw bones.<sup>43</sup> Finally, it may be important to rethink the design of future clinical and experimental trials using intraoral QST as high variability between and within subjects at different levels needs to be accounted for and may substantially influence the required sample size.<sup>85</sup> Further research is needed to fill this knowledge gap, and overcome these issues.

### **Correlation with pathogenesis and severity**

QST can provide indirect insights into the underlying mechanisms of pathophysiology, as has been demonstrated for polyneuropathy, postherpetic neuralgia and post-traumatic nerve injuries.<sup>86</sup> In each of these pathologies, specific QST patterns are dominant, and may thus correlate with the underlying pathophysiology, which would allow easy differentiation between these entities.<sup>87</sup> A previous study identified a significant interaction between treatment with oxcarbazepine and the irritable or non-irritable phenotype, regardless of the cause.<sup>88</sup> This indicates that QST can play a role in elucidating the common pathophysiological pathways of diseases and in guiding treatment choices, thus supporting the field of personalized medicine.

To further investigate the correlation of QST with pathogenesis, we need a more thorough understanding of pathophysiology and disease progression, and of how QST results change over time. Patients undergoing orthognathic surgery may be a good clinical model for assessing longitudinal changes. These patients undergo elective surgery, which allows for baseline QST acquisition, and they often have a standardized follow-up protocol. Due to the position of the inferior alveolar nerve during a sagittal split osteotomy, most patients experience postsurgical neurosensory disturbances but typically recover in the following months.<sup>89</sup> In this setting, QST profiling, randomization and treatment effects could be analyzed and followed up. One study analyzed the correlation of intraoperative nerve damage with postoperative QST and electrophysiological findings, revealing a large variation in the sensitivity and specificity of the various modality test methods.<sup>60</sup> They suggested using a combination of nerve conduction study, touch detection thresholds and thermal QST to achieve adequate sensitivity and specificity. These results were confirmed in their more recent work.<sup>2</sup>

### **Current and future roles of QST in clinical decision making**

One randomized, double-blind, placebo-controlled trial evaluated the effects of oxcarbazepine in peripheral neuropathy patients with different sensory profiles, and reported the usefulness of stratifying patients into different profiles (in this case, irritable nociceptor versus non-irritable nociceptor phenotypes) rather than according to etiology (e.g., diabetic neuropathy versus posttherapeutic neuropathy).<sup>88</sup> Stratification by profiles yielded a lower number needed to treat and revealed a significant effect between treatment and phenotype. This indicates that cohorts in clinical trials should be stratified according to their baseline sensory profile rather than their underlying etiology, and potentially enriched with patients most likely to respond to study drugs.

To date, no such trials exist in the orofacial domain. A large number of patients experience orofacial pain, which can be the result of many pathologies, some of which are difficult to differentiate. Orofacial QST could play an important role in identifying populations that would benefit from a tested drug. However, no such interventional studies using orofacial QST have been published. We further wonder whether orofacial QST could be used to evaluate treatment effects over time and to identify whether the underlying pathophysiology is arrested. No published studies have assessed orofacial QST parameters as a follow-up tool in orofacial pain patients.

## **Longitudinal QST**

Orofacial QST is primarily used as a diagnostic tool. In healthy volunteers, QST has shown to be reliable over time.<sup>24</sup> A recent study in 22 healthy volunteers showed reliable QST results over a 10-week period, supporting the use of QST to assess changes over time in clinical trials.<sup>10</sup> Another study reported reliable QST results for touch and cold detection thresholds after orthognathic surgery at follow-up times of two weeks, three months and twelve months.<sup>90</sup> Moreover, the touch detection thresholds showed an excellent correlation with patient-reported subjective neurosensory disturbances. A multicenter study was conducted to assess the reliability of intra-oral QST in atypical odontalgia and healthy controls. Atypical odontalgia patients showed more QST abnormalities than the healthy controls, and the QST results had a good-to-excellent correlation with QualST. Additionally, the authors reported fair-to-excellent interrater and intrarater observations and test-retest reliability.<sup>74,91</sup> Finally, another study assessed only one modality, and demonstrated that QST was reliable within and between patients.<sup>47</sup> More research is needed to assess orofacial QST in measuring treatment response or disease.

## **Practical issues**

The most frequently mentioned problem with QST is the assessment duration.<sup>6</sup> To assess one extraoral area and compare it with the contralateral side, the investigator and patient must spend about one hour on testing, depending on their understanding of the tasks and the need for a break. Intraoral testing entails a more difficult application and necessitates allowing jaw relaxation or swallowing between the tests such that this assessment takes about 1.5 hours. This is cumbersome and limits QST implementation in routine clinical practice.

Several studies have assessed the correlation between QualST and QST, looking for a means of obtaining reliable results more quickly. One study compared QualST and QST in patients undergoing local anesthetic blocks, and found that both assessment methods correctly indicated sensory loss at the infraorbital and mental nerve at several time-points after block administration compared with saline injection.<sup>92</sup> However, QualST did not detect a significant difference between ten minutes and two hours after block anesthesia, whereas QST revealed a return towards normal baseline stimulus perception at the two-hours interval. Notably, other studies have shown glaring discrepancies between QualST and QST results.<sup>2,60,93,94</sup> Most studies report that qualitative (clinical) sensory testing has a high specificity and a low

sensitivity.<sup>2,93</sup> This indicates that these tests could be useful in the clinical setting to assist in making a differential diagnosis and can be performed to exclude the presence of neurosensory disturbances. Thus, QualST could be used as an initial screening tool to indicate whether further QST testing is required. Others nuance these findings and report moderate correlation between QST and QualST.<sup>74</sup> This indicates that more research may be needed to develop better or combined QualST methods and to compare these with QST to assess the usefulness in healthy and pathological cohorts. A combination of some QST parameters such as thermal and mechanical thresholds with other methods such as neurography could have an additional benefit on test duration.<sup>2</sup> Until now, we could not find any reports that charted this time aspect.

### **Alternative diagnostic tools**

Few published studies have compared QST with other diagnostic methods. One previously mentioned investigation compared some QST modalities with nerve conduction studies (NCS) of the inferior alveolar nerve, reporting that NCS showed a higher sensitivity compared to QST or QualST.<sup>2</sup> Additionally, one study evaluated QualST with magnetic resonance neurography in 42 patients with nerve injury after molar extraction. The results showed that nerve caliber and signal intensity measured on MRI were moderately-to-well correlated with clinical sensory testing performed using spatial, tactile, thermal and pain thresholding.<sup>95</sup> Imaging could potentially play a more important role in the diagnosis of orofacial neuropathies in the future, but currently, only functional MRI and diffusion tensor imaging studies can provide functional information about neurophysiology and abnormalities.<sup>96</sup> Additionally, the trigeminal nerve has a very difficult trajectory, with a broad distribution of thin fibers surrounded by an extensive vasculature, complicating radiographic evaluation. Susceptibility artifacts may further complicate the assessment.<sup>97</sup> Further studies should compare QST and imaging findings, to determine their roles in clinical decision making.

## **Conclusion**

Evidence concerning orofacial QST and its diagnostic value has markedly increased over recent years, demonstrating that QST is a reliable method for assessing neurosensory function under normal and pathological conditions. Translation of QST to clinical practice remains challenging due to several factors, and additional research is needed to enable differentiation between pathological entities. Integration of the entire QST battery, or the use of some QST parameters

combined with other diagnostic tools, could further increase accuracy and support QST implementation in routine practice.

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# SECTION 2



prediction and outcome



## CHAPTER 3

### Patient-reported versus clinician-reported measures

*This chapter is based on the following manuscript:*

Meewis J, Renton T, Jacobs R, Politis C, **Van der Cruyssen F.** Post-traumatic trigeminal neuropathy: correlation between objective and subjective assessments and a prediction model for neurosensory recovery. *J Headache Pain.* 2021;22(1):44.

# **Abstract**

## **Introduction**

Post-traumatic trigeminal neuropathy (PTN) can have a substantial effect on patient well-being. However, the relation between the neuropathic symptoms and their effect on psychosocial functioning remains a matter of debate. The purpose of this study was to evaluate the association between objective and subjective assessments of neurosensory function in PTN and predict neurosensory outcome using baseline measurements.

## **Methods**

This prospective observational cohort study included patients diagnosed with PTN at the Department of Oral and Maxillofacial Surgery, University Hospital Leuven, Belgium, between April 2018 and May 2020. Standardized objective and subjective neurosensory examinations were recorded simultaneously on multiple occasions during the follow-up period. Correlation analyses and principal component analysis were conducted, and a prediction model of neurosensory recovery was developed.

## **Results**

Quality of life correlated significantly ( $P < 0.05$ ) with percentage of affected dermatome ( $\rho = -0.35$ ), the presence of brush stroke allodynia ( $\rho = -0.24$ ), gain-of-function sensory phenotype ( $\rho = -0.41$ ), Medical Research Council Scale ( $\rho = 0.36$ ), and Sunderland classification ( $\rho = -0.21$ ). Quality of life was not significantly correlated ( $P > 0.05$ ) with directional discrimination, stimulus localization, two-point discrimination, or sensory loss-of-function. The prediction model showed a negative predictive value for neurosensory recovery after six months of 87%.

## **Conclusions**

We found a strong correlation of subjective well-being with the presence of brush stroke allodynia, thermal and/or mechanical hyperesthesia, and the size of the neuropathic area. These results suggest that positive symptoms dominate the effect on affect. In patients reporting poor subjective well-being in the absence of positive symptoms or a large neuropathic area, additional attention towards psychosocial triggers might enhance treatment outcome. The prediction model could contribute to establishing realistic expectations about the likelihood of neurosensory recovery but remains to be validated in future studies.

## Introduction

Post-traumatic trigeminal neuropathy (PTN) is a well-known complication in the oral and maxillofacial field.<sup>1</sup> Many procedures may lead to iatrogenic lesions of the trigeminal nerve, and 45%–70% of PTN arises from the removal of third molars.<sup>2,3</sup> Other procedures include local anesthetic injection, dental implant surgery, endodontic treatment, and several other interventions.<sup>3–12</sup> There is a dominant representation of lingual nerve (LN) and inferior alveolar nerve (IAN) injuries, accounting for up to 90% of all cases of PTN.<sup>2,3,13</sup> In major maxillofacial or tumor ablation surgery, these injuries are often a calculated risk. However, in all other cases, the postoperative presence of permanent neurosensory impairment is unexpected. Fortunately, 90% of these injuries are temporary and subside within eight weeks.<sup>4,7</sup>

Nevertheless, PTN can interfere with a wide variety of social functions and daily activities such as eating and drinking, shaving, kissing, tooth brushing, and applying make-up.<sup>13</sup> In addition, PTN can lead to a substantial psychosocial and affective burden, particularly in patients who experience severe neuropathic pain as part of the condition.<sup>14</sup> In these cases, the more specific term “post-traumatic trigeminal neuropathic pain” is used, as described in the recently introduced International Classification of Orofacial Pain (ICOP) criteria.<sup>1</sup> In our study, we use the umbrella term PTN to describe either a painful or a non-painful PTN. Robert et al. reported that 78% of oral and maxillofacial surgeons will be involved in one or more cases of permanent IAN injury and 46% in one or more instances of permanent LN injury over their practice lifetimes.<sup>15</sup> Therefore, every oral and maxillofacial surgeon should understand the proper prevention, prediction, and management of PTN because failing to do so can lead to significant patient distress and often trigger litigation.<sup>16,17</sup>

To date, consensus is lacking regarding which therapy or timing is best. Different surgical procedures have been applied with varying success.<sup>18,19</sup> A reintervention carries the risk of escalating neuropathic symptoms, and the consequence is that 33% of patients decline reparative surgery when offered.<sup>20</sup> In addition, patients with PTN have mixed responses to medications, which all have significant side effects. Therefore, the outcome of PTN treatment is largely disappointing, leaving both patient and doctor frustrated. All interventions are targeted to improving quality of life through pain reduction, sensory improvement, functional recovery, the development of efficient coping strategies, or a combination of these. Some patients show limited symptoms yet still report a poor quality of life, whereas others experience a relatively high degree of physical impairment but seem to cope well.

Although reports have described objective neurosensory functioning and subjective well-being in PTN, few studies have evaluated the correlation between these objective and subjective measurements. Here, we sought to answer the following three questions: Is there a correlation between the objective and subjective measurements? Which of these objective measurements has the greatest correlation with subjective well-being? Can we predict neurosensory outcome using baseline measurements?

## Methods

This study is reported in accordance with the EQUATOR guidelines (Enhancing the Quality and Transparency of Health Research) and STROBE agreement (Strengthening the Reporting of Observational Studies in Epidemiology). Ethical approval was obtained from the Ethics Committee of the University Hospital Leuven (S61077, B322201835541). It was performed in accordance with Good Clinical Practice standards and the Declaration of Helsinki.

### Patient selection

This prospective observational study included 46 patients (16 men, 30 women) who were diagnosed with PTN at the Department of Oral and Maxillofacial Surgery, University Hospital Leuven, Belgium, between April 2018 and May 2020. Whenever ICOP<sup>1</sup> diagnostic criteria for PTN were met, patients were seen for a neurosensory consultation at our department by one investigator (FVDC). After patients gave informed consent, baseline and follow-up for both objective and subjective assessment of neurosensory function were performed by FVDC, as described below. Case-wise deletion was used to ensure a true correlation matrix.

### Data collection

#### *Objective assessment*

Neurosensory testing started with delineating and photographing the neuropathic zone. With this approach, both the patient and practitioner can review the digital photograph, which can then be added to the patient's file. We used this image to describe a percentage of the affected dermatome as well as to visualize its evolution. For this purpose, the reverse end of an anesthetic needle was moved across the surface from the unaffected to affected area.<sup>21,22</sup> Then, two-point discrimination, stimulus localization, and directional discrimination were examined using a light brush technique, along with response to hot and cold stimuli, all based on previously described methods.<sup>3,21,23,24</sup> When applicable, the presence of brush stroke allodynia was noted

separately. A Medical Research Council Scale (MRCS) score for sensory recovery (**Supplemental Table S1**)<sup>25</sup> was recorded, and a Sunderland clinical rating scale was used (Miloro modification, **Supplemental Figure S1**). Based on these findings, a code for sensory phenotype was assigned to each individual. All codes consist of a letter L (loss-of-function or sensory deficit) and a letter G (gain-of-function or hyperesthesia), followed by number 0 (none), 1 (thermal), 2 (mechanical), or 3 (mixed). For example, L3G0 indicated a patient with mixed sensory loss and no mechanical or thermal hyperesthesia. Depending on the indication, quantitative sensory testing was performed according to the German Research Network on Neuropathic Pain protocol<sup>26,27</sup>, as well as magnetic resonance neurography (MRN), according to the institutional protocol.<sup>28</sup>

#### *Subjective assessment*

Subjective measurements consisted of several questionnaires completed during each follow-up visit or afterwards by mail or telephone. These questionnaires are the EuroQol five-dimension scale (EQ5D-5L), General Anxiety Disorder 7 (GAD-7), Patient Health Questionnaires (PHQ) 9 and 15, Douleur Neuropathique 4 (DN4), and the Brief Pain Inventory (BPI). Pain was assessed on a visual analogue scale (VAS; ranging from 0 to 100).

The EQ5D-5 L assesses five domains on a five-point ordinary scale. The domains are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A score of 0 indicates no problems at all in a domain, 1 indicates slight problems, 2 suggests moderate problems, 3 indicates severe problems, and 4 indicates extreme problems. Patients self-rated their health on the VAS from 0 (worst) to 100 (best health they could imagine).

The PHQ-9 questionnaire consists of nine questions about the severity of depressive complaints based on the DSM-IV criteria. Each question is scored from 0 (not at all) to 3 (almost daily), resulting in a total score of 0 to 27 points. Score ranges are 0–4 for no/minimal depression, 5–9 for mild depression, 10–14 for moderate depression, 15–19 for moderately severe depression, and 20 or greater for severe depression.

Symptoms of anxiety were assessed using the GAD-7 questionnaire. The score is calculated in the same way as the PHQ-9 questionnaire, using response scores of 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day), which are added together for the seven questions. Cutoffs are a score of 5 for mild anxiety, 10 for moderate anxiety, and 15 for severe anxiety.

The PHQ-15 is a self-administered version of the PRIME-MD diagnostic used for the detection of patients at risk for somatoform disorders. The PHQ-15 covers 15 somatic symptoms of the

PHQ, with each one scored from 0 (no symptoms of ... at all) to 2 (a lot of symptoms of ...). Cutoffs are scores of 5 for low somatic symptom severity, 10 for medium severity, and 15 for high severity.

Pain quality was assessed using the seven yes/no questions of the DN4. Patients were asked if the pain had the characteristics of burning, painful cold, or electrical shocks and whether the pain was accompanied by a tingling, stinging, numbness, or itching sensation in the same area. A point is given for every positive answer (maximum, 7 points), and a score of 3 or greater supports a diagnosis of neuropathic pain.

Pain intensity and pain interference in activity were assessed using the BPI questionnaire, measuring pain intensity in four categories (worst, least, on average, currently) and pain interference in six categories (general activity, mood, ability to walk, normal work, social interaction, joy in life). Each category is rated on a scale from 0 to 10, with 10 indicating complete interference in the respondent's life.

Patients were asked to score their current subjective function, ranging from 0 (complete anesthesia) to 20 (20 for the worst pain imaginable). A score of 10 indicates normal function and no deficit.

Secondary study variables collected for each patient were demographic data, signs and symptoms of the neuropathic sensation, and type of procedure associated with the injury. Possible injuries were local anesthesia, third molar removal, (ortho)gnathic surgery, implant placement, endodontic treatment, facial trauma, nonwisdom tooth extraction, or other. Additional information gathered included site of injury (branch and side) in the trigeminal distribution area, elapsed time since the traumatic event, preferred imaging modalities, selected therapy, whether or not a diagnostic test (quantitative sensory testing or MRN) was performed, and whether or not the result of any such tests affected established policy.

## **Statistical analysis**

All data were assessed by a certified statistician using Rstatistics version 4.0.3 (The R-Foundation for Statistical Computing). Descriptive statistics were used to compare demographic data with the neurosensory test findings. Univariate relations between variables were assessed with the Pearson correlation coefficient, except when at least one of the variables was categorical. In those cases, the Spearman rank correlation coefficient was used. Principal component analysis for binary and categorical data was applied. Biplots were drawn using the loadings and scores from the principal component analysis with respect to the first two principal

components. A stepwise model selection for the generalized linear model for binary data using a logit link was applied to find the combination of variables with the best relation to recovery status after six months.

## Results

In this prospective cohort study, from April 2018 to May 2020, 46 patients were diagnosed with PTN at our department. Nine of these patients were excluded because of missing data, and one patient declined informed consent. The remaining group of 36 patients consisted of 23 women and 13 men, with a mean age of 42 years (SD 12.5, range 23–68). Patient characteristics are shown in **Supplemental Table S2**. Almost all patients were referred by an oral and maxillofacial surgery specialist ( $n = 32$ ; 89%). The remaining four patients were referred by an external dentist.

The mean duration of injury to initial clinical examination was 210 days (SD 289, range 3–1073). The average follow-up period was 566 days (SD 218, range 149–865), with an average of six follow-up visits during which objective and subjective assessments were repeated (range 3–8). In total, 199 neurosensory consultations were held.

Distribution of cases by mechanism of injury identified third molar removal as the most common, in 47% of patients ( $n = 17$ ), followed by 11% each for implant placement and facial trauma (each,  $n = 4$ ), 8% for local anesthesia ( $n = 3$ ), and 6% for non-wisdom tooth extraction and endodontic treatment ( $n = 2$ ). A total of 14% of cases were classified as “other” ( $n = 5$ ) (**Supplemental Figure S2**).

The IAN was affected in 23 patients (64%), the LN in 10 (28%), the maxillary nerve in 7 (19%), and the ophthalmic nerve in one (3%). Right-sided PTN was present in 19 patients (53%), and 17 patients reported left-sided PTN (47%). No cases of bilateral involvement were detected.

Quantitative sensory tests were performed in five patients. Of seven patients in whom magnetic resonance imaging was performed, findings for five of them resulted in a change in management, including surgical reintervention in three. Microsurgery was performed in seven cases (19%). Surgical treatment was always exploratory in nature and consisted of external neurolysis, internal neurolysis, neurorrhaphy, and/or neuroma excision. No interpositional grafts were used in this series.

## **Objective assessments**

Mean percentage of affected dermatome was 91% (SD 21%) at baseline. At final follow-up, the mean percentage of affected dermatome decreased to 40% (SD 46%). In 11 patients (31%), the area remained identical to baseline findings, and in 16 patients (44%), neurosensory tests could no longer define an affected area. In this last group, it took an average of 253 days (median 187, SD 200) until the neuropathic zone could no longer be demarcated.

Initial two-point discrimination showed an average of 14 mm (SD 7 mm) for the affected side and 6 mm (SD 3 mm) for the unaffected side. These measurements evolved to an average final two-point discrimination of 8 mm (SD 5 mm) for the affected side in the total study population. Nine patients (25%) had an uncompromised two-point discrimination at baseline. In patients whose two-point discrimination for the affected side reached values identical to the unaffected side, the average time to that outcome was 227 days.

Eleven patients (31%) had brush stroke allodynia on initial presentation. During the follow-up period, 15 patients (42%) presented with brush stroke allodynia at least once. At the final follow-up, brush stroke allodynia remained present in five patients (14%), among whom three had it at the initial presentation and two developed it and experienced its persistence afterwards.

Stimulus localization was completely absent in 11 patients (31%) at time of initial measurements, whereas in 18 patients (50%), stimulus localization was unimpaired at baseline. At final follow-up, however, 28 patients (78%) had values similar to those in healthy individuals, with an average time to this outcome of 70 days (SD 53). Eight patients (22%) continued to experience a suboptimal ability to locate a stimulus.

Directional discrimination showed a similar pattern: It was absent in 10 patients (28%), and 18 patients (50%) had no impairment at baseline. A total of 29 patients (81%) reached optimal final follow-up values in 81 days, on average (SD 102). Seven patients with PTN could not perfectly discriminate direction of movement at the end of the evaluation period.

Baseline and follow-up MRCS and Sunderland scores are shown in **Supplemental Figure S3** and **Supplemental Figure S4** respectively. At baseline, the MRCS score was S0 for five patients, S2 for one patient, S2+ for ten patients, S3 for eight patients, and S3+ for 11. One patient had a baseline MRCS score of 4. Upon study completion, 23 patients (64%) showed

complete recovery (S4), seven had a score of S3+, and for one, the score was S3, for a total of eight additional patients (22%) with limited negative clinical symptoms and no residual overresponse to stimuli. The remaining five patients (14%) did not experience recovery beyond S2+ and thus continued to have positive symptomatology.

Distribution by Sunderland classification showed unimpaired level A testing (group I) in 10 patients (28%) at baseline and mildly impaired contact detection (level B testing; group II) in five patients (14%). Level C testing revealed a moderately impaired pain sensitivity in five patients (14%, group III), severely impaired in 11 patients (31%, group IV), and complete anesthesia in five patients (14%, group V). Upon study completion, 25 patients (69%) were classified into group I, 3 patients (8%) into group II, and 2 (6%) into group III, and 6 (17%) remained in group IV.

Distribution by sensory phenotype is shown in **Supplemental Figure S5**. Most patients began with mixed sensory loss (22 patients; 61%) and absence of hyperesthesia (19 patients; 53%). Isolated mechanical hypoesthesia was seen in 9 (25%) patients, and one patient (3%) had thermal hypoesthesia. Five patients (14%) had isolated mechanical hyperesthesia, and one (3%) had thermal hyperesthesia. Four patients (11%) showed no negative symptoms, and eleven (31%) had mixed positive symptoms at the initial presentation.

### **Subjective assessments**

The most reported symptom was numbness in 31 cases (86%), followed by pain in 16 cases (44%) and stinging pain in 11 (31%). Nagging, burning, sensitive, and swollen sensations were all described by 10 patients (27%). A stinging or pulling sensation was each reported by seven patients (19% each), and an electrical or tickling sensation was each mentioned by six patients (17% each) (**Supplemental Table S2**).

Mean QoL increased from 59/100 to 72/100 during the study period. In patients with pain as their main complaint, mean baseline Pain-VAS was 46/100 (SD 27), and mean QoL was 52/100 (SD 20). At the final follow-up, mean pain on the VAS in this group was 26/100 (SD 37), and mean QoL was 69/100 (SD 16). On initial presentation, 8 of 13 men (62%) reported pain, whereas only 8 of 23 women (35%) did so. For painful PTN, women had a mean baseline Pain-VAS of 33/100 (SD 21) and an increased final VAS score of 41/100 (SD 44). In contrast, men with painful PTN started with a mean VAS score of 57/100 (SD 28) and ended with a VAS of 15/100 (SD 28). Women with painful PTN had a mean QoL of 50/100 (SD 24) at the initial

visit, which increased to 64/ 100 (SD 20). Men with painful PTN went from an average QoL of 54 (SD 17) to 74 (SD 13).

GAD-7 questionnaires revealed a baseline absence of anxiety in 16 patients (44%), mild anxiety in 15 patients (42%), moderate anxiety in one patient (3%), and severe anxiety in 4 patients (11%). At final follow-up, the group without anxiety increased to 22 patients (61%), mild anxiety decreased to 8 patients (22%), moderate anxiety ended with 2 patients (5%), and severe anxiety with 3 patients (8%). Three of the four patients with severe anxiety at baseline still had severe anxiety at the last follow-up. The fourth patient had moderate anxiety at the final follow-up, but with complete resolution of the neurosensory disturbances.

Results for the PHQ-9 questionnaires showed no depression in 12 individuals (33%) at initial measurement, mild depression in 15 patients (42%), moderate depression in 5 patients (14%), moderately severe depression in 2 (6%), and severe depression in 2 (6%). At the end of the study, the group without depression had grown to 20 patients (56%), mild depression had decreased to 8 patients, (22%), and moderate depression to one patient (3%). The number of patients with moderately severe depression increased to three (8%), and the number with severe depression increased to four patients (11%).

At the initial diagnosis, somatic severity of symptoms (PHQ-15) was absent in 13 (36%), low in 8 (22%), medium in 11 (31%), and high in 4 (11%) patients. After the follow-up period, symptoms were absent in 18 (50%), low in 9 (25%), medium in 7 (19%), and high in 2 (6%).

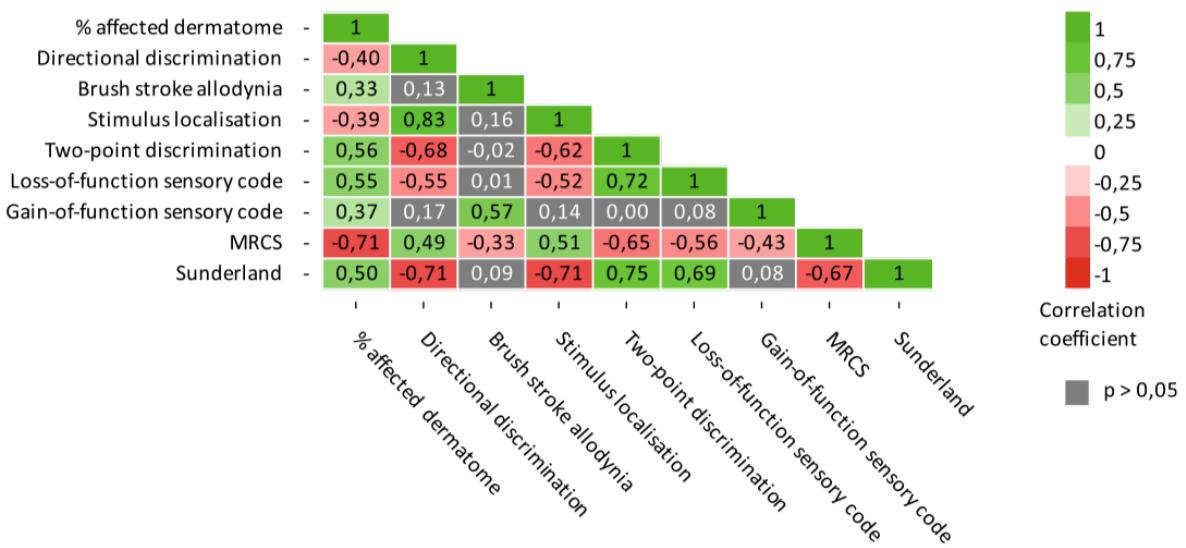
The total study population scored an average of 3/7 on the DN4 questionnaire at baseline. This value decreased over time to an average of 1/7 at the final follow-up.

Self-perceived subjective functioning is shown in **Supplemental Figure S6**. At baseline, 23 patients reported neurosensory loss as a primary burden, whereas 13 patients reported that their impaired functioning was mainly caused by pain complaints or other positive symptoms. As the study progressed, recurring questions concerning self-perceived functioning revealed similar trends in time and magnitude towards normal functioning, with a small number of outliers represented on both sides who did not experience a return to self-perceived normal functioning.

## Correlations

### Objective measurements

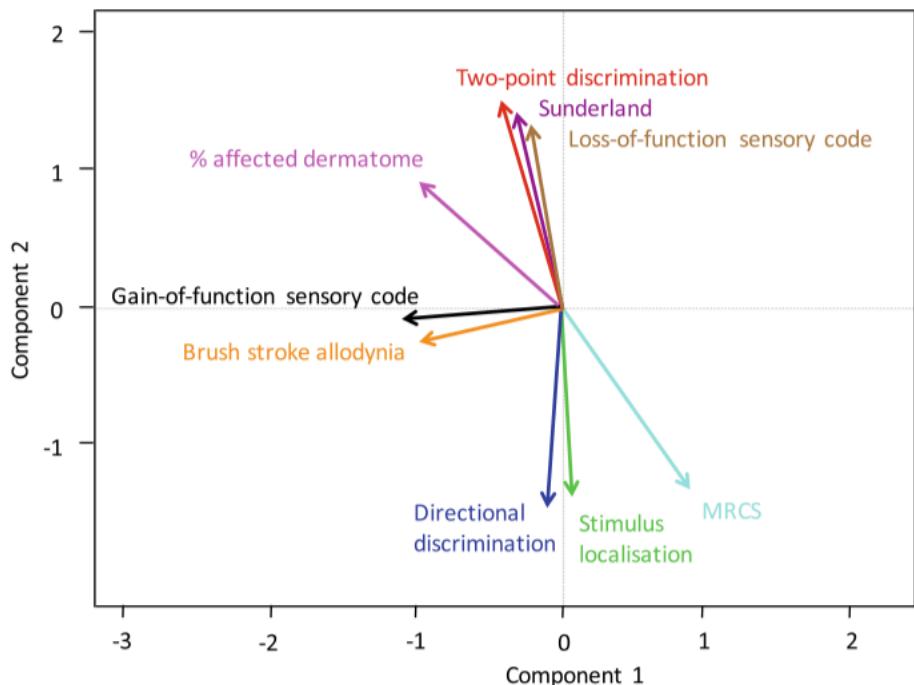
Correlations between all objective measurements are shown in **Figure 1**.



*Figure 1. Correlation between objective neurosensory measurements. Correlation coefficients of significant positive correlations ( $P < 0.05$ ) are shown in green. Correlation coefficients of significant negative correlations ( $P < 0.05$ ) are shown in red. Non-significant correlations ( $P < 0.05$ ) are displayed in grey. Neurosensory tests consisted of percentage of affected dermatome, directional discrimination, the presence of brush stroke allodynia, stimulus localization, two-point discrimination, sensory phenotype loss- and gain-of-function, MRCS, and Sunderland score.*

This figure shows that most of the objective neurosensory measurements were statistically significantly ( $P < 0.05$ ) correlated with each other. A very strong positive correlation was seen between stimulus localization and directional discrimination ( $\rho = 0.83$ ), between loss-of-function sensory code and two-point discrimination ( $\rho = 0.72$ ), and between two-point discrimination and the Sunderland score ( $\rho = 0.75$ ). A very strong negative correlation was seen between MRCS score and percentage of affected dermatome ( $\rho = -0.71$ ), directional discrimination and Sunderland ( $\rho = -0.71$ ), and stimulus localization and Sunderland ( $\rho = 0.71$ ). Brush stroke allodynia and gain-of-function sensory code correlated significantly ( $P < 0.05$ ) only with percentage of affected dermatome, MRCS score, and each other.

Biplots were drawn using the loadings and scores from the principal component analysis. A biplot of all objective measurements is shown in **Figure 2**.



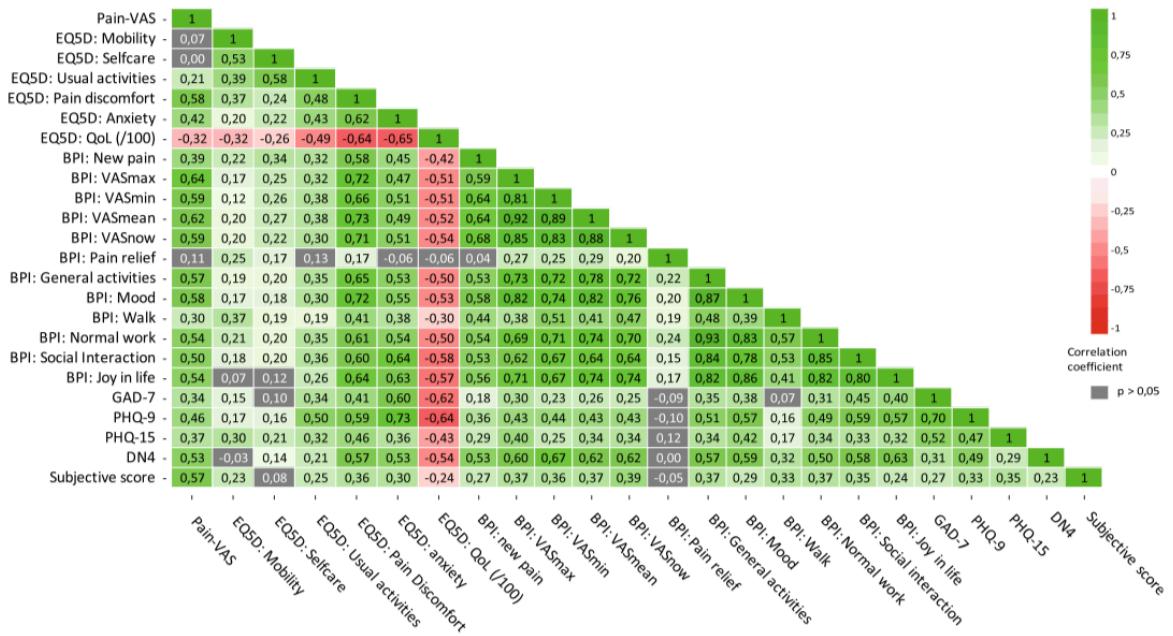
*Figure 2. Biplot of objective neurosensory measurements. An acute angle indicates a positive correlation. A 90-degree angle indicates no correlation between the two variables, and an obtuse angle indicates a negative correlation. The more similar the direction of two vectors, the stronger the correlation between these variables. This biplot shows a strong correlation between two-point discrimination, Sunderland score, loss-of-function sensory code and percentage of affected dermatome. Also, directional discrimination, stimulus localization, and MRCS score show a strong correlation. Gain-of-function sensory code and brush stroke allodynia show a strong correlation with each other but are far less correlated with the other variables.*

The orientation of the vectors relative to each other illustrates their correlation to one another. An acute angle between the different measurements indicates a positive correlation. A 90-degree angle implies no correlation between the two variables, and an obtuse angle signifies a negative correlation. The more similar the direction of two vectors, the stronger the correlation between the neurosensory tests. **Figure 2** shows that a higher two-point discrimination, Sunderland score, and loss-of-function sensory code were strongly correlated with each other and with the percentage of affected dermatome. Their vectors almost look like the mirror image of directional discrimination, stimulus localization, and MRCS score, indicating a strong

negative correlation for these factors. Gain-of-function sensory code and brush stroke allodynia showed a strong correlation with each other but were far less correlated with the other variables.

### Subjective measurements

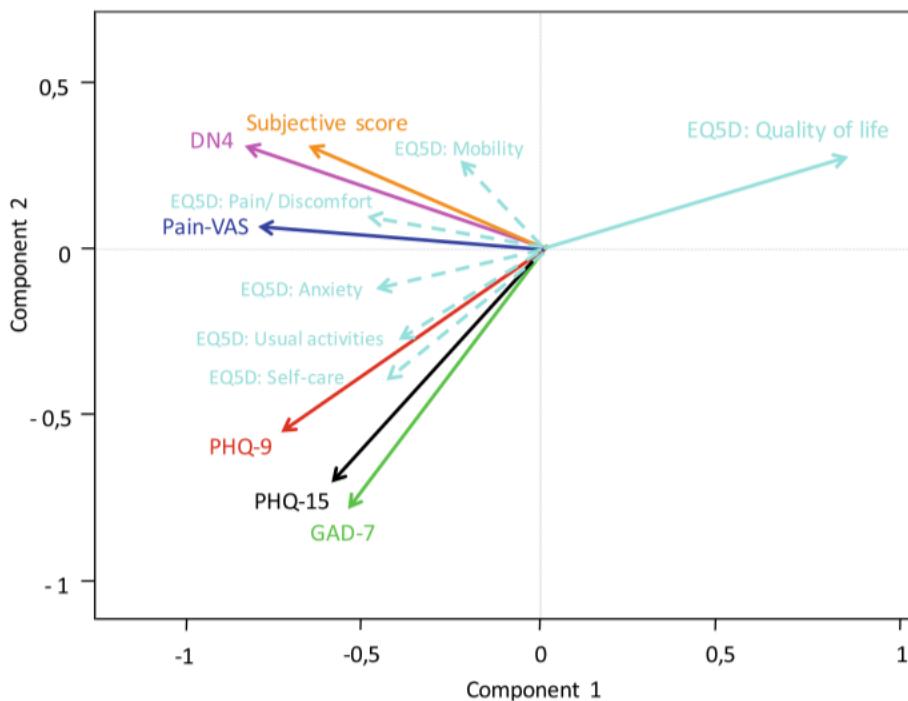
Correlations between all subjective measurements are shown in **Figure 3**.



**Figure 3. Correlation between subjective neurosensory measurements. Correlation coefficients for significant positive correlations ( $P < 0.05$ ) are shown in green. Correlation coefficients for significant negative correlations ( $P < 0.05$ ) are shown in red. Non-significant correlations ( $P > 0.05$ ) are displayed in grey. The questionnaires were the pain visual analogue score (VAS) score, the EuroQol five-dimension scale (EQ5D-5 L), Brief Pain Inventory (BPI), General Anxiety Disorder 7 (GAD-7), Patient Health Questionnaire 9 and 15 (PHQ-9 and PHQ-15), Douleur Neuropathique 4 (DN4), and subjective functioning. This figure shows that most of the questionnaires were statistically significantly correlated with each other e.g. PainVAS correlated significantly with GAD-7, PHQ-9, PHQ-15, DN4, subjective score, and quality of life (EQ5D:QoL). Also, Quality of life showed a significant negative correlation (in red) with most questionnaire scores. GAD-7 and PHQ-9 showed the strongest negative correlation with quality of life.**

As the figure indicates, most of the subjective neurosensory measurements were statistically significantly ( $P < 0.05$ ) correlated with one another. Pain VAS correlated significantly with GAD-7, PHQ-9, PHQ15, DN4, subjective score, and QoL. Also, results of the following

questionnaires correlated with each other on a statistically significant level: GAD-7 with PHQ-9, PHQ15, DN4, and subjective score; PHQ-9 with PHQ-15, DN4, and subjective score; PHQ-15 with DN4 and subjective score; and DN4 with subjective score. There was a statistically significant negative correlation between quality of life and GAD-7, PHQ-9, PHQ-15, DN4, and subjective score. Thus, a higher score on one of these questionnaires was generally associated with lower self-perceived quality of life, and the scores for PHQ-9 and GAD-7 showed the strongest correlation with quality of life. Pain relief (BPI) using a prescribed drug regimen correlated statistically significantly with EQ5D-5L scores for pain discomfort, mobility, and self-care and with VAS max, VAS min, VAS mean, and VAS now, but not with the other questionnaires. A biplot of all subjective measurements is shown in **Figure 4**.



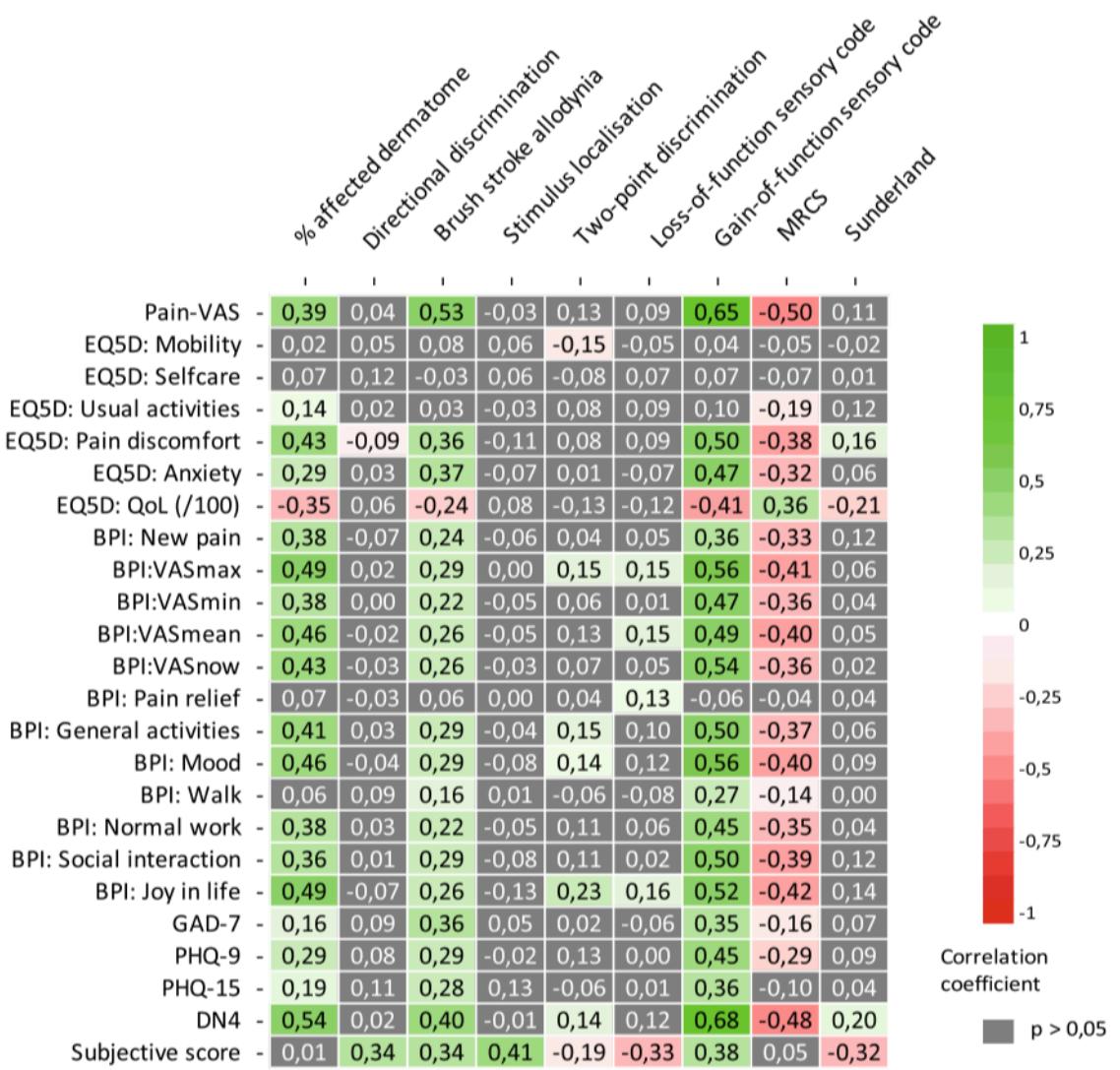
*Figure 4. Biplot of subjective neurosensory measurements. The more similar the direction of two vectors, the stronger the correlation between these variables. A strong positive correlation suggests that the two questionnaires offer virtually the same information. This figure shows a negative correlation between quality of life and all other questionnaires. There is a strong positive correlation between Pain-VAS, DN4, and subjective score, as well as between PHQ-9, PHQ-15, and GAD-7 scores. Also, concerning the correlation between the individual questions for each questionnaire, those of the EQ5D-5 L scale were the least correlated with one another. However, these individual questions did correlate significantly with the other categorically related questionnaires, e.g., EQ5D-Pain correlated with DN4 and Pain-VAS, and EQ5D-*

*Anxiety correlated with GAD-7 and PHQ-9 and -15. Therefore, the EQ5D-5 L can act as good screening questionnaire for assessing a patient's subjective well-being.*

The more similar the direction of two vectors, the stronger the correlation between the different questionnaires. A strong positive correlation suggests that the two questionnaires offered virtually the same information. Quality of life was negatively correlated with all other questionnaires. Pain-VAS, DN4, and subjective score project in similar directions toward the upper left quadrant, indicating a strong positive correlation among these measurements. The PHQ-9, PHQ-15, and GAD-7 questionnaire scores all project in similar directions toward the lower left quadrant, indicating a strong positive correlation among them. Also, concerning the correlation between the individual questions for each questionnaire, those of the EQ5D-5 L scale were the least correlated with one another and show the greatest scatter over the quadrants on the biplot. However, these individual subscales did correlate significantly with the other categorically related questionnaires, e.g., EQ5D-Pain correlated with DN4 and Pain-VAS, and EQ5D-Anxiety correlated with GAD-7 and PHQ-9 and -15. Therefore, these subscales of the EQ5D-5 L can act as good screenings for assessing a patient's subjective well-being.

#### *Objective and subjective measurements*

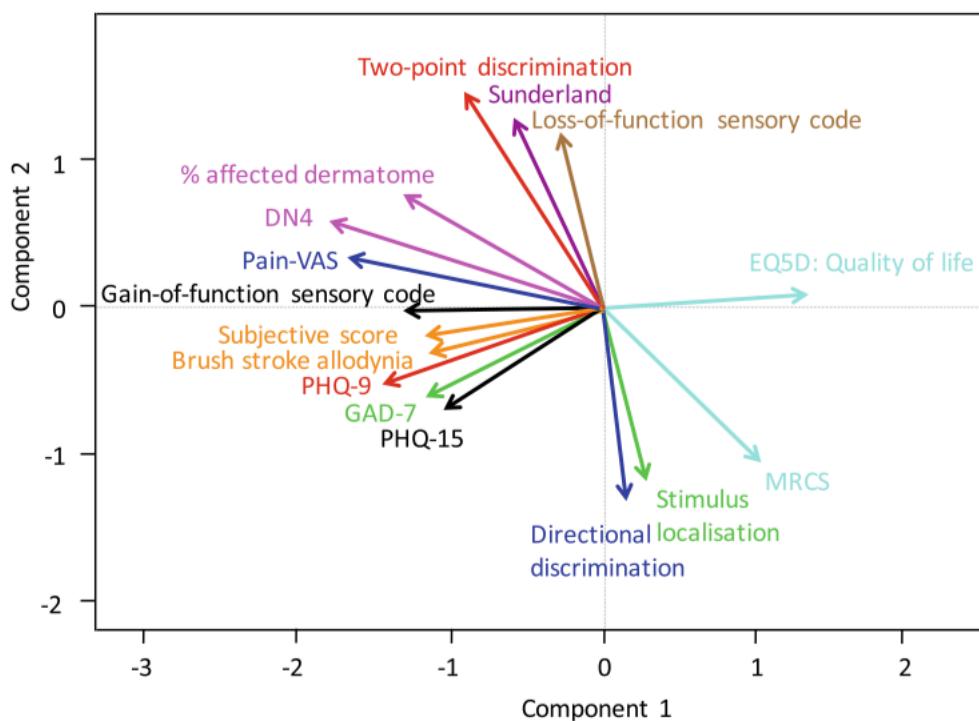
Correlations between all objective and subjective measurements are shown in **Figure 5**.



*Figure 5. Correlation between objective (columns) and subjective (rows) neurosensory measurements. Correlation coefficients for significant positive correlations ( $P < 0.05$ ) are shown in green. Correlation coefficients of significant negative correlations ( $P < 0.05$ ) are shown in red. Non-significant correlations ( $P > 0.05$ ) are shown in grey. This figure shows a pattern where generally the size of the affected area, the presence of brush stroke allodynia, and positive symptoms correlated with the different questionnaire scores e.g. Quality of life (EQ5D-QoL) correlated significantly with percentage of affected dermatome, brush stroke allodynia, gain-of-function sensory code, MRCS, and Sunderland. Pain-VAS, GAD-7, and PHQ-9 each correlate significantly with percentage of affected dermatome, brush stroke allodynia, gain-of-function sensory code, and MRCS. PHQ-15 correlated significantly with percentage of affected dermatome, brush stroke allodynia, and gain-of-function sensory code, but not with MRCS. The DN4 scores showed a significant correlation with percentage of affected dermatome, brush stroke allodynia, two-point discrimination, gain-of-function sensory code, MRCS, and Sunderland.*

As the figure shows, most of the objective neurosensory measurements did not correlate ( $P < 0.05$ ) with the subjective questionnaires. Quality of life, however, correlated significantly with percentage of affected dermatome, the presence of brush stroke allodynia, gain-of-function sensory code, MRCS, and Sunderland. Quality of life did not correlate significantly with directional discrimination, stimulus localization, two-point discrimination, or loss-of-function sensory code. Pain-VAS, GAD-7, and PHQ-9 each correlated significantly with percentage of affected dermatome, brush stroke allodynia, gain-of-function sensory code, and MRCS. PHQ-15 correlated significantly with percentage of affected dermatome, brush stroke allodynia, and gain-of-function sensory code, but not with MRCS. The DN4 scores showed a significant correlation with percentage of affected dermatome, brush stroke allodynia, two-point discrimination, gain-of function sensory code, MRCS, and Sunderland. The pattern is generally that the size of the affected area, presence of brush stroke allodynia, and positive symptoms correlated with the different questionnaire scores.

A biplot of all objective and subjective measurements is shown in **Figure 6**.



*Figure 6. Biplot of all objective and subjective neurosensory measurements. An acute angle indicates a positive correlation. A 90-degree angle indicates no correlation between the two variables, and an obtuse angle indicates a negative correlation. There was a negative correlation of quality of life with gain-of-function sensory code, brush stroke allodynia, and*

*percentage of affected dermatome. In addition, the other questionnaire scores (PHQ-15, GAD-7, PHQ-9, subjective score, Pain-VAS, and DN4) correlated positively with sensory gain-of-function, brush stroke allodynia, and percentage of affected dermatome. Little to no correlation was identified between the different questionnaire scores and the objective measurements of stimulus localization, directional discrimination, two-point discrimination, Sunderland score, and sensory loss-of-function.*

As noted, the more similar the direction of two vectors, the stronger the correlation between the variables. Quality of life negatively correlated with gain-of-function sensory code, brush stroke allodynia, and percentage of affected dermatome. In addition, the other questionnaire scores (PHQ-15, GAD-7, PHQ-9, subjective score, Pain-VAS, and DN4) positively correlated with gain-of-function sensory code, brush stroke allodynia, and percentage of affected dermatome. A poor to no correlation was found for each of the questionnaire scores and the objective measurements of stimulus localization, directional discrimination, two-point discrimination, Sunderland score, and loss-of-function sensory code.

### Prediction model

A prediction model for neurosensory recovery after six months of follow-up was constructed using baseline measurements and in accordance with the TRIPOD statement. Criteria used to define near-to-complete recovery are shown in **Supplemental Table S3**. All criteria had to have been checked to qualify for a status of near-to-complete recovery. Details of the prediction model after six months are shown in **Table 1**.

*Table 1. Prediction model for neurosensory recovery in PTN after six months.*

Variable	Coefficient	Confidence interval
Intercept	3.4109	-1.4975; 8.3192
Pain-VAS	0.048	0.0079; 0.088
Percentage affected dermatome	-0.0316	-0.071; 0.0078
Sensory code: gain	-1.1032	-2.3562; 0.1499
Two-point discrimination (affected side)	-0.1708	-0.4153; 0.0737

For the model, values for Pain-VAS (0–100), percentage of affected dermatome (0%–100%), gain-of-function sensory code (0–3), and two-point discrimination of the affected side (in mm) were multiplied by their corresponding coefficient. Then, these values were summed, and the intercept value was added to the total sum. If the result was greater than or equal to zero, the

model predicted that the PTN will have resolved at six months. If the value was negative, the model predicted no PTN resolution after six months. The power of this association is illustrated in **Table 2**. When the model predicted no recovery after six months, chances of no recovery were high, for a negative predictive value of 87%. However, when the result was positive and thus predicted near-to full recovery at six months, the positive predictive value was only 60%. Model sensitivity was 43%, and specificity was 93%.

*Table 2. Power of the prediction model for neurosensory recovery in PTN after six months. The model shows a negative predictive value of 87% and a positive predictive value of 60%.*

	Predicted recovery: no	Predicted recovery: yes
Recovery: no	27	2
Recovery: yes	4	3

## Discussion

This study sought to answer the following three questions: Is there a correlation between the objective and subjective measurements? Which of these objective measurements has the greatest correlation with subjective well-being? Can we predict neurosensory outcome using baseline measurements? We evaluated the correlation between clinical neurosensory tests and subjective questionnaires in patients with PTN who were followed and treated at the Department of Oral and Maxillofacial Surgery, University Hospital Leuven, during a two-year period. Both types of information were collected simultaneously on multiple occasions during an average follow-up of 566 days.

Demographics of the study population (age, sex, cause of injury, affected division of trigeminal nerve, etc.) are similar to what others have described previously<sup>2,8,10,14,22,26,29,30</sup> and discussing these findings as such would be beyond the scope of this paper. Similarly, the evolution of separate clinical neurosensory tests or individual subjective assessments would likely interest only researchers evaluating specific interventions in PTN. We do want to mention, however, the difficulty of objectively declaring a clinical neurosensory examination as “improved” given that improvement might be of little value for the patient, and identical clinical examinations could even be perceived differently. Furthermore, in the process of neurosensory recovery, positive symptomatology can arise, leaving the patient in a potentially worse situation. It is

therefore important that we understand the correlation between these clinical neurosensory tests and the patient's subjective well-being.

### **Correlation analysis**

We found a statistically significant correlation ( $P < 0.05$ ) between subjective well-being and some aspects of the clinical neurosensory evaluation. When neuropathy presented with brush stroke allodynia, mechanical or thermal hyperesthesia, or a large zone size, the effect on the patient's subjective well-being is expected to be substantial. In contrast, limited two-point discrimination, inability to determine direction of movement or locate a stimulus in a compromised dermatome were not significantly correlated with self-assessed well-being. Although both positive and negative symptomatology can co-exist in PTN, these results do suggest that positive symptoms dominate the effect on affect.

Only a handful of studies have compared the relation between objective and subjective data in PTN. Pogrel found that semi-objective assessment of patients does not always correspond with the patient's subjective evaluation.<sup>31</sup> Shintani et al. found no evidence of an association between subjective and objective symptoms after lingual nerve repair.<sup>32</sup> In contrast, Susarla et al. described a strong correlation in this regard.<sup>33</sup> In their study, patients who experienced greater neurosensory improvement reported lower frequencies of related oral dysfunction.

Furthermore, higher scores for pain-VAS, subjective functioning, GAD-7, PHQ-9, PHQ-15, and the DN4 questionnaire all correlated significantly with a poorer quality of life and with one another in the current work. These results are in accordance with past observations of an association of depression and anxiety with somatic symptoms<sup>34-36</sup> and more severe pain with elevated levels of depression, pain catastrophizing, and reduced quality of life and coping efficacy levels.<sup>14,23</sup>

This also suggests that the routine use of multiple validated questionnaires in daily practice provides little additional information in comparison to using only one or two questionnaires to assess patient subjective well-being. We found the EQ5D-5 L scale to be the most clinically useful because it is short and its individual questions each provide mainly new information.

Nevertheless, managing PTN requires a holistic approach with sufficient attention to psychosocial well-being. It is the combination of environmental, psychosocial, and genetic

factors that cause identical injuries to produce a large variability in PTN.<sup>37–39</sup> In addition, improvement on qualitative sensory testing cannot be viewed as successful if the patient is still suffering from other debilitating symptoms.<sup>18</sup> Furthermore, in patients reporting poor subjective well-being in the absence of positive symptoms or a large neuropathic area, additional attention towards psychosocial triggers might enhance treatment outcome.

### **Prediction model**

To our knowledge, this study is the first to propose a clinical prediction model using baseline clinical neurosensory test values to give an indication of expected neurosensory recovery in patients with PTN. A negative predictive value of 87% for six months of follow-up was found. The positive predictive value of the model was quite limited, however. Whether this model can be validated in future studies remains to be seen, but if so, it could contribute to establishing realistic expectations about the likelihood of neurosensory recovery.

### **Limitations**

The study was conducted at a single referral center. Also, case-wise deletion excluded nine patients because of missing data. Furthermore, observer bias is possible because only one observer (FVDC) saw all patients. This bias is, however, somewhat controlled by the standardized protocol that was used. Similar studies can be performed in larger samples or other referral centers to evaluate the validity of the prediction model and the observed correlations.

## **Conclusion**

We found a statistically significant correlation between subjective well-being and brush stroke allodynia, mechanical or thermal hyperesthesia, and the size of the neuropathic area in patients with PTN. No significant correlation was found for two-point discrimination, directional discrimination, stimulus localization, or sensory loss-of-function phenotype.

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## Supplemental data

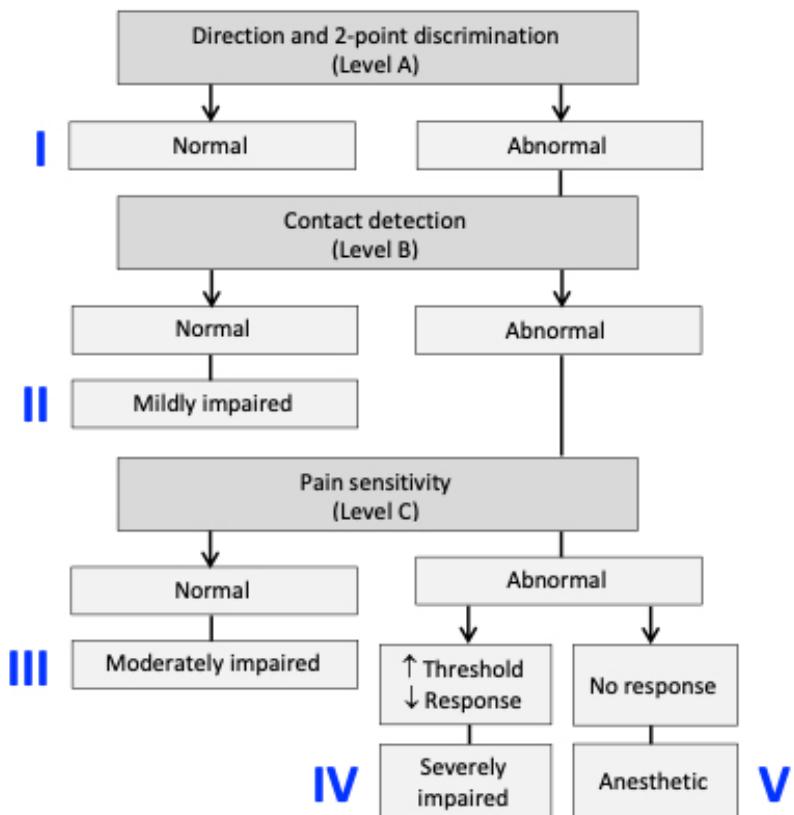


Figure S1. Sunderland Clinical classification system (Miloro Modification).

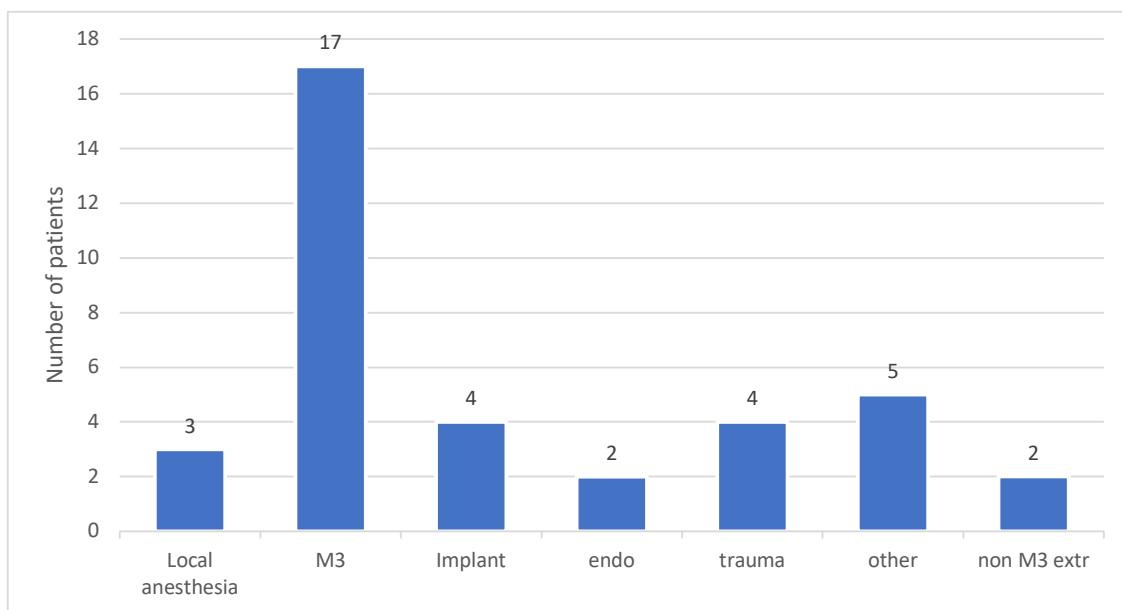
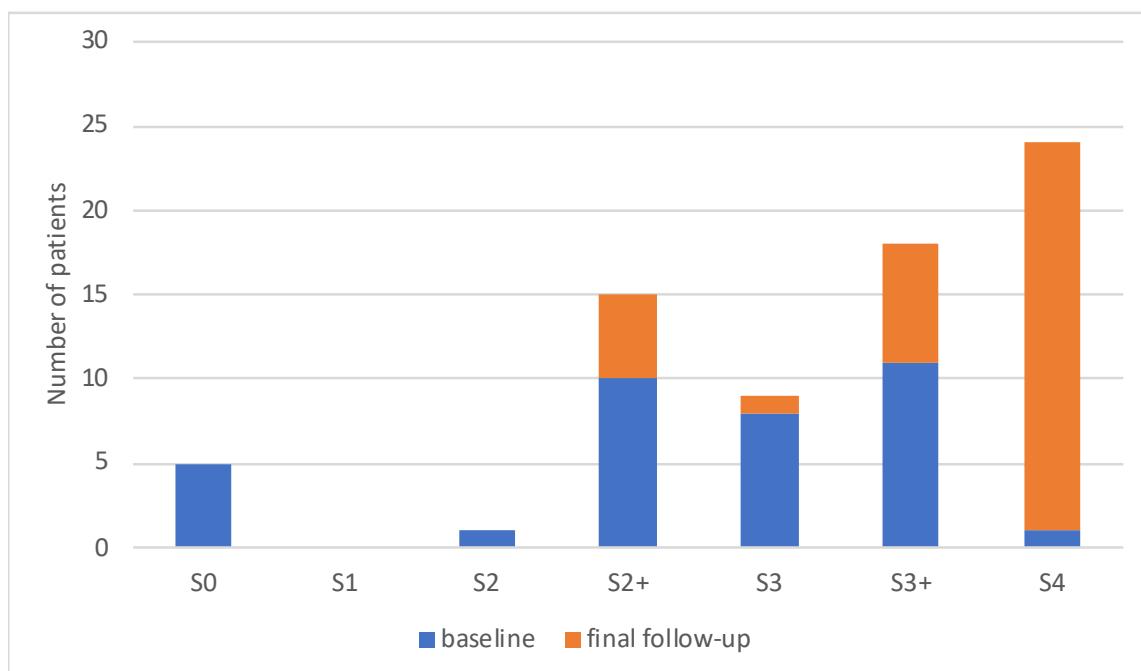
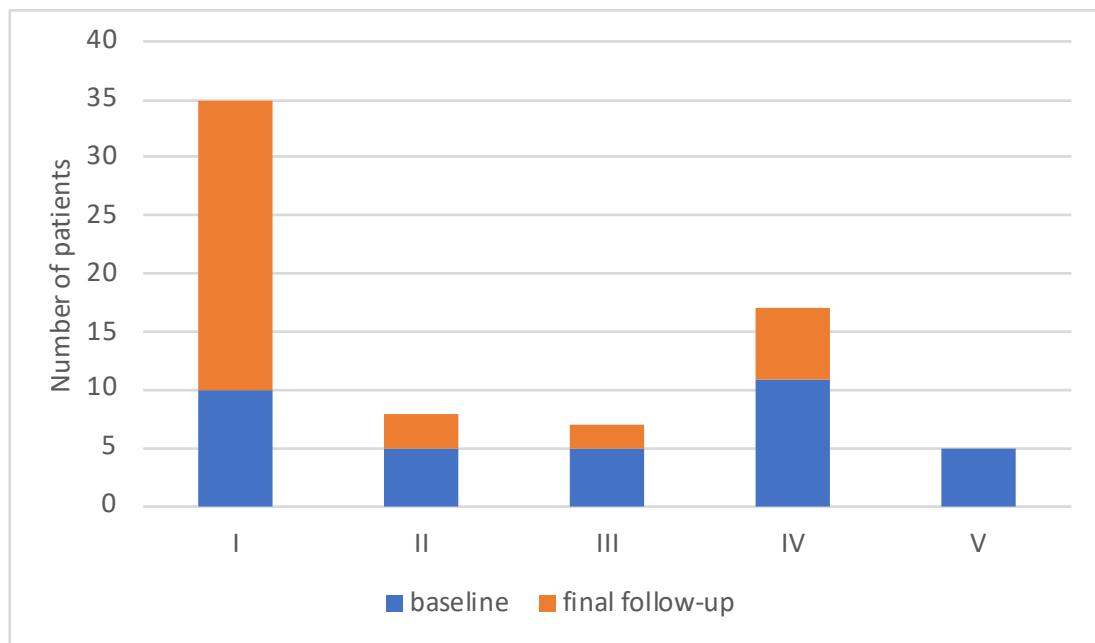


Figure S2. Distribution of PTN cases by mechanism of injury.

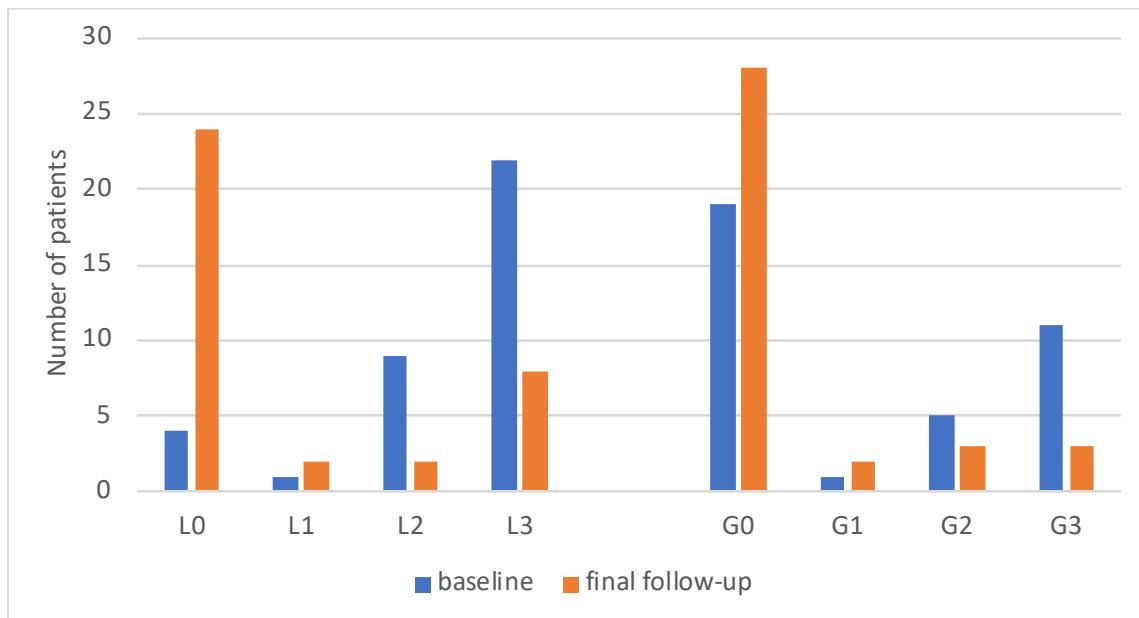


*Figure S3. Distribution of PTN cases by MRCS-score at baseline vs. at final follow-up moment.*

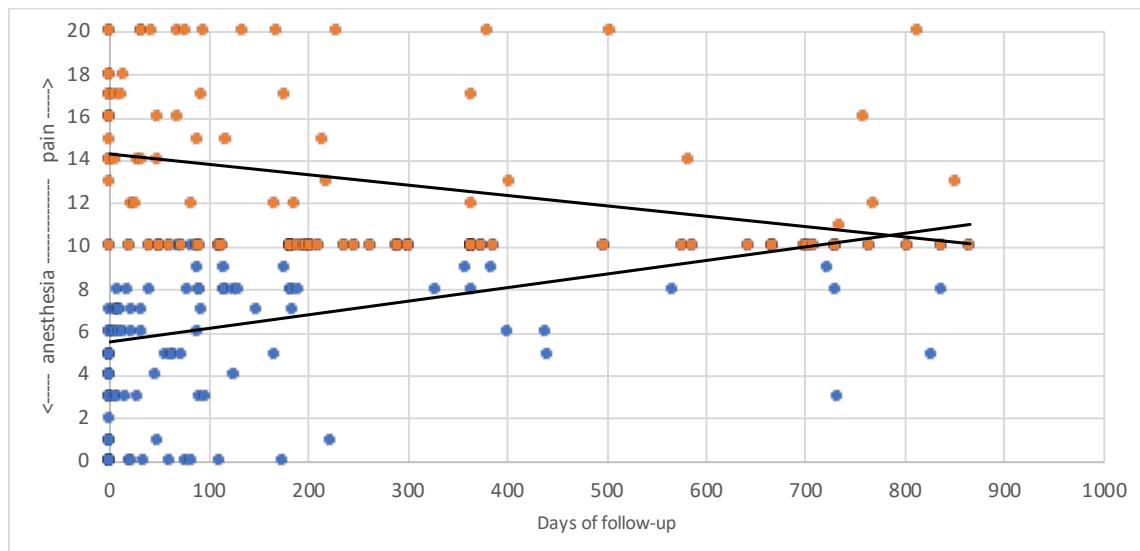
*S0 = Absence of sensibility in the autonomous area of the nerve. S1 = Recovery of deep cutaneous pain and tactile sensibility. S1+ = Recovery of superficial pain sensibility. S2 = Recovery of some degree of superficial cutaneous pain and tactile sensibility. S2+ = as in S2, but with overresponse. S3 = Return of pain and tactile sensibility with disappearance of overresponse, static 2PD>15mm, moving 2PD>7mm. S3+ = Return of sensibility as in S3 with some recovery of two-point discrimination, static 2PD: 7-15mm, moving 2PD: 4-7mm. S4 = complete recovery, static 2PD: 2-6mm, moving 2PD: 2-3mm.*



*Figure S4. Distribution of PTN cases by Sunderland Clinical classification score at baseline vs. at final follow-up moment.*



*Figure S5. Distribution of PTN cases by sensory phenotype at baseline vs at final follow-up. A code for sensory phenotype was assigned to each individual. All codes consist of a letter L (Loss of function or sensory deficit) and a letter G (Gain of function or hyperesthesia), followed by number 0 (none), 1 (thermal), 2 (mechanical) or 3 (mixed). For example, L3G0 stands for a patient with mixed sensory loss and no mechanical or thermal hyperesthesia.*



*Figure S6: Evolution of subjective functioning in PTN. Patients were asked to score their current subjective function, ranging from 0 (complete anesthesia) to 20 (20 for the worst pain imaginable). A score of 10 would mean a normal function and no deficit. This figure shows trends for both positive and negative symptoms evolve in the same direction towards self-perceived normal functioning. A small group of outliers fail to return to this undisrupted state.*

*Table S1. Medical Research Council Scale for sensory recovery. s2PD: static two-point discrimination; m2PD: moving two-point discrimination.*

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S0: Absence of sensibility in the autonomous area of the nerve
S1: Recovery of deep cutaneous pain and tactile sensibility
S1+: Recovery of superficial pain sensibility
S2: Recovery of some degree of superficial cutaneous pain and tactile sensibility
S2+: As in S2, but with overresponse
S3: Return of pain and tactile sensibility with disappearance of overresponse, s2PD>15mm, m2PD>7mm
S3+: Return of sensibility as in S3 with some recovery of 2-point discrimination, s2PD: 7-15mm, m2PD: 4-7mm
S4: Complete recovery, s2PD: 2-6mm, m2PD: 2-3mm

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*Table S2. Patient characteristics.*

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Total	n	36
Age	Years (SD, range)	42 (12.5, 23-68)
Gender	23 female	13 male
Time since injury	Days (SD, range)	210 (289, 3-1073)
Follow-up period		566 (218, 149-865)
		<b>n (%)</b>
Mechanism of injury	Third molar removal	17 (47)
	Implant placement	4 (11)
	Facial trauma	4 (11)
	Local anesthesia	3 (8)
	Non-wisdom tooth extraction	2 (6)
	Endodontic treatment	2 (6)
	Other	5 (14)
Site of injury	Inferior alveolar nerve	23 (64)
	Lingual nerve	10 (28)
	Maxillary nerve	7 (19)
	Ophthalmic nerve	1 (3)
	Right-sided PTN	19 (53)
	Left-sided PTN	17(47)
QST	Total	5 (14)
Surgical reintervention	Total	7 (19)
	Buccal fat wrapping	5 (14)
	Microsurgical repair	2 (6)
	Decompression	2 (6)
	Neuroma excision	2 (6)
	Foreign body removal	1 (3)
MRN	Total	7 (19)
	Lead to change of policy	5 (71)
	Lead to surgical reintervention	3 (43)

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Reported symptoms	Numbness		31 (86)	
	Pain		16 (44)	
	Stinging pain		11 (31)	
	Nagging		10 (28)	
	Burning		10 (28)	
	Sensitive		10 (28)	
	Swollen		10 (28)	
	Stinging		7 (19)	
	Pulling		7 (19)	
	Electrical		6 (17)	
	Tickling		6 (17)	
<b>Neurosensory assessment</b>			<b>Baseline</b>	<b>Final follow-up</b>
Percentage of affected dermatome		% (SD)	91 (21)	40 (46)
Two-point discrimination		mm (SD)	14 (7)	8 (5)
Stimulus localization		/5 (SD)	3 (1)	4 (2)
Directional discrimination		/10 (SD)	6 (3)	9 (3)
Brush stroke allodynia		n (%)	11 (31)	5 (14)
MRCS	S0	n (%)	5 (14)	0 (0)
	S1		0 (0)	0 (0)
	S2		1 (3)	0 (0)
	S2+		10 (28)	5 (14)
	S3		8 (22)	1 (3)
	S3+		11 (31)	7 (19)
	S4		1 (3)	23 (64)
Sunderland	V	n (%)	5 (14)	0 (0)
	IV		11 (31)	6 (17)
	III		5 (14)	2 (6)
	II		5 (14)	3 (8)
	I		10 (28)	25 (69)
Sensory phenotype	Loss of function	L0	n (%)	4 (11)
		L1		1 (3)
		L2		9 (25)
		L3		22 (61)
	Gain of function	G0	n (%)	19 (53)
		G1		1 (3)
		G2		5 (14)
		G3		11 (31)
Pain (pain-VAS)		/100 (SD)	20 (26)	13 (25)
Quality of life (EQ5D)	Mobility	≥ 3/5, %	1 (3)	1 (3)
	Selfcare		0 (0)	0 (0)
	Daily activities		3 (8)	0 (0)
	Discomfort		5 (14)	3 (8)

	Anxiety		1 (3)	0 (0)
	VAS Quality of Life	/100 (SD)	59 (18)	72 (22)
Anxiety (GAD-7)	Severe	n (%)	7 (11)	3 (8%)
	Moderate		1 (3)	2 (5)
	Mild		15 (42)	8 (22)
Depression (PHQ-9)	Severe	n (%)	2 (6)	4 (11)
	Moderately severe		2 (6)	3 (8)
	Moderate		5 (14)	1 (3)
	Mild		15 (42)	8 (22)
Somatic severity of symptoms (PHQ-15)	High	n (%)	4 (11)	2 (6)
	Medium		11 (31)	7 (19)
	Low		8 (22)	9 (25)
Neuropathic pain (DN4)		≥ 3/7, %	18 (50)	10 (28)
BPI	Pain severity	Worst pain in past 24h	≥ 3/10, %	22 (61)
		Least pain in past 24h		12 (33)
		Average pain		21 (58)
		Pain now		17 (47)
Pain medication			Number of prescriptions	
	Corticosteroids		27	
	Vitamin B IM		26	
	Vitamin B per os		28	
	Acetaminophen		6	
	Ibuprofen		21	
	Amitriptyline		4	
	Baclofen		1	
	Pregabalin		4	
	Oxcarbazepine		1	
	Carbamazepine		2	
	Duloxetine		1	
	other		2	
	Percentage of relief provided in past 24h (SD)		41 (40)	28 (41)
Pain interference	General activities	≥ 3/10, %	17 (47)	7 (19)
	Mood		15 (42)	9 (25)
	Walking ability		8 (19)	2 (6)
	Normal Tasks		14 (39)	9 (25)
	Social interaction		12 (33)	5 (14)
	Joy in life		15 (42)	8 (22)
Subjective score (SD)			8 (4)	10 (5)

QST = quantitative sensory tests; MRN = magnetic resonance imaging; MRCS = Medical research council scale for sensory recovery; EQ5D = EuroQol five-dimension scale; GAD-7 = General Anxiety Disorder questionnaire; PHQ-9 & PHQ-15 = Public Health questionnaire 9 and 15; DN4 = Douleur Neuropathique 4 questionnaire

*Table S3. Criteria for near to complete neurosensory recovery.*

<b>Variable</b>	<b>Criterion</b>
% affected dermatome	$\leq 10\%$
VAS	$\leq 10/100$
Directional discrimination	$\geq 9/10$
Brush stroke allodynia	0
Stimulus localization	$\geq 4/5$
Two-point discrimination (affected - control side)	$\leq 3\text{mm}$
Sensory phenotype Loss of function	0
Sensory phenotype Gain of function	0
MRCS	S3+ or S4
Sunderland	I or II

\*All criteria must be checked in order to qualify for a status of near to complete recovery.



# CHAPTER 4

## Predicting the outcome

*This chapter is based on the following manuscript:*

**Van der Cruyssen F, Peeters F, De Laat A, Jacobs R, Politis C, Renton T.** Prognostic factors, symptom evolution, and quality of life of post-traumatic trigeminal neuropathy. *Pain*. 2022;163(4):e557-e571.

## **Abstract**

Neurosensory disturbances (NSDs) caused by injury to the trigeminal nerve can affect many aspects of daily life. However, factors affecting the persistence of NSDs in patients with post-traumatic trigeminal neuropathies (PTNs) remain largely unknown. The identification of such risk factors will allow for the phenotyping of patients with PTNs, which is crucial for improving treatment strategies. We therefore aimed to identify the prognostic factors of NSD persistence, pain intensity, and quality of life (QoL) in patients with PTNs and to use these factors to create a prognostic prediction model. We first performed a bivariate analysis using retrospective longitudinal data from 384 patients with NSDs related to post-traumatic injury of the trigeminal nerve (mean follow-up time:  $322 \pm 302$  weeks). Bivariate and multivariate analyses were performed. The multivariable prediction model to predict persistent NSDs was able to identify 76.9% of patients with persistent NSDs, with an excellent level of discrimination (area under the receiver operating characteristic curve: 0.84; sensitivity: 81.8%; specificity: 70.0%). Furthermore, neurosensory recovery was significantly associated with sex; injury caused by local anesthesia, extraction, third molar surgery, or endodontic treatment; and the presence of thermal hyperesthesia. Pain intensity and QoL analysis revealed several factors associated with higher pain levels and poorer QoL. Together, our findings may aid in predicting patient prognosis after dental, oral, and maxillofacial surgery and might lead to personalized treatment options and improved patient outcomes.

## Introduction

The trigeminal nerve has the largest representation in the human sensory cortex, reflecting the disproportionate sensory input that comes from the orofacial region. The reception of sensory input from trigeminal dermatomes protects vital processes that underpin our survival.<sup>1</sup> Pain in the trigeminal nerve area interferes with eating, speaking, sleeping, applying makeup, shaving, kissing, tooth brushing, and drinking—just about every daily routine that we take for granted. As a result, this has a significant negative effect on patients’ self-image, quality of life, and psychology.<sup>2</sup> Renton et al. reported that 36% of patients with post-traumatic trigeminal neuropathic pain (PTNP) show signs of depression, and a similar proportion of patients have a clinically significant anxiety level.<sup>3,4</sup> Apart from patient morbidity, there is also a societal and economic burden caused by reduced labor force participation and absenteeism.<sup>5</sup>

Post-traumatic neuropathies can be painful or non-painful and are an increasingly recognized post-surgical issue for patients.<sup>6</sup> In the orofacial region, these conditions have been defined by the International Classification of Orofacial Pain (ICOP), which is endorsed by both the International Headache Society (IHS) and the International Association for the Study of Pain (IASP).<sup>7</sup> PTNP may arise after injury to the sensory nerves. It can cause sensory abnormalities associated with hyposensitivity and/or hypersensitivity, with allodynia and hyperalgesia. When no neuropathic area is evident, patients may fit the criteria of chronic post-surgical pain (CPSP). This is a well-recognized complication after routine surgery, with significant rates of pain affecting patients who have undergone limb amputation, breast surgery, thoracotomy, and cardiac surgery.<sup>6</sup> However, questions remain as to whether CPSP and PTNP are different phenotypes of the same condition.<sup>8</sup>

Risk factors for CPSP are well established and include both patient- and surgery-related factors.<sup>9</sup> To date, there is limited evidence regarding the presentation and outcome of patients with post-traumatic trigeminal neuropathies (PTN), and potential prognostic predictors have not been thoroughly investigated.<sup>10,11</sup> Likely predictors for chronification can be identified in the preoperative, intraoperative, and postoperative periods, and cover six broad domains: genetic, demographic, psychosocial, pain, clinical, and surgical factors.<sup>12,13</sup> Most studies have focused on the preoperative risk factors of trigeminal neurosensory disturbances (NSDs).<sup>14–17</sup> The identification of these risk factors is important because they may allow the phenotyping of patients in the future. This phenotyping is crucial if we wish to improve treatment outcomes.<sup>18</sup> As yet, there have been no large longitudinal studies investigating the outcomes of post-traumatic trigeminal nerve injuries. Furthermore, prognostic prediction models are lacking.

The aim of this study was to identify prognostic factors in PTN patients by running a multivariable analysis based on the retrospective longitudinal data of a large patient cohort from a tertiary referral center in Belgium (University Hospitals Leuven), and to build a prognostic prediction model using these data. We aimed to determine if and when neurosensory disturbances persist, and how symptoms evolve over time. Also, we aimed to predict quality of life (QoL) and compare clinical features, pain quality and characteristics between low and high pain intensity cohorts.

## Methods

### Source of data

The data used in this study originated from the TrigNerveBeUK (TNVBUK) registry. The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855). The study was conducted according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.<sup>19</sup> Data was retrieved from patient charts at Department of Oral and Maxillofacial Surgery and the Orofacial Pain Clinic between October 2018 and January 2019.

### Patient selection

The charts of patient visiting between January 2010 and October 2018 were screened for post-traumatic (including iatrogenic) injury to branches of the trigeminal nerve. No age restrictions were made. Inclusion criteria were as follows: presentation with a post-traumatic injury of the trigeminal nerve or its branches, and a clinical neurological diagnosis of a neurosensory deficit in the distribution of the trigeminal nerve according to previously described methods<sup>1</sup>, which are summarized below. Patients were excluded if the deficit presented in a region outside of the innervation zone of the trigeminal nerve, or if the follow-up time was less than three months. Patients diagnosed with neurosensory disturbances (NSD) after orthognathic surgery were excluded. Orthognathic surgery patients are tracked in a different care pathway at the authors' clinic. Including these patients would result in introducing selection bias.

### Clinical assessment method

The neuro-assessment protocol was conducted according to previously reported algorithms<sup>20,21</sup> and included qualitative sensory testing by mapping the neurosensory deficit over the affected dermatome using blunt forceps (intraorally and/or extraorally, depending upon the affected

nerve). This was done using a running needle technique from normal towards neuropathic area. The patient was asked to raise their hand as soon as the sensation was not perceived normal. The borders were marked with a pen to allow the next assessments to be conducted within the neuropathic area versus the contralateral side. In case of bilateral involvement, the adjacent dermatome served as control. Light touch assessment was performed using a cotton bud (to assess subjective function and the presence of mechanical allodynia) and sharp/blunt discrimination by using a dental probe (to assess mechanical hyperalgesia and hyperpathia). Each stimulus was presented five times and two scores out of five were noted if the patient correctly identified the presence of light touch and discriminated correctly between sharp or blunt. It was noted if mechanical allodynia or hyperalgesia were present. Two-point discrimination to assess mechanoperception was conducted using a staircase method of levels starting with closed calipers and stepwise increasing separation of one millimeter until a reliable level was reached. If a thermal component (hot or cold allodynia or hyperalgesia) was described, this was also recorded. In addition, hyperesthesia (allodynia, hyperalgesia, and hyperpathia) or hypoesthesia (reduced sensation or anesthesia) were recorded. An NSD was defined as abnormal according to the algorithm proposed by Miloro.<sup>20</sup> This meant an abnormal or absent response to any of the conducted sensory tests compared to the contralateral side or the adjacent trigeminal dermatome in case of bilateral involvement. Two-point discrimination was considered abnormal if it exceeded 15 millimetres.<sup>22</sup> Neuropathic pain was diagnosed in accordance with a study by Finnerup et al.<sup>23</sup>

Patients were categorized into painful PTNP and non-painful PTN groups based on the recent ICOP criteria for PTNP.<sup>7</sup> Non-painful PTN patients fulfilled all ICOP criteria except criterium A: pain, in a neuroanatomically plausible area within the trigeminal distribution.

Based on the symptoms reported during history taking and the clinical findings, including qualitative neurosensory testing, patients were further stratified into the following sensory profiles: sensory loss, thermal hyperalgesia or allodynia (hereafter referred to as “thermal hyperesthesia”), mechanical hyperalgesia or allodynia (hereafter referred to as “mechanical hyperesthesia”), and combinations (hereafter referred to as “mixed”).

## Predictors

Preoperative predictor variables included age, gender, and smoker status. The number of other pain diagnoses in a patient’s history was considered a separate variable.

Perioperative variables included the different affected trigeminal nerve branches (the inferior alveolar nerve, the maxillary nerve or its infraorbital and superior alveolar terminal branches,

or the lingual nerve) and the initiating event (local anesthesia, third molar surgery, tooth extraction, endodontic treatment, or dental implant placement).

Postoperative variables were the duration of symptoms (constant or intermittent), presence of pain (yes/no), pain visual analog scale (VAS) score (Likert scale ranging from 0 to 10, with 0 meaning no pain and 10 meaning the most severe pain imaginable), sensory profile (sensory loss, thermal hyperesthesia, mechanical hyperesthesia, or mixed). Only treatments initiated for their condition were considered, and these were further categorized into any treatment (yes/no), systemic (yes/no), topical (yes/no), and surgical (yes/no). Finally, quality of life was assessed at the end of the follow-up period using the EQ5D-5L questionnaire, which considers five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a 5-point ordinal scale (0: no problems; 1: slight problems; 2: moderate problems; 3: severe problems; 4: extreme problems). These domains were dichotomized into no problems (score 0) and any problems (scores 1 to 4). Patients also indicated their self-rated health on a VAS, from 0 (worst) to 100 (the best health they could imagine).

### **Prediction models of outcome variables**

Three regression models were constructed. First, time to complete symptom resolution was predicted. For this outcome, the duration of symptoms (in weeks) since the initiating event was calculated. Patients who continued to experience NSD three months post-surgery were considered to have persistent NSD; if not, they were considered to have temporary NSD, as suggested by the IASP and IHS criteria.<sup>24,25</sup> Patients were seen on a regular basis until symptom resolution. If no symptom resolution occurred, most patients were followed up on a three-monthly basis until the end of data accrual. Improvements were recorded from the last follow-up visit on a categorical scale as worse, same, some improvement, improved a lot but still has symptoms, or improved a lot with no more symptoms. No differentiation was made between improvement in pain or in NSD. All clinical observations were made by the clinical staff, who were independent from the investigators.

In a second model we predicted QoL using the EQ5D-5L self-rated health VAS-score at final follow-up. The third model aimed to predict pain intensity at the final follow-up moment.

### **Comparison of low versus moderate to severe pain intensity cohorts**

Based on the pain VAS score (ranging from 0 to 10) assessed during the last follow-up moment, patients were categorized into low (<5) or moderate to severe ( $\geq 5$ ) pain intensity cohorts. This

allowed for a comparison of clinical features, pain quality and pain characteristics between both cohorts.

### **Sample size and missing data**

No similar studies have been conducted to be able to estimate the incidence and frequency of persistent NSD in our study population. However, based on simulation studies, a minimum of ten events per variable are required, rendering a sample size of 230 patients.<sup>26,27</sup> Missing data were handled by listwise exclusion to build the logistic regression model after verifying the randomness and frequency of missing values.

### **Statistical analysis**

All data were handled by a certified statistician using SPSS version 25.0 (IMB Corp, Armonk, NY).

The exploratory data analysis consisted of five steps. 1—Descriptive data analysis by calculating the means, standard deviations, counts, and frequencies. 2—Bivariate analysis, for which Kendall's tau-b correlation was used to determine the relationship between continuous variables and the outcome variables: persistence of NSD and pain intensity. A chi-squared test for association was conducted between binomial variables. If expected cell counts were less than five, a Fisher's exact test was used. Strength of association was evaluated using Cramer's V test. 3—Multivariable modeling by performing binomial logistic regression to ascertain the effects of age, gender, initiating event, injured nerve branch, VAS pain score, and sensory profile on the likelihood that participants had a persistent trigeminal nerve injury. Similarly, the effects of age, gender, initiating event, injured nerve branch, sensory profile and persistence of NSD was assessed on the likelihood that participants reported moderate to severe pain intensities. Variables were selected based on the bivariate analysis ( $P < 0.05$ ), strength of correlation, and after discussion by the investigators. Treatment effects were simulated in both bivariate and multivariable models. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box–Tidwell procedure.<sup>28</sup> A Bonferroni correction was applied using all terms in the model.<sup>29</sup> Sensitivity, specificity, and positive and negative predictive values were determined, as well as the area under the receiver operating characteristic curve (AUC).<sup>30</sup> Based on this assessment, all continuous independent variables were linearly related to the logit of the dependent variables. 4—A point-biserial correlation analysis was used to determine the relationship between the dichotomous predictors and the self-perceived health related QoL after evaluation of normality (visual inspection of Q-Q plots)

and equality of variances using Levene's test. In case assumptions were not met, Kendall's tau b-correlation test was used. For continuous independent variables, a Spearman's correlation test was performed. 5—Multiple regression to predict the QoL from the above-mentioned predictors. Linearity was assessed by inspection of partial regression plots and a plot of studentized residuals against predicted values. Independence of residuals was verified using a Durbin-Watson test. Multicollinearity was set at tolerance values greater than 0.2. The assumption of normality was assessed on a Q-Q plot.

We used a bootstrap method for internal validation of the selected variables. A random selection with replacement of 1000 samples was derived. The  $\beta$  coefficient and 95% confidence intervals were then calculated for each variable.

Last, Kaplan-Meier curves were constructed to assess the effects of risk factors on persistent NSD over time. In consultation with the investigators, the following factors were withheld for the Kaplan-Meier analysis: age, gender, painful versus non-painful PTN, initiating event, injured branch, and sensory profile. A correction for multiple comparisons was applied and censoring percentages were analyzed. The pairwise log-rank test was used to detect any significant differences between the constructed curves.  $P$  values smaller than 0.05 were considered statistically significant.

## Results

### Population characteristics

A total of 384 patients were included, with a mean follow-up time of  $322 \pm 302$  weeks. **Table 1** shows patient characteristics and the considered variables. Sixty percent of patients had a persistent trigeminal nerve injury. There were more females than males (66% vs 34%) and the mean age of patients was  $50.1 \pm 16.6$  years. The inferior alveolar nerve was most frequently damaged (45%), followed by the maxillary nerve and its terminal branches (35%). Third molar surgery was the causative procedure in 34% of all cases, followed by tooth extraction (29%) and dental implant placement (19%). Most patients had sensory loss (40%) and pain (24%), with a mean pain VAS score of 2.3 out of 10. Treatments varied and included over-the-counter analgesics in 65% of patients, followed by antidepressants (45%). Opioids were used in 14% of patients. Eighteen percent of patients had some sort of topical treatment. In 8% of cases, a surgical intervention was performed. Improvement was seen in 42% of patients. In about half of the patients, symptoms remained the same or showed only some improvement. Half of the

patients indicated some health-related problems on the EQ5D quality-of-life questionnaire. The overall mean self-perceived health state was  $70 \pm 20$ .

*Table 1. Patient characteristics of 384 patients with post-traumatic trigeminal neuropathy. SD: standard deviation.*

Characteristic (N)	N	Count (%)	Mean (SD)
Gender	373		
Male		126 (33.8)	
Female		247 (66.2)	
Age	373		50.1 (16.6)
Injured nerve			
Inferior alveolar nerve	367	166 (45.2)	
Lingual nerve	367	53 (14.4)	
Maxillary nerve	367	127 (34.6)	
Mandibular nerve	367	10 (2.7)	
Inferior alveolar and maxillary nerve	367	11 (3.0)	
Initiating event			
Local anesthesia	252	15 (6.0)	
Third molar surgery	252	86 (34.1)	
Tooth extraction	252	74 (29.4)	
Endodontic treatment	252	30 (11.9)	
Dental implant placement	252	47 (18.7)	
Clinical findings			
Pain VAS Score	185		2.3 (3.4)
Sensory profile	367		
Pain		87 (23.7)	
Sensory Loss		145 (39.5)	
Thermal Hyperesthesia		14 (3.8)	
Mechanical Hyperesthesia		55 (15.0)	
Mixed		66 (18.0)	
Treatment			
Any treatment	384		
Yes		339 (88.3)	
No		45 (11.7)	
Systemic treatment	384		
OTC analgetics		252 (65.6)	
Antiepileptics		104 (27.1)	
Antidepressants		174 (45.3)	
Benzodiazepines		66 (17.2)	
Opioids		54 (14.1)	
Topical treatment	384	68 (17.7)	

Characteristic (N)	N	Count (%)	Mean (SD)
Surgical treatment	384	30 (7.8)	
Prognosis			
Duration	343		
Temporary injury		111 (28.9)	
Persistent injury		232 (60.4)	
Improvement	287		
Worse		4 (1.4)	
Same		69 (24.0)	
Some improvement		92 (32.1)	
A lot of improvement, still symptoms		77 (26.8)	
A lot of improvement, no more symptoms		45 (15.7)	
Follow-up time in weeks	322		302 (358)
Quality of Life (EQ5D-5L)			
Dimensions			
No problems	384	190 (49.5)	
Any problem	384	194 (50.5)	
Health state	190		70.4 (19.8)

### Bivariate analysis between temporary and persistent NSD

Several patient- and surgery-related predictors were significantly associated with persistent NSD (**Table 2**). Bivariate analysis revealed that females had more persistent NSD compared with males (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.39–3.58,  $P < 0.0001$ ). Older age was associated with significantly higher rates of persistent NSD (OR 1.03, 95% CI 1.02–1.05,  $P < 0.0001$ ). Lingual nerve injuries were associated with significant lower rates of persistent NSD (OR 0.48, 95% CI 0.27–0.85,  $P < 0.0001$ ). Maxillary nerve lesions were more associated with persistent NSD (OR 3.05, 95% CI 1.80–5.18) than with temporary NSD.

If the cause of NSD was the administration of local anesthesia, the OR for persistent NSD was 0.08 (95% CI 0.02–0.36,  $P < 0.0001$ ), meaning that patients were less likely to sustain persistent NSD. Likewise, third molar surgery had an unadjusted OR of 0.36 (95% CI 0.22–0.61,  $P < 0.0001$ ).

*Table 2. Comparison of variables between patients with temporary and persistent neurosensory disturbances (NSD), and the results of bivariate analyses assessing the relationship between patient- and surgery-related factors and NSD cohorts. Persistent means present for more than three months after the injury was inflicted.*

Characteristic	Temporary	Persistent	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
Age, mean (SD)	44 (1.7)	52 (1.0)	$\tau_b = 0.186$ $p < 0.0001$ n = 343	1.03	1.02	1.05
Gender n (%)						
Male	51 (45.9)	64 (27.6)	$\chi^2(1) = 11.355$			
Female	60 (54.1)	168 (72.4)	$p = 0.001$ $\varphi = 0.182$ n = 343	2.23	1.39	3.58
Smoker n (%)						
No	34 (65.4)	66 (62.3)	$\chi^2(1) = .146$			
Yes	18 (34.6)	40 (37.7)	$p = 0.702$ $\varphi = 0.030$ n = 158	1.15	0.57	2.29
Injured nerve						
Inferior alveolar nerve n (%)						
No	49 (44.1)	122 (52.6)	$\chi^2(1) = 2.140$			
Yes	62 (55.9)	110 (47.4)	$p = 0.143$ $\varphi = 0.079$ n = 343	0.71	0.45	1.12
Lingual nerve n (%)						
No	84 (75.7)	201 (86.6)	$\chi^2(1) = 6.421$			

Characteristic	Temporary	Persistent	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
Yes	27 (24.3)	31 (13.4)	$p = 0.011$ $\varphi = -0.137$ n = 343	0.48	0.27	0.85
Maxillary nerve n (%)						
No	88 (79.3)	129 (55.6)	$\chi^2(1) = 18.109$			
Yes	23 (20.7)	103 (44.4)	$p < 0.0001$ $\varphi = 0.230$ n = 343	3.06	1.80	5.18
Initiating event						
Local anesthesia n (%)						
No	100 (90.1)	230 (99.1)	FET(1)			
Yes	11 (9.9)	2 (0.9)	$p < 0.0001$ $\varphi = -0.222$ n = 343	0.08	0.02	0.36
Third molar surgery n (%)						
No	72 (64.9)	194 (83.6)	$\chi^2(1) = 15.171$			
Yes	39 (35.1)	38 (16.4)	$p < 0.0001$ $\varphi = -0.210$ n = 343	0.36	0.22	0.61
Tooth extraction n (%)						
No	90 (81.1)	189 (81.5)	$\chi^2(1) = 0.007$			
Yes	21 (18.9)	43 (18.5)	$p = 0.932$ $\varphi = -0.005$ n = 343	0.98	0.55	1.74
Endodontic treatment n (%)						
No	102 (91.9)	212 (91.4)	$\chi^2(1) = 0.025$			
Yes	9 (8.1)	20 (8.6)	$p = 0.873$	1.07	0.47	2.43

Characteristic	Temporary	Persistent	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
Dental implant placement n (%)			$\varphi = 0.009$ n = 343			
No	101 (91.0)	196 (84.5)	$\chi^2(1) = 2.739$			
Yes	10 (9.0)	36 (15.5)	$p = 0.098$ $\varphi = 0.089$ n = 343	1.86	0.89	3.89
Clinical findings						
Duration n (%)			$\chi^2(1) = 0.510$			
Constant	73 (90.1)	161 (87.0)	$p = 0.475$			
Intermittent	8 (9.9)	24 (13.0)	$\varphi = 0.044$ n = 266	1.36	0.58	3.17
Pain VAS score, mean (SD)	0.8 (0.3)	3.6 (0.4)	$\tau_b = 0.367$ $p < 0.0005$ n = 169	1.35	1.19	1.53
Pain n (%)						
No	28 (25.2)	21 (9.1)	$\chi^2(1) = 16.039$			
Yes	83 (74.8)	211 (90.9)	$p < 0.0005$ $\varphi = 0.216$ n = 343	3.39	1.82	6.30
Sensory loss n (%)						
No	32 (28.8)	134 (57.8)	$\chi^2(1) = 25.160$			
Yes	79 (71.2)	98 (42.2)	$p < 0.0005$ $\varphi = -2.71$ n = 343	0.30	0.18	0.48
Thermal hyperesthesia n (%)						

Characteristic	Temporary	Persistent	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
No	106 (95.5)	187 (80.6)	$\chi^2(1) = 13.371$			
Yes	5 (4.5)	45 (19.4)	$p < 0.0005$ $\varphi = .197$ n = 343	5.10	1.97	13.25
Mechanical hyperesthesia n (%)						
No	87 (78.4)	147 (63.4)	$\chi^2(1) = 7.809$			
Yes	24 (21.6)	85 (36.6)	$p = 0.005$ $\varphi = .151$ n = 343	2.10	1.24	3.54
Number of other pain diagnoses, mean (SD)	0 (0.0)	0.2 (0.04)	$\tau_b = 0.188$ $p < 0.0005$ n = 343	26.20	1.58	434.99
Treatment						
Any treatment n (%)						
No	13 (11.7)	19 (8.2)	$\chi^2(1) = 1.101$			
Yes	98 (88.3)	213 (91.8)	$p = 0.294$ $\varphi = .057$ n = 343	1.50	0.71	3.13
Systemic treatment n (%)						
No	16 (14.4)	25 (10.8)	$\chi^2(1) = 0.944$			
Yes	95 (85.6)	207 (89.2)	$p = 0.331$ $\varphi = .052$ n = 343	1.40	0.71	2.73
Topical treatment n (%)						
No	106 (95.5)	170 (73.3)	$\chi^2(1) = 23.583$			
Yes	5 (4.5)	62 (26.7)	$p < 0.0005$	7.73	3.01	19.85

Characteristic	Temporary	Persistent	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
Surgical treatment n (%)			$\phi = .262$ n = 343			
No	107 (96.4)	209 (90.1)	$\chi^2(1) = 4.122$			
Yes	4 (3.6)	23 (9.9)	$p = 0.042$ $\phi = .110$ n = 343	2.94	0.99	8.73
Quality of life (EQ5D-5L)						
Dimensions n (%)						
No problems	52 (46.8)	101 (43.5)	$\chi^2(1) = 0.333$			
Any problem	59 (53.2)	131 (56.5)	$p = 0.564$ $\phi = .031$ n = 343	1.41	0.73	1.80
Health state, mean (SD)	80 (1.4)	65 (1.9)	$\tau_b = -0.306$ $p < 0.0005$ n = 343	0.94	0.92	0.97

$\phi$ : phi coefficient or Cramer's V; FET: Fisher's exact test;  $\tau_b$  : Kendall's tau-b correlation coefficient, CI: confidence interval

Persistent NSD was also associated with the presence of pain and higher pain VAS scores (OR 3.39, 95% CI 1.82–6.30,  $p < 0.0005$  and OR 1.35, 95% CI 1.19–1.53,  $P < 0.0005$ , respectively).

In addition, the presence of thermal hyperesthesia was more frequent in the persistent NSD group (OR 5.10, 95% CI 1.97–13.25,  $P < 0.0005$ ). Patients with mechanical hyperesthesia were twice as likely to have persistent NSD (OR 2.10, 95% CI 1.24–3.54,  $P < 0.005$ ).

A higher number of pain diagnoses was also associated with persistence of NSD (OR 26.20, 95% CI 1.58–434.99,  $P < 0.0005$ ). Moreover, lower quality of life (a lower self-perceived health state, scored as a lower VAS score) was associated with persistent NSD (OR 0.94, 95% CI 0.92–0.97,  $P < 0.0005$ ). Patients with persistent NSD scored their current health state as  $65 \pm 1.9$  out of 100, compared with  $80 \pm 1.4$  in the cohort with temporary NSD ( $P < 0.0005$ ).

Presence of any treatment did not have a significant correlation with persistence. Yet, topical treatment did correlate (OR 7.73, 95% CI 3.01–19.85,  $P < 0.0005$ ).

### Multivariable prediction model of persistent NSD

After the bivariate analysis of 23 variables (**Table 2**), 15 were entered into the logistic regression model. The logistic regression model was statistically significant ( $\chi^2(15) = 69.9$ ,  $P < 0.0005$ ). The model explained 46% (Nagelkerke's  $R^2$ ) of the variance in persistent trigeminal nerve injuries, and correctly classified 76.9% of cases. The sensitivity was 81.8%, specificity was 70.0%, positive predictive value (PPV) was 79.4%, and negative predictive value (NPV) was 73.1%.

Of the 15 predictor variables, six were statistically significant: gender; pain caused by local anesthesia, extraction, third molar surgery, or endodontic treatment; and the presence of thermal hyperesthesia (**Table 3**).

*Table 3. Multivariable binomial regression model assessing the relationship between patient- and surgery-related factors and the presence of persistent neurosensory disturbances.*

Characteristic	B	SE	Wald	df	p	Odds Ratio	95% CI for Odds Ratio	95% CI after Bootstrap Resampling		
							Lower	Upper	Lower	Upper
Gender	1.02	.41	6.28	1	.012	2.78	1.25	6.20	.85	1.22
Age	.01	.01	.40	1	.530	1.01	.98	1.04	.01	.01
<b>Injured nerve</b>										
Inferior alveolar nerve	1.09	.96	1.29	1	.255	2.99	.45	19.67	1.03	1.17
Lingual nerve	1.69	1.03	2.70	1	.100	5.41	.72	40.47	1.48	2.00
Maxillary nerve	1.21	1.08	1.24	1	.266	3.34	.40	27.99	1.14	1.28
<b>Initiating event</b>										
Local anesthesia	-3.21	1.27	6.33	1	.012	.04	.00	.49	-3.36	-3.10
Third molar surgery	-1.25	.55	5.09	1	.024	.29	.10	.85	-1.38	-1.11
Extraction	-2.00	.68	8.53	1	.003	.14	.04	.52	-2.03	-1.98
Endodontic treatment	-2.84	1.24	5.24	1	.022	.06	.01	.67	-2.90	-2.79
Implant placement	-1.06	.82	1.66	1	.197	.35	.07	1.73	-1.13	-.99
<b>Clinical findings</b>										
VAS Pain score	.11	.14	.62	1	.430	1.11	.85	1.45	.10	.12
Pain	-.14	.46	.09	1	.767	.87	.35	2.16	.37	.15
Sensory loss	-1.23	1.01	1.50	1	.221	.29	.04	2.10	-1.41	-1.10
Thermal hyperesthesia	2.75	1.35	4.15	1	.042	15.66	1.11	220.69	2.62	2.88
Mechanical hyperesthesia	.43	.63	.46	1	.498	1.54	.44	5.31	.34	.51
Constant	-.18	1.51	.01	1	.905	.83				

Note: Gender is for females compared to males.

AUC = .84,  $\chi^2(15) = 69.9$ ,  $p < .0001$ . A total of 1000 bootstrap subsamples were run. CI: confidence interval. VAS: visual analog scale (0-10). SE: standard error.

The model showed an excellent level of discrimination (according to Hosmer et al. 2013), with an overall AUC of 0.84 (95% CI 0.79–0.90).

An individual risk of persistent NSD may be calculated using the supplemental calculator (**Supplemental Table 1**). The risk is calculated by the formula:

$$\text{risk of persistent NSD} = \frac{e^{\text{risk score}}}{1 + e^{\text{risk score}}}$$

Where *risk score* is calculated as the sum of the intercept and the sum of the multiplication of the regression coefficients and their respective values.

### Bivariate and multivariable analysis of pain intensity

After dichotomizing pain intensity into low and moderate to high pain levels we found a significant correlation with age, gender, injured nerve (lingual and maxillary nerve), and initiating event (third molar surgery) (**Table 4**). The presence of NSD, thermal or mechanical hyperesthesia increased the odds of having a moderate to severe pain intensity. Logically, patients who received some treatment were more likely to experience moderate to severe pain (OR 4.69, 95% CI 1.06-20.76,  $P = 0.026$ ). On the other hand, third molar surgery was less likely to be associated with moderate to severe pain (OR 0.23, 95% CI 0.10-0.52,  $P < 0.0005$ ). A lower HrQoL was associated with moderate to severe pain intensity.

Table 4. Bivariate correlation analysis between low pain and moderate to severe pain intensity cohorts.

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds Ratio	95% CI for Odds Ratio
					Lower      Upper
Age, mean (SD)	41.39 (15.69)	57.87 (14.98)	$\tau_b = 0.345$ $p < 0.0005$ $n = 185$	1.07	1.04      1.09
Gender n (%)					
Male	66 (49.6)	15 (28.8)	$\chi^2(1) = 6.557$	2.43	1.22      4.84
Female	67 (50.4)	37 (71.2)	$p = 0.010$ $\varphi = 0.188$ $n = 185$		
Smoker n (%)					
No	43 (59.7)	14 (63.6)	$\chi^2(1) = .108$	0.85	0.32      2.28
Yes	29 (40.3)	8 (36.4)	$p = 0.742$ $\varphi = -0.034$ $n = 94$		
Injured nerve					
Inferior alveolar nerve n (%)					
No	54 (40.6)	29 (55.8)	$\chi^2(1) = 3.477$	0.54	0.28      1.04
Yes	79 (59.4)	23 (44.2)	$p = 0.062$ $\varphi = -0.137$ $n = 185$		
Lingual nerve n (%)					
No	92 (69.2)	46 (88.5)	$\chi^2(1) = 7.339$	0.29	0.12      0.74
Yes	41 (30.8)	6 (11.5)	$p = 0.007$ $\varphi = -0.199$ $n = 185$		
Maxillary nerve n (%)					
No	118 (88.7)	27 (51.9)	$\chi^2(1) = 29.872$	7.28	3.39      15.65
Yes	15 (11.3)	25 (48.1)	$p < 0.0005$ $\varphi = 0.402$ $n = 185$		
Initiating event					
Local anesthesia n (%)					
No	127 (95.5)	51 (98.1)	FET(1)	0.42	0.05      3.53
Yes	6 (4.5)	1 (1.9)	$p = 0.675$ $\varphi = -0.061$ $n = 185$		
Third molar surgery n (%)					

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
No	74 (55.6)	44 (84.6)	$\chi^2(1) = 13.588$	0.23	0.10	0.52
Yes	59 (44.4)	8 (15.4)	$p < 0.0005$ $\varphi = -0.271$ n = 185			
Tooth extraction n (%)						
No	115 (86.5)	39 (75.0)	$\chi^2(1) = 3.524$	2.13	0.96	4.74
Yes	18 (13.5)	13 (25.0)	$p = 0.061$ $\varphi = 0.138$ n = 185			
Endodontic treatment n (%)						
No	129 (97.0)	49 (94.2)	FET(1)	1.97	0.43	9.14
Yes	4 (3.0)	3 (5.8)	$p = 0.403$ $\varphi = 0.065$ n = 185			
Dental implant placement n (%)						
No	123 (92.5)	45 (86.5)	$\chi^2(1) = 1.582$	1.91	0.69	5.33
Yes	10 (7.5)	7 (13.5)	$p = 0.208$ $\varphi = 0.092$ n = 185			
Clinical findings						
Duration n (%)						
Constant	96 (96.0)	43 (93.5)	FET(1)	1.67	0.36	7.81
Intermittent	4 (4.0)	3 (6.5)	$p = 0.508$ $\varphi = 0.055$ n = 185			
Persistency n (%)						
Temporary	64 (53.8)	6 (12.0)	$\chi^2(1) = 25.330$	8.53	3.38	21.54
Persistent	55 (46.2)	44 (88.0)	$p < 0.0005$ $\varphi = 0.387$ n = 169			
Sensory loss n (%)						
No	12 (9.0)	41 (78.8)	$\chi^2(1) = 89.162$	0.03	0.01	0.07
Yes	121 (91.0)	11 (21.2)	$p < 0.0005$ $\varphi = -0.694$ n = 185			
Thermal hyperesthesia n (%)						
No	126 (94.7)	39 (75.0)	$\chi^2(1) = 15.103$	6.00	2.24	16.09

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds Ratio	95% CI for Odds Ratio
					Lower      Upper
Yes	7 (5.3)	13 (25.0)	$p < 0.0005$ $\varphi = 0.286$ $n = 185$		
Mechanical hyperesthesia n (%)					
No	120 (90.2)	24 (46.2)	$\chi^2(1) = 42.092$	10.77	4.89    23.74
Yes	13 (9.8)	28 (53.8)	$p = 0.005$ $\varphi = 0.477$ $n = 185$		
Number of other pain diagnoses, mean (SD)	0.09 (0.42)	0.15 (0.61)	$t_b = 0.047$ $p = 0.522$ $n = 185$	1.29	0.69    2.40
Treatment					
Any treatment n (%)					
No	21 (15.8)	2 (3.8)	FET(1)	4.69	1.06    20.76
Yes	112 (84.2)	50 (96.2)	$p = 0.026$ $\varphi = 0.163$ $n = 185$		
Systemic treatment n (%)					
No	25 (18.8)	3 (5.8)	FET(1)	3.78	1.09    13.12
Yes	108 (81.2)	49 (94.2)	$p = 0.038$ $\varphi = .163$ $n = 185$		
Topical treatment n (%)					
No	125 (94.0)	35 (67.3)	$\chi^2(1) = 22.764$	7.59	3.02    19.05
Yes	8 (6.0)	17 (32.7)	$p < 0.0005$ $\varphi = 0.351$ $n = 185$		
Surgical treatment n (%)					
No	125 (94.0)	50 (96.2)	FET(1)	0.63	0.13    3.05
Yes	8 (6.0)	2 (3.8)	$p = 0.728$ $\varphi = -0.043$ $n = 185$		
Quality of life (EQ5D-5L)					
Dimensions n (%)					
No problems	65 (48.9)	25 (48.1)	$\chi^2(1) = 0.009$	1.03	0.54    1.96
Any problem	68 (51.1)	27 (51.9)	$p = 0.923$ $\varphi = 0.007$		

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds Ratio	95% CI for Odds Ratio	
					Lower	Upper
n = 185						
Health state, mean (SD)	79.31 (12.66)	59.77 (24.88)	$\tau_b = -0.339$ $p < 0.0005$	0.94	0.91	0.97
n = 185						
VAS: visual analogue scale; $\phi$ : phi coefficient or Cramer's V; FET: Fisher's exact test; $\tau_b$ : Kendall's tau-b correlation coefficient, CI: confidence interval						

A logistic regression model was significant ( $P < 0.0001$ ) with an AUC of 0.987 and Nagelkerke's  $R^2 = 87.3\%$  (Table 5). The sensitivity and specificity were 96.2% and 98.3% respectively. PPV and NPV were 96.2% and 98.4%. We used the same input variables as in the previous regression model (replacing the pain variables by persistent NSD).

*Table 5. Multivariable binomial regression model predicting moderate to severe pain intensity based on predetermined patient- and surgery-related factors.*

Characteristic	B	SE	Wald	df	p	Odds	95% CI for Odds		95% CI after Bootstrap	
						Ratio	Ratio	Resampling		
							Lower	Upper	Lower	Upper
Gender	1.66	1.49	1.24	1	0.266	5.27	0.28	98.50	-96.64	155.48
Age	-0.02	0.05	0.17	1	0.684	0.98	0.90	1.08	-2.65	3.58
<b>Injured nerve</b>										
Inferior alveolar nerve	3.67	2.51	2.15	1	0.143	39.33	0.29	5356.36	-116.35	268.61
Lingual nerve	0.19	3.10	0.00	1	0.951	1.21	0.00	521.74	-172.87	205.49
Maxillary nerve	4.23	2.91	2.11	1	0.146	68.64	0.23	20561.07	-121.30	391.54
<b>Initiating event</b>										
Local anesthesia	-23.12	17828.28	0.00	1	0.999	0.00	0.00	0.00	-315.92	261.90
Third molar surgery	1.87	2.49	0.56	1	0.453	6.47	0.05	842.36	-42.09	277.56
Extraction	2.39	2.48	0.93	1	0.335	10.94	0.09	1413.70	-95.41	163.33
Endodontics	-0.34	2.54	0.02	1	0.893	0.71	0.01	102.56	-129.69	324.02
Implant placement	1.20	2.10	0.33	1	0.569	3.31	0.05	203.96	-92.38	223.41
<b>Clinical findings</b>										
Persistent NSD	1.04	2.87	0.13	1	0.717	2.83	0.00	780.63	-105.61	128.41
Sensory loss	-6.36	2.07	9.45	1	0.002	0.00	0.33	0.10	-422.31	-4.01
Thermal hyperesthesia	2.01	1.58	1.61	1	0.205	7.42	0.03	164.90	-84.15	117.93
Mechanical hyperesthesia	2.05	2.78	0.54	1	0.462	7.74	0.03	1797.92	-92.20	165.55
Any treatment	8.79	6.27	1.96	1	0.161	6553.60	0.03	1,43E+12	-40.56	550.21
EQ5D Health state	-0.13	0.09	2.33	1	0.127	0.88	0.74	1.04	-16.71	0.25

Constant	-2.58	7.52	0.12	1	0.732	0.08
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Note: Gender is for females compared to males.

AUC = 0.987,  $\chi^2(16) = 83.221, p < .0001$ . A total of 1000 bootstrap subsamples were run. CI: confidence interval. SE: standard error.

None of the individual features showed a significant contribution to the model except sensory loss ( $P = 0.002$ ). Also, we noted bootstrap confidence intervals which were largely different from the sample distribution. A risk score can be calculated by our tool in **Supplemental Table 1**.

### Bivariate and multivariable analysis of QoL

Bivariate analysis revealed that the following variables were significantly associated with the QoL health state: age, gender, injured nerve (lingual and maxillary nerve), initiated by third molar surgery, persistence of NSD, sensory loss phenotype and number of other pain diagnoses (**Table 6**). QoL was adversely affected when maxillary nerve lesions were present, when NSD was persistent or when multiple pain diagnoses were present.

*Table 6. Bivariate correlation analysis between patient- and surgery-related factors and quality of life measured by the EQ5D-5L VAS health state.*

Characteristic	mean QoL health state (SD)	Test of correlation
Age	-	$r_s = -0.299$ $p < 0.0005$ $n = 190$
Gender n (%)		
Male	74.36 (17.60)	$r_{pb} = -0.146$
Female	68.30 (20.70)	$p = 0.044$ $n = 190$
Smoker n (%)		
No	75.24 (16.65)	$r_{tb} = -0.156$
Yes	66.29 (21.54)	$p = 0.078$ $n = 93$
Injured nerve		
Inferior alveolar nerve n (%)		
No	71.16 (19.72)	$r_{pb} = -0.035$
Yes	69.77 (20.01)	$p = 0.629$

<b>Characteristic</b>	<b>mean QoL health state (SD)</b>	<b>Test of correlation</b>
<b>n = 190</b>		
Lingual nerve n (%)		
No	68.61 (19.93)	$r_{pb} = 0.222$
Yes	81.00 (15.78)	$p = 0.002$
		$n = 190$
Maxillary nerve n (%)		
No	72.64 (19.23)	$r_{pb} = -0.143$
Yes	66.82 (20.40)	$p = 0.049$
		$n = 190$
<hr/>		
Initiating event		
Local anesthesia n (%)		
No	70.35 (20.06)	$r_{pb} = 0.026$
Yes	73.60 (8.20)	$p = 0.719$
		$n = 190$
Third molar surgery n (%)		
No	67.36 (19.57)	$r_{pb} = 0.284$
Yes	80.66 (17.24)	$p < 0.0005$
		$n = 190$
Tooth extraction n (%)		
No	70.59 (20.08)	$r_{pb} = -0.016$
Yes	69.73 (18.89)	$p = 0.822$
		$n = 190$
Endodontic treatment n (%)		
No	70.43 (19.89)	$r_{pb} = 0.001$
Yes	70.50 (19.80)	$p = 0.989$
		$n = 190$
Dental implant placement n (%)		
No	70.48 (19.72)	$r_{pb} = -0.006$
Yes	70.13 (21.08)	$p = 0.937$
		$n = 190$
<hr/>		
Clinical findings		
Duration n (%)		
Constant	69.14 (19.99)	$r_{pb} = 0.154$

<b>Characteristic</b>	<b>mean QoL health state (SD)</b>	<b>Test of correlation</b>
Intermittent	77.48 (15.72)	$p = 0.060$ $n = 150$
Persistency n (%)		
Temporary	80.86 (10.84)	$\tau_b = -0.306$
Persistent	65.68 (21.31)	$p < 0.0005$ $n = 187$
Pain VAS score	-	$r_s = -0.446$ $p < 0.0005$ $n = 93$
Pain n (%)		
No	-	-
Yes	70.44 (19.83)	
Sensory loss n (%)		
No	64.53 (21.79)	$\tau_b = 0.246$
Yes	76.53 (15.66)	$p < 0.0005$ $n = 190$
Thermal hyperesthesia n (%)		
No	71.04 (19.95)	$r_{pb} = -0.067$
Yes	67.55 (19.31)	$p = 0.358$ $n = 190$
Mechanical hyperesthesia n (%)		
No	71.70 (19.30)	$r_{pb} = -0.099$
Yes	67.41 (20.90)	$p = 0.175$ $n = 190$
Number of other pain diagnoses	-	$r_s = -0.296$ $p < 0.0005$ $n = 190$
Treatment		
Any treatment n (%)		
No	66.68 (24.66)	$r_{pb} = 0.063$
Yes	70.85 (19.26)	$p = 0.386$ $n = 190$
Systemic treatment n (%)		

Characteristic	mean QoL health state (SD)	Test of correlation
No	67.14 (23.48)	$r_{pb} = 0.060$
Yes	70.87 (19.34)	$p = 0.408$ $n = 190$
Topical treatment n (%)		
No	71.62 (20.13)	$r_{pb} = -0.124$
Yes	65.36 (17.86)	$p = 0.088$ $n = 190$
Surgical treatment n (%)		
No	70.94 (19.26)	$r_{pb} = -0.087$
Yes	64.53 (25.69)	$p = 0.231$ $n = 190$
SD: standard deviation. $r_{pb}$ : point-biserial correlation. $r_s$ : Spearman's correlation. $\tau_b$ : Kendall's tau-b correlation.		
Note: 1. Where both dependent and independent variable were continuous, only the Spearman's correlation coefficient is given. 2. No valid cases were available in the category of "No pain" to assess correlation with their health state.		

The multiple regression model to predict QoL was statistically significant  $F(15, 77) = 4.47, P < 0.0005$ . The adjusted  $R^2$  was 0.361. The following variables were significant to the prediction: initiating event (third molar surgery and implant-related injury), VAS pain score, presence of any treatment,  $P < 0.05$ . Multicollinearity was present between any treatment and systematic treatment. After backward regression analysis, only *any treatment* and the previously mentioned predictors (age, gender, injured nerve, initiating events, sensory profiles, pain VAS score) were taken forward into the regression model. Results are illustrated in **Table 7**.

*Table 7. Multiple regression model assessing the relationship between patients' quality of life health state and patient- and surgery-related factors.*

Characteristic	B	SE B	<i>p</i>	95% CI for B				R <sup>2</sup>	ΔR <sup>2</sup>
				Lower	Upper	β			
Model								0.520	0.415
Gender	2.30	11.48	0.508	-4.59	9.20	0.06			
Age	-0.15	-0.13	0.209	-0.39	0.09	-0.13			
Injured nerve									
Inferior alveolar nerve	-5.29	6.35	0.407	-17.95	7.37	-0.14			
Lingual nerve	1.61	6.71	0.811	-11.76	14.99	0.04			
Maxillary nerve	-7.30	7.23	0.316	-21.72	7.11	-0.17			
Initiating event									
Local anesthesia	-1.43	10.00	0.887	-21.36	18.51	-0.01			
Third molar surgery	8.37	4.67	0.077	-0.94	17.67	0.22			
Extraction	7.63	5.74	0.188	-3.80	19.07	0.14			
Endodontic treatment	11.53	8.46	0.177	-5.32	28.38	0.13			
Implant placement	16.74	6.15	0.008	4.49	28.99	0.25			
Clinical findings									
Persistent NSD	-8.54	4.07	0.039	-16.65	-0.43	-0.22			
VAS Pain score	-2.98	1.01	0.004	-4.99	-0.97	-0.54			
Sensory loss	-12.90	7.16	0.076	-27.17	1.38	-0.32			
Thermal hyperesthesia	-5.84	5.37	0.281	-16.54	4.86	-0.11			
Mechanical hyperesthesia	-2.64	4.84	0.587	-12.28	7.00	-0.05			
Any treatment	10.60	5.00	0.037	0.64	20.57	0.20			
Constant	91.22	11.48	< 0.0005	68.35	114.09				

*Note:* Gender is for females compared to males.

B: unstandardized regression coefficient. SE B: standard error of the coefficient. CI: confidence interval. VAS: visual analog scale (0-10). R<sup>2</sup>: coefficient of determination. ΔR<sup>2</sup>: adjusted R<sup>2</sup>.

An individual QoL health state prediction may be calculated using the supplemental calculator (**Supplemental Table 1**).

### Kaplan–Meier distributions

Pairwise comparisons of Kaplan–Meier distributions revealed a statistically significant difference in NSD frequency over time between gender, age, painful and non-painful PTN, initiating event, injured nerve, and sensory profile (**Figure 1**). All survival distributions were significantly different (log-rank test  $P < 0.0005$ ). Older age, female gender, and a diagnosis of painful PTN all negatively affected the time to symptom resolution. Most improvement was observed during the first 20 weeks after injury. Little improvement was seen after 60 weeks. Painful PTN showed less tendency for recovery of NSD, with 86.2% of patients still complaining of NSD after two years. However, improvement continued to be observed even when symptoms were long-standing.

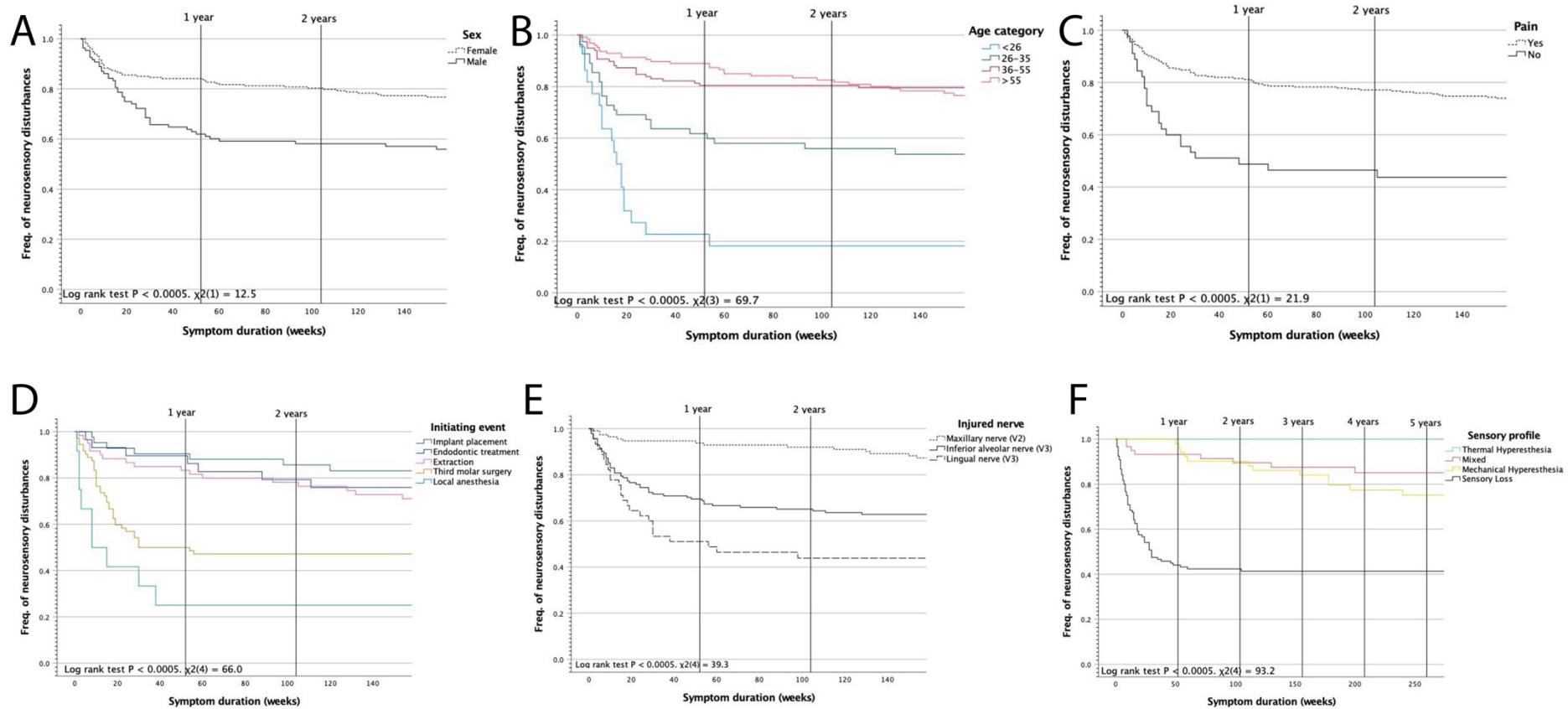


Figure 1. Kaplan–Meier analysis of neurosensory disturbances (NSD) over time comparing gender (A), age (B), painful and non-painful post-traumatic trigeminal neuropathies (PTN) (C), initiating event (D), injured nerve branch (E), and sensory profile (F). Between-group pairwise comparisons were all statistically significant ( $P < 0.0005$ , pairwise log-rank test).

Patients with lingual nerve injuries had the best long-term outcomes, with only 44% still experiencing NSD after two years; again, most improvement was seen in the first 20 weeks. In contrast, patients with a maxillary nerve lesion reported almost no improvement of NSD over time (92% still experienced NSD after two years). For inferior alveolar nerve lesions, persistent NSD was reported in 64% of cases after two years.

When comparing the most frequent initiating injury events, most neurosensory disturbances after local anesthesia administration injury resolved within 40 weeks, although 25% of patients still experienced NSD after two years. For injuries after third molar surgery, 47% of patients still reported NSD after two years. Endodontic-, implant-, or extraction-related injuries had a worse course of symptoms, with around 80% of patients still experiencing NSD after two years. Implant-related injuries were considered the worst of these, with little improvement in NSD over time; 86% of patients still had symptoms after two years.

When comparing sensory profiles, mechanical and thermal hyperesthesia and mixed profiles had the worst outcome, with higher rates of long-term NSD (ranging around 80%). Approximately 40% of patients with a sensory loss profile had persistent NSD after two years.

## Discussion

### Main findings

After the occurrence of trigeminal nerve injury, there was a high tendency toward persistent NSD in the present study. Sixty percent of patients who visited our tertiary center had symptoms that persisted for more than three months. This is in line with findings by Bagheri and Meyer, who reported permanent inferior alveolar injury in 78% of nerve injury patients after third molar surgery, and persistent lingual nerve injury in 46% of such patients.<sup>31–34</sup> Furthermore, Libersa et al. evaluated insurance records and reported a permanent injury in 22% of nerve injury cases after third molar surgery, 15% of cases after endodontic-related injury, and 75% of cases after implant-related injury;<sup>35</sup> Although high variance exists, there appears to be a relatively high conversion rate to permanent NSD after nerve injury has occurred.

### Patient profiles and predictors

As clinicians and researchers, we know that not every nerve injury presents or evolves in the same way. Increasing numbers of studies have demonstrated the usefulness of phenotyping patients based on multiparametric data.<sup>36</sup> In the future, it is hoped that this phenotyping will allow cost-effective treatment strategies to be tailored to each patient.<sup>18</sup>

The reported multivariable prediction model based on pre- and peri-operative factors was able to identify 77% of patients with long-term NSD. The following clinical predictors were statistically significant: (1) gender, (2) initiating event (all except implant placement), and (3) presence of thermal hyperesthesia.

Females were almost three times more likely than males to have persistent NSD. Similarly, a study by Selvi et al. reported a five-fold increase in NSD in females compared with males.<sup>37</sup> These authors also reported that older age and a close relationship between the third molar and the inferior alveolar nerve are associated with PTN after third molar surgery.

We also reported that patients with thermal hyperesthesia were sixteen times more likely to have persistent NSD. A recent report of PTNP demonstrated that increased patient age and an allodynia signature are significant factors that predict the permanency of neuropathy.<sup>38</sup> The importance of sensory phenotyping is further supported by the finding of different treatment outcomes according to nociceptor phenotype.<sup>36</sup> This study could not reveal unequivocal associations between treatment or non-treatment and outcome measures being persistence of NSD or final QoL.

One follow-up study by Pigg et al. evaluated 37 patients with persistent dentoalveolar pain, which is likely to be a neuropathic pain.<sup>39</sup> These authors illustrated a similar symptom course as in this report. However, they were unable to detect predictive factors, including sensory profiles, for persistent pain after seven years of follow-up. A low baseline pain score was the only predictor for symptom resolution, although no stratification was performed for etiology or injured nerve branch.

### Pain intensity

The present study further confirms age- and gender related associations with more severe pain.<sup>10</sup> Third molar surgery was less likely to be associated with moderate to severe pain. Other initiating events were not statistically significant associated with moderate to severe pain. Small numbers per variable may explain why most variables did not contribute significantly to the analysis.

It was striking that PTN at the level of the maxilla was seven times more likely to be associated with moderate to severe pain. Lingual and inferior alveolar nerve-related injuries were less likely to result in moderate to severe pain. This strengthens the clinical suspicion that the degree of nerve damage does not necessarily correlate with the final pain intensity.<sup>40</sup> It even seems that PTN at the level of the maxilla, where one finds mainly submillimetric peripheral nerve branches and usually undergoes less extensive surgery, poses a higher risk than mandibular

wisdom tooth surgery, which is considered more invasive, and takes place at the level of a 2-3 mm thick lingual or inferior alveolar nerve. It is true that even minimal interventions such as root canal treatment may result in persistent pain.<sup>41</sup>

More research will be needed to assess the role of nerve injury classifications in prediction models.<sup>42</sup> One interesting follow-up study would be to investigate the role of nerve fiber distributions and density in relation to PTNP and its triggering mechanisms.

### **Course of symptoms**

Most global improvement occurred within the first three months after trauma was inflicted. Notably, the evolution was markedly different between certain patient groups, based on the previously discussed variables. For example, a patient who had lingual nerve damage after wisdom tooth surgery with a sensory loss phenotype had a better chance of spontaneous recovery compared with a patient who had inferior alveolar nerve damage after endodontic treatment and complained of thermal hyperesthesia. The Kaplan-Meier distributions highlight the different clinical course, and perhaps different underlying pathophysiology, between cohorts.

Other studies have reported a similar cut-off for spontaneous recovery.<sup>43,44</sup> Time-to-recovery is an important factor to consider. For example, there is support for the theory that faster systemic treatment of post-surgical neuropathies or CPSP can lead to better outcomes or even avoid the development of CPSP or neuropathic pain.<sup>45</sup> Furthermore, in the case of severe nerve injury, microsurgical neural repair should be performed within three months of the injury occurrence to improve outcomes.<sup>46</sup> Another study, by Tabrizi et al., revealed a significant association between time to treatment and neurosensory recovery after mandibular body fractures.<sup>47</sup> This finding illustrates the importance of early diagnosis in nerve injury patients. Nevertheless, further research is needed to identify the most cost-effective treatments for the different phenotypes of nerve injury patients.

### **Quality of life**

In the end, the quality of life is what matters most to our patients. We identified a significant difference between patients who sustained transient nerve injuries (EQ5D VAS  $80 \pm 1.4$ ) and patients with persistent injuries ( $65 \pm 1.9$ ). When this was put into perspective with national population data, we noticed a worse quality of life in the patients with persistent symptoms. Szende et al. reported that the mean Belgian EQ5D VAS score for the 45–54-year age group is 77.2.<sup>48</sup> We also observed that approximately half of all patients with temporary or persistent

nerve damage reported health problems. This proportion is markedly higher than the average national figures, which are approximately 30%.<sup>48</sup>

Previous studies have identified a significant psychosocial burden in patients with trigeminal nerve injuries.<sup>2,4</sup> Smith et al. also reported that severity of pain is related to poorer quality of life in such patients.<sup>4</sup> These results support our finding of higher quality-of-life scores in patients with transient damage. Indeed, in these patients, pain was present less frequently, and was also less severe. Together, these findings demonstrate the importance of paying attention to psychosocial impacts and improving patients' quality of life.

### **Strengths and limitations**

To our knowledge, this study is the first to investigate a large population of PTN and PTNP patients with a long follow-up. For the first time, risk factors for developing persistent PTN were identified and quantified. Additionally, the course of symptoms was plotted to compare cohorts based on gender, etiology, injured nerve, presence of pain, and sensory profile. Such longitudinal data are unique in the current literature. However, the different symptom courses of patients with PTNP hide an underlying pathophysiology that remains insufficiently understood. Also, the lack of universally accepted treatment protocols makes it difficult to understand treatment effects on outcome.

Limitations of the present study included its retrospective nature and its tertiary setting, which may have led to selection bias. Sensory testing was mainly qualitative in nature which comes with its own limitations. Also, psychosocial measures were limited. Because of the large number of variables, some variables had few events per predictor, which may explain the contradictory results of some of the bivariate and multivariate predictions. Moreover, the data-driven approach that we used on the retrospective data should be externally validated.

### **Implications**

After a trigeminal nerve injury was inflicted, there was a high tendency toward persistent NSD in patients in our tertiary center. This is an alarming finding considering that dental, oral, and maxillofacial surgery is one of the most frequently performed procedures. Thus, investigating preventive strategies and educating clinicians about PTN should be on the top of the academic agenda.

Most global improvement was observed within the first three months after trauma was inflicted. Multiple patient- and surgery-related factors played a role in neurosensory recovery. The proposed multivariable prediction model may aid in predicting an individualized estimate of

neurosensory recovery but further prospective validation is needed. Important factors were identified which might aid the design of a future prospective registry study for patients with NSD.

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## **Supplemental data**

*Supplemental Table 1. Clinical calculators based on the presented prediction models. Using the different tabs, persistence of NSD, pain intensity and quality of life risk scores can be calculated by imputing patient-, clinical-, and surgery-related factors.*

Online access: <https://links.lww.com/PAIN/B435>



# SECTION 3



magnetic resonance neurography



## CHAPTER 5

# Magnetic resonance neurography: a systematic review

*This chapter is based on the following manuscript:*

**Van der Cruyssen F, Peeters F, Croonenborghs TM, Fransen J, Renton T, Politis C, Casselman J, Jacobs R.** A systematic review on diagnostic test accuracy of magnetic resonance neurography versus clinical neurosensory assessment for post-traumatic trigeminal neuropathy in patients reporting neurosensory disturbance. *Dentomaxillofacial Radiology*. 2020;50(1):20200103.

## **Abstract**

### **Objectives**

To perform a systematic review of published studies on diagnostic accuracy of magnetic resonance neurography (MRN) versus clinical neurosensory testing (NST) for post-traumatic trigeminal neuropathy (PTN) in patients reporting neurosensory disturbances (NSD).

### **Methods**

Human studies except case reports, reviews, systematic reviews and meta-analyses were included. PubMed, Embase, Web of Science and Cochrane Library were consulted. Risk of bias assessment was conducted using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Predetermined data extraction parameters were noted and summarized.

### **Results**

Eight studies met eligibility criteria of which seven were retrospective, representing 444 subjects. Most studies were at high risk of bias with low applicability concerns. Populations and objectives were divergent with a large variation in timing (3 days–17 years post injury) and parameters (multiple coil designs, fat suppression techniques, additional contrast agent) of MRI acquisition. T2 weighted 3T imaging with short echo times (2.2–100 ms) and fat suppression was applied in seven studies, techniques varied. Determination of sensitivity and specificity could not be performed due to the methodological variation between studies and lacking comparative data between index and reference tests. Based on limited data, PTN correlated reasonably well between clinical assessment, intraoperative findings and MRN abnormalities ( $k = 0.57$ ). Increased signal intensity correlated with persistency of neurosensory disturbances in one study. Intra- (ICC 0.914–0.927) and interobserver ( $k = 0.70$ –0.891) MRN variability was considered good to excellent. One retrospective study showed substantial impact of MRN on clinical decision making in one-third of patients.

### **Conclusion**

Currently, there is insufficient scientific knowledge to support or refute the use of MRN. Based on limited data, MRN seems promising and reliable in detection and grading of PTN. Methodological issues underline the importance for prospective blinded studies with standardization of signal intensity calculation and rigorous reporting of MRI acquisition parameters.

## Introduction

The peripheral trigeminal nerves are a daily concern for anyone operating in the head and neck area.<sup>1</sup> There is a risk of damage to these branches in numerous dentoalveolar and oral or maxillofacial surgeries such as wisdom tooth extraction, endodontic treatments, placement of implants and administration of local anesthesia.<sup>2</sup> Once damage occurs, there is usually a neurosensory disturbance which can be superimposed with neuropathic pain and phenomena such as allodynia and hyperalgesia. Diagnosing these post-traumatic trigeminal neuropathies (PTN) and predicting prognosis in the early post-traumatic period is not straightforward.<sup>3-5</sup> Currently, diagnosis is mainly based on patient-reported neurosensory disturbances (NSD) and qualitative or quantitative psychophysical neurosensory tests (NST), which have their own methodological problems.<sup>6</sup> Electrophysiological tests are available but are difficult to apply in the trigeminal distribution.<sup>6</sup> Additionally, they cannot precisely depict the localization and extent of trauma, which is important if surgical management is considered.

From a clinical but also medicolegal point of view, it is important to be able to make a distinction in severity between nerve damage, localization and sensory profiles.<sup>3,7</sup> Many patients experience spontaneous recovery, but in select cases with severe nerve damage, a microsurgical release or repair may be appropriate. It is generally agreed that a faster intervention leads to better neurosensory recovery.<sup>8-12</sup> The current standard in diagnosing pathology of the peripheral sensory nervous system is quantitative sensory testing (QST). It was introduced by the German Research Network on Neuropathic Pain in 2006 and is already strongly substantiated in its value, being that it can clarify if a neurosensory deficit is present or not.<sup>13-19</sup> However, for the time being, it remains unclear how these tests evolve in the transition from the acute to the chronic phases of trigeminal nerve damage and if they can predict prognosis and treatment outcomes in PTN.<sup>17,20,21</sup>

Magnetic resonance neurography (MRN) is an MRI technique in which dedicated sequences are used to enhance the visualization of the peripheral nervous system and its pathology.<sup>22</sup>

It has the potential to visualize and quantify nerve injuries and the associated severity of damage.<sup>23</sup> Evidence has already been demonstrated for plexus lesions and in neuromusculoskeletal imaging, but to the best of our knowledge no aggregate analysis of literature is known for the diagnostic accuracy and value in post-traumatic trigeminal nerve lesions.<sup>22,24,25</sup> Therefore, the main objective of this study was to conduct a systematic review of

diagnostic test accuracy (DTA) of MRN versus clinical neurosensory testing or patient-reported NSD in patients with PTN. Secondary objectives were to identify currently used MRN sequences, their parameters and performance as well as how they correlate with nerve injury severity. Finally, we looked for any impact on clinical decision-making when adding MRN to the diagnostic workup.

## Methods

### Systematic search

The PICO question included (P) patients suffering from PTN resulting in NSD within the trigeminal distribution who (I) underwent MRI in (C) comparison with clinical (neurological) examination or patient-reported NSD and (O) to assess techniques reported, its diagnostic accuracy, performance and correlation with nerve injury severity. The current systematic review was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; [https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=117971; number: CRD42018117971](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=117971; number: CRD42018117971)) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Diagnostic Test Accuracy (DTA) guidelines (see Appendix). The abstract was written using the Preferred Reporting Items for Systematic Reviews and Meta Analysis-DTA for Abstracts checklist. An experienced librarian was consulted before starting the study to co-create the search method. A systematic search was conducted in PubMed, Embase, Web of Science, and Cochrane Library in October 2019 and updated in February 2020. The search query is illustrated in **Table 1** and consisted of two concepts: “MRI” and “PTN”. These concepts were combined using the AND operator. Reference lists of included studies also were screened.

*Table 1. Overview of the applied search strategy.*

Database	Concept 1: MRI	Concept 2: PTTN
Pubmed	"Magnetic Resonance Imaging"[Mesh] OR magnetic-resonance-imag*[tiab] OR MRI[tiab] OR NMR-Imag*[tiab] OR MR-tomography[tiab] OR NMR-tomography[tiab] OR MRI-scan*[tiab] OR fMRI[tiab] OR functional-MRI[tiab] OR functional-magnetic-resonance-imag*[tiab] OR spin-echo-imag*[tiab] OR diffusion-magnetic-resonance-imag*[tiab] OR fusion-MRI[tiab] OR nuclear-magnetic-resonance-imag*[tiab] OR arterial-spin-label*[tiab] OR diffusion-tensor-imag*[tiab] OR diffusion-weighted-imag*[tiab] OR dynamic-contrast-enhanced-magnetic-resonance-imag*[tiab] OR multiparametric-magnetic-resonance-imag*[tiab] OR neurography[tiab]	"Trigeminal Nerve Injuries"[Mesh] OR trigeminal-nerve-injur*[tiab] OR Fifth-Cranial-Nerve-Injur*[tiab] OR Traumatic-Fifth-Nerve-Palsies[tiab] OR Traumatic-Trigeminal-Neuropath*[tiab] OR Injury-Cranial Nerve-V[tiab] OR Traumatic-Fifth-Nerve-Palsy[tiab] OR Trauma-Trigeminal-Nerve[tiab] OR Cranial-Nerve-V-Injury[tiab] OR Fifth-Nerve-Trauma[tiab] OR Trigeminal-Nerve-Contusion[tiab] OR Trigeminal-Nerve-Transsection[tiab] OR Trigeminal-Nerve-Avulsion[tiab] OR inferior-alveolar-nerve[tiab] OR lingual-nerve[tiab] OR mandibular-nerve[tiab]
Embase	'magnetic resonance imaging'/exp OR 'magnetic resonance imag*':ti,ab,kw OR 'arterial spin label*':ti,ab,kw OR 'diffusion tensor imag*':ti,ab,kw OR 'diffusion weighted imag*':ti,ab,kw OR 'dynamic contrast-enhanced magnetic resonance imag*':ti,ab,kw OR 'functional magnetic resonance imag*':ti,ab,kw OR 'multiparametric magnetic resonance imag*':ti,ab,kw OR 'perfusion weighted imag*':ti,ab,kw OR 'NMR imag*':ti,ab,kw OR 'MR tomography':ti,ab,kw OR 'MRI scan':ti,ab,kw OR 'functional MRI':ti,ab,kw OR 'functional magnetic resonance imag*':ti,ab,kw OR 'spin echo imag*':ti,ab,kw OR 'diffusion magnetic resonance imag*':ti,ab,kw OR 'diffusion MRI*':ti,ab,kw OR 'diffusion weighted MRI*':ti,ab,kw OR 'neurography':ti,ab,kw OR 'NMR':ti,ab,kw	'trigeminal nerve injury'/exp OR 'trigeminal nerve injur*':ti,ab,kw OR 'fifth-cranial nerve injur*':ti,ab,kw OR 'traumatic fifth nerve palsies':ti,ab,kw OR 'traumatic trigeminal neuropath*':ti,ab,kw OR 'injury cranial nerve V':ti,ab,kw OR 'traumatic fifth nerve palsy':ti,ab,kw OR 'trauma trigeminal nerve':ti,ab,kw OR 'cranial nerve V injury':ti,ab,kw OR 'fifth nerve trauma':ti,ab,kw OR 'trigeminal nerve contusion':ti,ab,kw OR 'trigeminal nerve transsection':ti,ab,kw OR 'trigeminal nerve avulsion':ti,ab,kw OR 'inferior alveolar nerve':ti,ab,kw OR 'lingual nerve':ti,ab,kw OR 'mandibular nerve':ti,ab,kw
Web of Science	"Magnetic resonance imag*" OR "MRI" OR "nuclear magnetic resonance imag*" OR "arterial spin label*" OR "diffusion tensor imag*" OR "diffusion weighted imag*" OR "dynamic contrast-enhanced magnetic resonance imag*" OR "functional magnetic resonance imag*" OR "multiparametric resonance imag*" OR "perfusion weighted imag*" OR "neurography" OR "NMR" OR "MR tomography" OR "NMR tomography" OR "MRI-scan" OR "functional MRI" OR "functional magnetic resonance imag*" OR "diffusion MRI" OR "diffusion weighted MRI" OR "nuclear magnetic resonance imag*" OR "fMRI"	"Trigeminal nerve injury" OR "Trigeminal nerve injur*" OR "fifth cranial nerve injur*" OR "traumatic fifth nerve palsies" OR "traumatic trigeminal neuropath*" OR "injury cranial nerve V" OR "traumatic fifth nerve palsy" OR "trauma trigeminal nerve" OR "cranial nerve V injury" OR "fifth nerve trauma" OR "trigeminal nerve contusion" OR "trigeminal nerve transsection" OR "trigeminal nerve avulsion" OR "inferior alveolar nerve" OR "lingual nerve" OR "mandibular nerve"
Cochrane library	# 1: [mh "magnetic resonance imaging"] # 2: ((magnet) NEXT resonance NEXT imag*) OR MRI):ti,ab,kw # 3: (nuclear NEXT magnetic NEXT resonance NEXT imag*):ti,ab,kw # 4: (arterial NEXT spin NEXT label*):ti,ab,kw # 5: (diffusion NEXT tensor NEXT imag*):ti,ab,kw # 6: (fusion NEXT weighted NEXT imag*):ti,ab,kw # 7: (dynamic NEXT contrast NEXT enhanced NEXT magnetic NEXT resonance NEXT imag*):ti,ab,kw # 8: (functional NEXT magnetic NEXT resonance NEXT imag*):ti,ab,kw # 9: (multiparametric NEXT resonance NEXT imag*):ti,ab,kw # 10: (perfusion NEXT weighted NEXT imag*):ti,ab,kw # 11: (neurography):ti,ab,kw # 12: (NMR):ti,ab,kw # 13: (MR NEXT tomography):ti,ab,kw # 14: (NMR tomography):ti,ab,kw # 15: (MRI-scan):ti,ab,kw # 16: (functional NEXT MRI):ti,ab,kw # 17: (functional NEXT magnetic NEXT resonance NEXT imag*):ti,ab,kw # 18: (diffusion NEXT MRI):ti,ab,kw # 19: (diffusion NEXT magnetic NEXT resonance NEXT imag*):ti,ab,kw # 20: (diffusion NEXT weighted NEXT MRI):ti,ab,kw # 21: (fMRI):ti,ab,kw # 22: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	# 1:[mh "trigeminal nerve injuries"] # 2: (trigeminal NEXT nerve NEXT injur*):ti,ab,kw # 3: (fifth NEXT cranial NEXT nerve NEXT injur*):ti,ab,kw # 4: (traumatic NEXT fifth NEXT nerve NEXT palsies):ti,ab,kw # 5: (traumatic NEXT trigeminal NEXT neuropath*):ti,ab,kw # 6: (injury NEXT cranial NEXT nerve NEXT V):ti,ab,kw # 7: (traumatic NEXT fifth NEXT nerve NEXT palsy):ti,ab,kw # 8: (trauma* NEXT trigeminal NEXT nerve):ti,ab,kw # 9: (cranial NEXT nerve NEXT V NEXT injury):ti,ab,kw # 10: (fifth NEXT nerve NEXT trauma):ti,ab,kw # 11: (trigeminal NEXT nerve NEXT contusion):ti,ab,kw # 12: (trigeminal NEXT nerve NEXT transsection):ti,ab,kw # 13: (trigeminal NEXT nerve NEXT avulsion):ti,ab,kw # 14: (inferior NEXT alveolar NEXT nerve):ti,ab,kw # 15: (lingual NEXT nerve):ti,ab,kw # 16: (mandibular NEXT nerve):ti,ab,kw #17: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

PTTN, post-traumatic trigeminal neuropathy.

Concept 1 and 2 were combined with the AND operator.

## Selection criteria

The search was limited to original research articles without restrictions on language or publication date. Inclusion criteria included cohort studies, observational case-control, cross-sectional, randomized controlled trials (RCTs) and case series. In general, studies were included if the investigated patients were diagnosed with PTN on the basis of sensory tests or patient-reported NSD and if MRN was examined as an index test. Exclusion criteria included animal trials, case reports, reviews, systematic reviews and meta-analyses.

## Screening and selection of records

The first author (FVDC) executed the literature search and exported all references to Rayyan QCRI after deduplication.<sup>26</sup> Two researchers (FVDC and FP) independently screened titles and

abstracts according to inclusion and exclusion criteria. Disagreements were resolved in a consensus meeting with a third researcher (TMC). The first author screened the reference lists for additional articles that did not appear in the systematic search. Both researchers again independently determined which articles should be retained and consensus was reached in a second consensus meeting with the three researchers.

### **Risk of bias assessment**

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the risk of bias and applicability concerns.<sup>27</sup> Four levels were tested, including patient selection, index test, reference standard and flow and timing. A total score was plotted and indicates if included studies were at high, low or unclear risk of bias or applicability concern. FVDC and FP both independently assessed the included studies according to the QUADAS-2 manual. Discrepancies were discussed in a meeting with a third researcher (TMC) aiding in reaching a consensus. Resulting scores were plotted on a stacked bar chart.

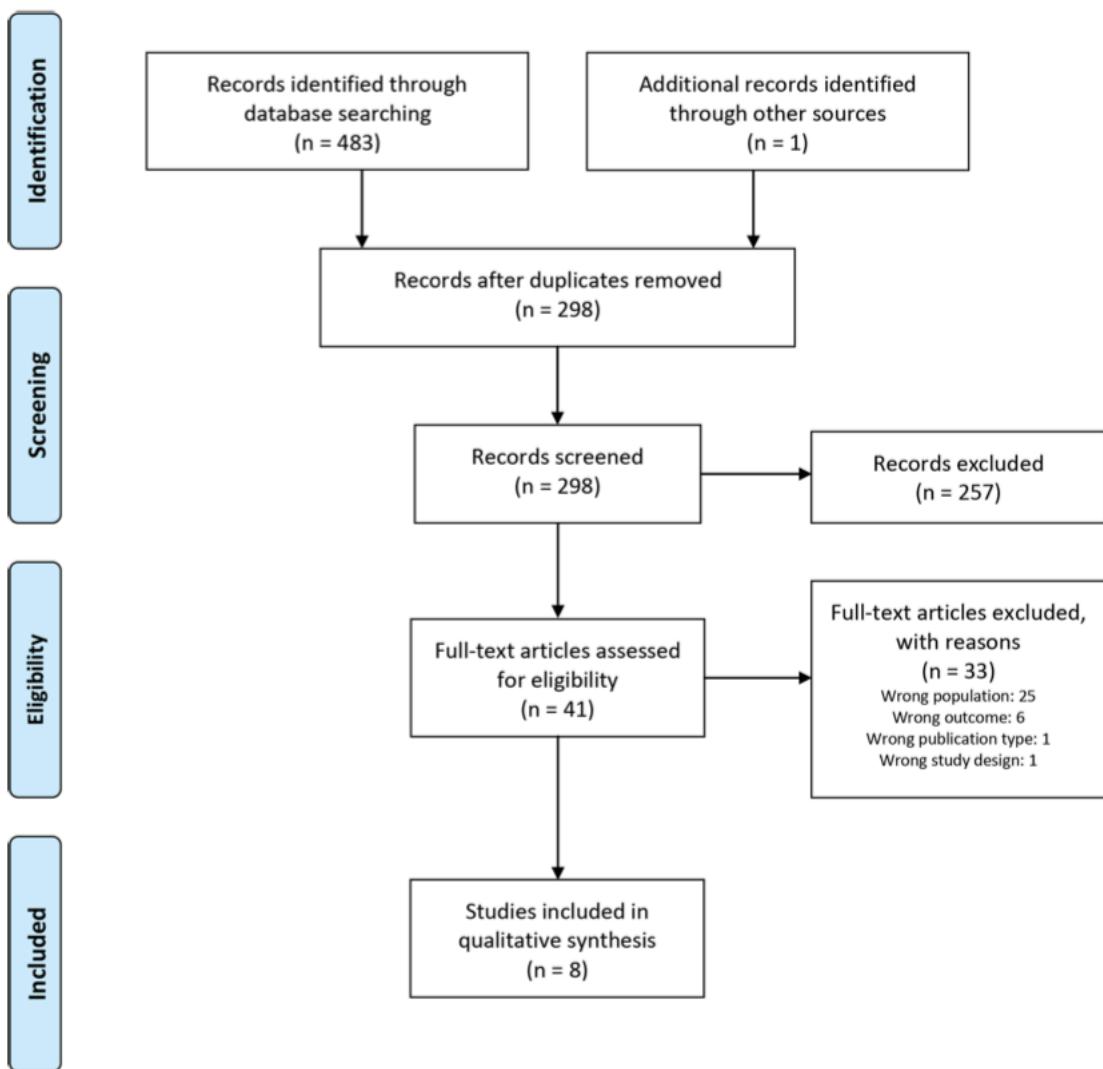
### **Recorded variables, data collection and analysis**

Predetermined variables were extracted from the selected articles when possible and included: type of study, use of a reporting guideline, number of patients, age and gender, inclusion criteria, review questions, timing of MRI acquisition, investigated nerve branch, number of nerves observed, reference test, MRI device, coil type, sequence and sequence settings, use of post-processing techniques, use of contrast, evaluator level, blinding of evaluators, number of readings, type of analysis, formulas used for calculations, measurement areas and region of interests, intra- and interobserver variability, nerve caliber and relative signal intensity, correlation of MRN with NST, clinical and surgical findings, impact on clinical management and the author's conclusions. The first author extracted the data and correctness was verified by the second author.

## **Results**

### **Study selection**

The search yielded 483 articles, and one additional article was retrieved by reference list screening. After deduplication, 298 articles remained. These were screened based on title and abstract, after which 41 articles remained for full-text analysis. Eight articles were retained for the systematic review. Overview of the selection procedure is shown in **Figure 1**.



*Figure 1.* Flow diagram according to PRISMA illustrating the systematic search and results.  
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

### Study characteristics

Most included studies were retrospective (7/8) and five of these were case series, representing 444 subjects in total.<sup>28–32</sup> Two studies applied a case-control design<sup>23,33</sup> and one study a prospective cohort design.<sup>34</sup> None of the articles mentioned the use of a reporting guideline. Using the QUADAS-2 tool, most studies were at high risk of bias but with low applicability concerns (**Table 2, Figure 2**).

Table 2. QUADAS-2 risk assessment for each included study. M3: third molar; “?”: unclear; ☺: high risk; ☻: low risk.

Study	Risk of bias					Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing		Patient selection	Index test	Reference standard
Zuniga et al. (2018)	☺	☺	☺	☺		☺	☺	☺
Dessouky et al. (2018)	☺	☺	☺	☺		☺	☺	☺
Terumitsu et al. (2017)	☺	☺	☺	☺	?	☺	☺	☺
Cox et al. (2016)	☺	☺	☺	☺		☺	☺	☺
Cassetta et al. (2014)	?	☺	☺	☺		☺	☺	☺
Terumitsu et al. (2011)	☺	?	☺	☺		☺	☺	☺
Kress et al. (2004)	☺	☺	☺	☺		☺	☺	☺
Kress et al. (2003)	☺	☺	☺	?		☺	☺	☺

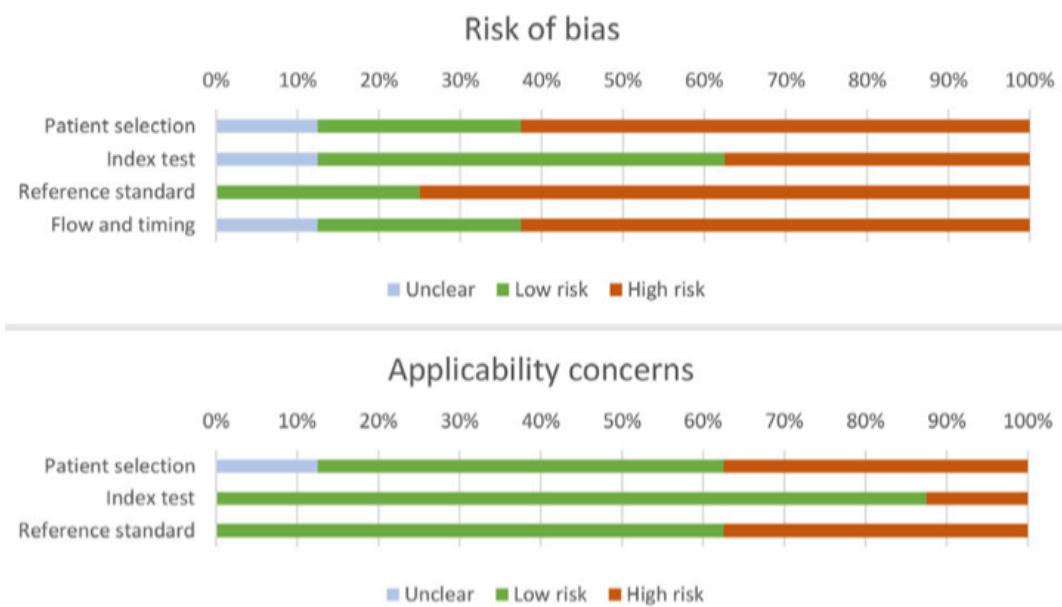


Figure 2. QUADAS-2 risk of bias assessment results. QUADAS 2, Quality Assessment of Diagnostic Accuracy Studies 2.

The inclusion criteria and study-specific research questions turned out to be divergent (**Table 3**). There was a large variation in the timing of the MRI acquisition (3 days–17 years). All studies assessed the inferior alveolar nerve (IAN) and some additionally included lingual nerve injuries (4/8). The reference test mostly consisted of a clinical (neurological) evaluation. Four studies added intraoperative findings as a reference test.<sup>23,31–33</sup> In three studies it was unclear which reference test was applied.<sup>29,30,33</sup> Due to the low methodological quality with widely varying methods, a DTA-analysis nor a meta-analysis could be performed. Consequently, after consultation with all authors, it was decided to provide a broad overview of the study and MRN characteristics, the evaluation methods used, their results and the conclusions drawn by the authors of the selected articles.

*Table 3. Characteristics of included studies. F, female; IAN, inferior alveolar nerve; LN, lingual nerve; M, male; MRN, magnetic resonance neurography; NS, not specified; NSD, neurosensory disturbances; NST, neurosensory testing; QST, quantitative sensory testing; SI, signal intensity.*

Study	Nature	Design	Reported guideline	Number of Patients (M/F)	Inclusion criteria	Review question	Timing of MRI acquisition	Investigated nerve (number of nerves investigated)	Reference test
Zuniga et al. (2018)	Retrospective	Case series	NS	60 Patients	Suspected peripheral trigeminal neuropathy	1. Can MRN differentiate normal from abnormal/non-injured nerves 2. Correlation of MRN with clinical NST and surgical findings	NS	IAN (20) LN (20) IAN (40)	Clinical NST (60/60) Intraoperative findings (26/60)
Dessouky et al. (2018)	Retrospective	Case-control	NS	24 Patients (10/14) 18 Controls (3/15)	Neurosensory disturbances of IAN or LN	1. MRN can differentiate between normal and injured nerves 2. Nerve injury classification correlates with MRN, NST and surgical classification	NS	IAN (NS) LN (NS) (122 in total)	Clinical NST (24) Intraoperative findings (24)
Terumitsu et al. (2017)	Retrospective	Case series	NS	19 (4/15)	Persistent neurosensory disturbances of IAN or LN	1. Anatomic evaluation IAN or LN using 3D AC-PROPELLOR sequence 2. Correlation of NSD severity with MRI morphology	Ranging from 1 month to 108 months after start of symptoms	IAN (12) LN (7)	Patient reported symptoms Contralateral side
Cox et al. (2016)	Retrospective	Case series	NS	17 Patients (7/10)	Suspected peripheral trigeminal neuropathy	1. Assess correlation of MRN with surgical findings 2. Assess impact of MRN on clinical management	Ranging from 2 weeks to 17 years after start of symptoms	LN (4) IAN (13)	Contralateral side? Intraoperative findings
Cassetta et al. (2014)	Prospective	Cohort	NS	196 Patients (112/84)	Indication for mandibular third molar extraction  AND on panoramic radiograph: root apices reach upper border mandibular canal  OR Superimposition of roots over mandibular canal	Course of inferior alveolar neurovascular bundle and SI after third molar surgery	3 days postoperative	IAN (343)	Clinical evaluation + QST (before and after operation)
Terumitsu et al. (2011)	Retrospective	Case series	NS	16 Patients (3/13)	Persistent neurosensory disturbances of IAN	Evaluating IAN using high-resolution 3D volume rendering	Ranging from 1 month to 8 years after start of symptoms	IAN (16)	Clinical evaluation Contralateral side
Kress et al. (2004)	Retrospective	Case-control	NS	30 Healthy subjects 41 Patients (39/2)	MRI following removal of third molar because of swelling, abscess or postoperative bleeding  All patients were free of neurological symptoms	Response of neurovascular bundle to trauma associated with third molar surgery	3-36 hours postoperative	IAN (73)	Contralateral side? Healthy mandibles
Kress et al. (2003)	Retrospective	Case series	NS	23 Patients (19/4)	Fracture of the mandible	1. Visualize the neurovascular mandibular bundle after mandibular fracture 2. Assess its continuity	After fracture but before operative reduction and fixation of the fracture	IAN (21)	Intraoperative evaluation of neurovascular bundle Healthy mandibles

## Synthesis of results

### *Characteristics of included studies & MRI parameters*

An overview of all MRN parameters is given in **Table 4**. The majority of included studies used 3.0 T Philips scanners (5/8). Three studies originated from the same research group.<sup>31,35,36</sup> This research group used a multichannel head coil; other groups used neurovascular (3/8), temporomandibular joint (1/8), or custom-made coils (1/8). Sequence protocols differed between all studies. However, six studies used gradient echo T2 weighted imaging with short echo times (2.2–100 ms). Slice thickness varied between 0.6 and 5 mm. Fat suppression was achieved by using adiabatic inversion pulses in the group of Chhabra et al. Terumitsu et al applied a chemical shift selective pulse. Three studies made use of contrast agents. Post-processing was done in all studies and included multiplanar reformatting (MPR) following the nerve trajectory.

*Table 4. MRI parameters for each study. SPGR: spoiled gradient recalled echo; FIESTA: fast spoiled gradient recalled echo; FFE; fast field echo; CH: channel; FOV: field of view; MPR: multiplanar reformatting; TE: time to echo; TR: repetition time; FA: flip angle; FS: fat saturated.*

Study	MRI device	MRI coil	Sequence protocol	Generic MRI Technique	Acquisition orientation	TE (echo time) (ms)	TR (repetition time) (ms)	Slice thickness (mm)	Matrix (pixels)	FOV (cm)	Number of excitations	Flip angle (°)	Other parameters	Fat suppression techniques	Post processing	Contrast
Zuniga et al. (2018)	1.5T Siemens Avanto	Multichannel headcoil	T2 SPAIR	Spectral attenuated inversion recovery	Axial	69	5320	3.5	320 x 342	Corpus callosum to chin	Adiabatic inversion pulse	MPR coronal and oblique following nerve trajectory	No			
	3.0T Philips Ingenia		T1W	Conventional	Axial	8.7	710	3.5	320 x 342	Corpus callosum to chin						
	3.0T Philips Achieva		CISS 3D	Balanced dual excitation	Axial	2.66	5.32	0.8	256 x 256	Suprasellar area to C2						
			DTI	Diffusion tensor imaging	Axial	83	7100	4	74 x 74	Skull base to chin						
			3D STIR SPACE	Short tau IR	Coronal	78	3000	1.5 (iso)	320 x 259	Corpus callosum to chin						
			3D DW PSIF	Reverse-echo gradient-echo	Coronal	3.25	12	0.9 (iso)	256 x 208	Corpus callosum to chin						
Dessouky et al. (2018)	1.5T Siemens Avanto	Multichannel headcoil	3D DW PSIF	Reverse-echo gradient-echo	Coronal	3.25	12	0.9 (iso)	256 x 208	Corpus callosum to chin	Adiabatic inversion pulse	MPR coronal and oblique following nerve trajectory	No			
	3.0T Philips Ingenia															
	3.0T Philips Achieva															
Terumitsu et al. (2017)	3.0T GE SIGNA	8CH neurovascular Custom 3-inch surface coil	PROPELLOR	Diffusion-weighted imaging	Coronal/axial	78.7	4000	5	128 x 128	18 x 18 (neurovascular coil) 11 x 11 (surface coil)	3				3DAC	No
Cox et al. (2016)	1.5T Siemens Avanto	Multichannel headcoil	T2 SPAIR	Spectral attenuated inversion recovery	Axial	69	5320	3.5	320 x 342	Corpus callosum to chin	Tau = 160 ms	Adiabatic inversion pulse	MPR coronal and oblique following nerve trajectory	2/17 Patients		
			T1W	Conventional	Axial	8.7	710	3.5	320 x 342	Corpus callosum to chin						
			CISS 3D	Balanced dual excitation	Axial	2.66	5.32	0.8	256 x 256	Suprasellar area to C2						
			DTI	Diffusion tensor imaging	Axial	83	7100	4	74 x 74	Skull base to chin						
			3D STIR SPACE	Short tau IR	Coronal	78	3000	1.5 (iso)	320 x 259	Corpus callosum to chin						
			3D DW PSIF	Reverse-echo gradient-echo	Coronal	3.25	12	0.9 (iso)	256 x 208	Corpus callosum to chin						
Cassetta et al. (2014)	3.0T GE Discovery	8CH neurovascular	3D FIESTA (T2)	Balanced gradient-echo	Axial	2.2	4.6	0.6	512 x 512	20 x 20	1				Standard + MPR following nerve trajectory	No
	MR750		3D SPGR (T1)	Fast gradient-echo	Axial	3	8	0.6	512 x 512	15 x 21	2					
Terumitsu et al. (2011)	3.0T GE	8CH neurovascular	3D SPGR (T1)	Incoherent gradient-echo	Not mentioned	4.06	15.576	1.0	320 x 256	18 x 18	2	20	Bandwidth kHz / Voxel size = 0.35 x 0.35 x 0.5 mm	31.2 Chemical shift-selective pulse (CHESS)	Standard + MPR following nerve trajectory Ray-casting process	No
Kress et al. (2004)	Philips (no further specifics)	Temporomandibular joint coil	T2 TSE T1 FFE	Turbo spin-echo Incoherent gradient-echo	Axial Sagittal	100 6.1	4523 15	3 1.5	512 x 326 512 x 326	23 x ? 27 x ?			Principle Of Selective Excitation Technique (Proset)	MPR parasagittal following nerve trajectory	Yes	
Kress et al. (2003)	1.5T (no further specifics)	Not mentioned	T1-weighted Proton density	Conventional Conventional	Not mentioned	6.1	15	1.5	512 x 326 512 x 326	27 x ? 27 x ?	30 15		Fat saturated	MPR parasagittal following nerve trajectory	Yes	

### *MRI evaluation*

The evaluation of MRN images and classification was carried out differently in each study (**Table 5**). Blinding of observers was not guaranteed in most studies (5/8). The number of readings was not mentioned in five articles. In addition to a qualitative analysis, four studies carried out a quantitative analysis. Signal intensities (SIs) or relative signal intensities (RSIs) of target areas were calculated based on different formulas, at different sites and with different measurement areas. These calculations were therefore not comparable.

*Table 5. MRI evaluation and analysis for each study. SI: signal intensity; RSI: relative SI; IAN: inferior alveolar nerve; LN: lingual nerve; ROI: region of interest; M1: first molar; M2: second molar; M3: third molar;  $Si_{rel}$ : relative intensity increase;  $Si_c$ : SI after contrast administration;  $Si_n$ : SI before contrast administration; NST: neurosensory testing; NS: not specified; T2SIR: signal intensity on T2 image; CNR: contrast-to-noise ratio; Y/N: yes/no.*

Study	Evaluation by	Blinded observer?	Number of readings	Type of analysis or measurement	Type of variable	Used formula	Signal intensity measurement area	Region of interest
Zuniga et al. (2018)	2 Musculoskeletal radiologists	No (aware of clinical findings, not of NST)	1	Modified Sunderland classification	Categorical	/	/	/
Dessouky et al. (2018)	Expert radiologist (classification) 2 Expert radiologists (measurements)	No (classification) Yes (measurements)	NS (Training with 6 scans)	Modified Sunderland classification T2SIR CNR Nerve thickness	Categorical Quantitative	$T2SIR = SI \text{ nerve} \div \sqrt{SI \text{ nerve}}$ $CNR = SI \text{ nerve} - SI \text{ pterygoid muscle} \div \sqrt{SI \text{ nerve}}$	SI: freehand ROI	Control group: predefined landmarks - Coronal midmandibular canal - Nerve thickness IAN: maximal transverse dimension in midmandibular canal - Nerve thickness LN: maximum transverse dimension in its midcourse
Terumitsu et al. (2017)	3 Neuroimaging researchers	Yes	NS	Isolated, deformity or incorporated nerve lesion	Categorical	/	/	/
Cox et al. (2016)	Multiple (radiologist attending, fellows)	No	1	Signal change/caliber change: Y/N Mass lesion: Y/N Perineural fibrosis: Y/N Final impression: Y/N	Categorical	/	/	/
Cassetta et al. (2014)	2 Expert radiologists	Yes	3	First session: course of IAN Second session: SI/RSI measurements Third session (1 month after 2nd session): RSI	Qualitative Quantitative	SI on coronal reconstructed FIESTA RSI = SI ROI nerve at surgical site/SI ROI masseter muscle	$15 \text{ mm}^2$	IAN at M3 masseter muscle (reference to calculate RSI)

Study	Evaluation by	Blinded observer?	Number of readings	Type of analysis or measurement	Type of variable	Used formula	Signal intensity measurement area	Region of interest
Terumitsu et al. (2011)	NS	NS	NS	Enlargement/tortuosity: Y/N Mass: Y/N Diffuse connective tissue: Y/N Other: Y/N	Categorical	/	/	/
Kress et al. (2004)	NS	NS	NS	Increase in SI was assessed on T1-weighted images comparing non-contrast versus contrast-enhanced sequences	Quantitative	$SI_{ref} = (SI_c - SI_n)/SI_n \times 100$	Area not defined	Ascending ramus Second premolar, M1, M2, M3
Kress et al. (2003)	Radiologist	Yes	NS	Continuity was assessed on PD images  Increase in SI was assessed on T1-weighted images comparing non-contrast versus contrast-enhanced sequences	Qualitative Quantitative	$SI_{ref} = (SI_c - SI_n)/SI_n \times 100$	15-32 voxels	2 regions proximal, 2 regions distal of fracture site

*Summary of findings*

PTN correlated with MRN abnormalities including nerve deformity and signal alterations (**Table 6**).

*Table 6. Summary of findings. SI: signal intensity; RSI: relative signal intensity; M3: third molar; IAN: inferior alveolar nerve; LN: lingual nerve; PTN: post-traumatic trigeminal neuropathy; SD: standard deviation; N/A: not applicable; NS: not specified; PCC: Pearson correlation coefficient; k: Cohen's kappa.*

Study	MRN	MRN	Relative signal	Nerve thickness of	Correlation with	Correlation with	Impact on clinical	Author's conclusion
	Intraobserver variability (ICC)	Interobserver agreement (k)	intensity of pathologic nerve	pathologic nerve	clinical/NST findings	surgical findings	management	
Zuniga et al. (2018)	NS	NS	Increased	Enlargement	$k = 0.57$	$k = 0.5$ PCC = 0.67		Good to moderate correlation of MRN with NST and surgical findings
Dessouky et al. (2018)	NS	0.75-0.83 (LN) 0.70-0.79 (IAN)	Increased	Enlargement	$k = 0.57$ PCC = 0.68	$k = 0.4$ PCC = 0.81		1. MRN is reliable and accurate for diagnosis of PTN related to third M3 extractions 2. Good to excellent correlation of imaging findings with clinical and surgical results
Terumitsu et al. (2017)	NS	NS	N/A	Enlargement	N/A	N/A		Deformity of the nerve is correlated with severity of symptoms
Cox et al. (2016)	NS	NS	Increased	Enlargement	NS	Moderate to excellent*	None: 5/17 Mild: 6/17 Substantial: 6/17	1. Moderate to excellent correlation between MRN and surgical exploration 2. Significant impact on clinical management
Cassetta et al. (2014)	0.927 (Reader 1) 0.914 (Reader 2)	0.891	Increased	Enlargement	NS	N/A	NS	1. Course of IAN did not differ 2. Neurosensory disturbances persisting beyond 3 months had higher nerve RSI
Terumitsu et al. (2011)	NS	NS	NS	Enlargement	N/A	N/A		15/16 cases with clinical symptoms showed MR abnormalities
Kress et al. (2004)	NS	NS	Increased	NS	NS	N/A	NS	SI increase after M3 removal comparing to healthy mandibles when measuring at second molar and second premolar area
Kress et al. (2003)	NS	NS	Increased	NS	NS	$k = 1$	NS	1. Continuity or discontinuity of IAN could be correctly observed on MRI 2. Fracture induced increased signal intensity after contrast administration compared to healthy mandibles

Terumitsu found that deformity of the nerve was correlated with severity of symptoms.<sup>29</sup> Nerve injury resulted in increased RSI in six studies. Cassetta et al concluded that higher RSIs correlated with PTN persisting beyond three months after injury.<sup>34</sup> Pathologic nerve enlargement in PTN patients was mentioned in six studies.

MRN intraobserver variability was reported in one study by Cassetta (intraclass correlation coefficient 0.914–0.927). Interobserver agreement was reported by Cohen's  $\kappa$  ( $k$ ) in three studies and ranged from 0.70 to 0.891.

Correlation of MRN findings with NST or clinical evaluation was reported by the group of Chhabra et al in two studies ( $k = 0.57$ ). Correlation of MRN findings with surgical exploration ranged from moderate to excellent and was reported in four studies.

The impact of MRN on clinical decision-making was reported in one study by Cox et al.<sup>36</sup> They stated that 29% did not have a change in clinical management and in 35% of cases MRN had substantial impact on their management, meaning a change in treatment.

## Discussion

MRN appears promising in the detection and grading of post-traumatic trigeminal lesions and correlates with clinical and surgical findings as well as neurosensory testing. However, there is a large heterogeneity in the reported studies with high risk of bias. None of the studies reported the use of a guideline or framework such as the STARD guideline.<sup>37</sup> This makes reproducibility and further MRN research difficult. Partly because of this, our primary objective to measure the diagnostic accuracy of MRN in patients with PTN was not achieved.

Most research groups used 3T scanners with T2-weighted gradient echo imaging. Coil type differed between studies, further complicating comparison between protocols. Uniform fat suppression is important to allow adequate evaluation of the peripheral nervous system.<sup>22</sup> Different methods have been described to achieve this and were observed in the selected studies of this review.<sup>38</sup> Future studies should identify which of these sequences render the best suppression and thus nerve selective imaging of the peripheral trigeminal branches.

Post-processing was performed in all studies in which multiplanar reformatting was applied along the course of the nerve. Given the tortuous course of the trigeminal nerve, this would allow for a more holistic assessment. An isotropic voxel size is preferable to further assess its

course in three dimensions, improving resolution and possibly reducing artifacts.<sup>39</sup> This requires a thin slice thickness to adequately visualize these fine nerve branches, which are often less than two millimeters in diameter.<sup>40</sup>

Image interpretation and reporting was diverse with considerable methodological concerns. The outcomes that were assessed ranged from qualitative anatomic considerations towards quantitative RSI calculations. SI calculations require a methodological approach to allow standardization, especially if pulsed sequences are used.<sup>41,42</sup> Since the RSI value seems of prognostic importance as illustrated by Cox et al, determining a standard approach and cutoff values is important for future research into DTA of MRN.<sup>32</sup> In the included studies no cutoff values for relative signal intensity were defined; however the study by Dessouky et al. did report sensitivity and specificity for MRN compared to clinical neurosensory testing and surgical findings, suggesting they determined cut-off values.<sup>35</sup> They reported moderate to good correlation of MRN with injury severity, which was measured using NST or was surgically observed. Additionally, we need to consider that the region of interest where RSI values are measured would depend on the etiology of the PTN and differ depending on the patient inclusion criteria, further complicating future comparison of studies. Therefore, mapping of the whole nerve trajectory could be a methodological approach to consider in future DTA studies.<sup>43</sup>

Finally, the use of MRN and its impact on clinical decision-making was demonstrated in one retrospective study by Cox et al.<sup>36</sup> They illustrated a substantial impact in about one-third of patients, meaning a change in treatment. Although this concerns a small number of patients, it immediately raises the question whether this also has had an impact on outcomes and quality of life. Additionally, future studies should add a cost–benefit analysis of adding MRN to the diagnostic workup. Limitations of this review are the small number of articles obtained, which were of low quality with different methodologies and results. No randomized controlled trials could be identified. Because of these arguments, DTA could not be determined.

In conclusion, there is insufficient scientific base to support or refute the use of MRN in the diagnosis and grading of PTN. MRN seems promising in improving PTN diagnostics and steering treatment decision. However, shortcomings in methodology currently prevent the determination of DTA in a PTN population. There is a need for prospective blinded DTA studies evaluating MRN versus QST in PTN with a rigorous and reproducible study design if a broader clinical implementation is to be achieved.

## **Implications**

This systematic review shows that MRN could aid in the diagnosis, treatment decision and prediction of neurosensory recovery of PTN. However, current studies are at high risk of bias, indicating the need for prospective blinded studies with a rigorous study design, allowing to determine diagnostic test accuracy.

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## **INTERMEZZO**

### **Diagnostic accuracy of non-nerve-selective MRI sequences**

*This chapter is based on the following manuscript:*

Peeters F, **Van der Cruyssen F**, Casselman J, Hermans R, Renton T, Jacobs R, Politis C. The Diagnostic Value of Magnetic Resonance Imaging in Post-traumatic Trigeminal Neuropathic Pain. *J Oral Facial Pain Headache*. 2021;35(1):35-40.

## **Abstract**

### **Aims**

To evaluate the diagnostic value of non–nerve-selective MRI sequences in post-traumatic trigeminal neuropathy (PTN).

### **Methods**

This study retrospectively analyzed all MRI protocols performed between February 2, 2012 and June 20, 2018 commissioned by the Department of Oral and Maxillofacial Surgery, University Hospitals Leuven. Demographic, clinical, and radiologic data were extracted from the records of patients with an MRI in the context of PTN. A contingency table was constructed based on the opinions of the treating physician and the radiologist who initially evaluated the MRI. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

### **Results**

The sample consisted of 27 women (65.9%) and 14 men (34.1%). The sensitivity and negative predictive value of MRI in PTN were 0.18 and 0.77, respectively. Artifacts interfered with visualization of a possible cause of the trigeminal pain in 24.4% of MRIs. Almost all artifacts (90%) were caused by metal debris originating from the causal procedure or post-traumatic surgeries. MRI resulted in changed management for PTNP patients only once.

### **Conclusion**

The diagnostic value of non–nerve-selective MRI sequences for PTNP is low and has little impact on clinical management. Therefore, there is a need for dedicated sequences with high resolution and low artifact susceptibility for visualizing the post-traumatic injuries of the trigeminal branches.

## Introduction

Although neuropathic pain has a low incidence of 8.2 per 1,000 persons a year, it is often considered one of the most difficult pain syndromes to diagnose and manage.<sup>1</sup> In 2020, the International Headache Society (IHS) published the first edition of the International Classification of Orofacial Pain (ICOP).<sup>2</sup> In this classification, post-traumatic trigeminal neuropathy (PTN) was defined and if concurrent with neuropathic pain (PTNP) it was defined as “unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction, and persisting or recurring for more than three months.”

The diagnosis of neuropathic pain in general and PTNP specifically poses a great challenge due to the complex trigeminal nerve system and the variety in clinical symptoms and causes. Therefore, disorders of the trigeminal nerve are often misdiagnosed, which can lead to unnecessary and invasive diagnostic or therapeutic interventions.<sup>3</sup> Until today, there was no gold standard for the diagnosis of PTN. Therefore, the diagnostic process relies on a history of relevant traumatic events, a clinical examination with positive or negative sensory signs in a plausible neuroanatomical distribution, and other diagnostic tests aiming to confirm a lesion of the peripheral trigeminal branch (eg, electromyography or imaging).<sup>4,5</sup> While conebeam CT (CBCT), as well as multislice computed tomography (CT), are used for the 3D evaluation of bony structures, magnetic resonance imaging (MRI) examination is preferred for soft tissue and neurovascular visualization. Therefore, these techniques are often routinely used in the diagnostic process of trigeminal pathologies.<sup>6</sup> Nontraumatic disorders of the trigeminal nerve, such as classical trigeminal neuralgia caused by a neurovascular compression or secondary trigeminal neuralgia caused by inflammation or infections, can be diagnosed based on MRI examination.<sup>7,8</sup> However, the visualization capability of MRI strongly depends on the chosen sequences.<sup>9</sup>

Therefore, it is believed that MRI could have the same impact on PTN, but its potential has not been able to be realized until presently due to the use of non–nerve-selective sequences.<sup>10</sup> The objective of this retrospective study is to assess the hypothesis that the diagnostic value of current non–nerve-selective MRI sequences used in clinical practice in the context of PTN is low and has a minor impact on the clinical management of these patients, hereby underlining the need for nerve-selective MRI sequences.

## **Materials and Methods**

### **Patient and Radiologic Characteristics**

This study was approved by the Ethics Committee of the University Hospitals Leuven (S62823) and conducted in compliance with Good Clinical Practice standards and the Declaration of Helsinki. All protocols of MRI scans that were performed between February 1, 2012 and June 20, 2018 commissioned by the Department of Oral and Maxillofacial Surgery of the University Hospitals Leuven were retrospectively analyzed. The medical records of patients with PTN were retrospectively evaluated for demographic, clinical, and radiologic characteristics. Demographic data consisted of age and sex of the patients. Information about the causal trauma and the affected trigeminal nerve branch was extracted from the medical file of the first consultation in the context of trigeminal pain. Findings of the physical examination were classified as positive sensory signs (e.g. hyperalgesia, allodynia), negative sensory signs (e.g. hypoesthesia, anesthesia), or a combination of positive and negative sensory signs. Based on these findings, patients were divided into two subgroups: painful neuropathy and nonpainful neuropathy. The initial management of the trigeminal pain problem was categorized into watchful waiting, pharmacologic treatment, or surgery. Medical records after the MRI were searched for information about the impact of the MRI findings on the initial management. If the MRI results changed the initial management, details about the treatment decisions were collected. The following MRI parameters were extracted from the radiologic reports: used MRI sequences; the use of a gadolinium-based contrast agent; the total nerve of interest visualized on MRI; the ability to visualize the most plausible cause of the trigeminal pain on MRI; and the presence of artifacts on the MRI that possibly limited the reporting of a lesion of the trigeminal nerve; and the type of artifact, categorized into movement artifact or metal artifact.

### **Contingency Table**

A contingency table was constructed based on clinical and radiologic opinions found in the medical records of the patients. The clinical opinion was considered positive when there was a relevant history of a neurologic lesion with sensory signs and/or pain in a neuroanatomically plausible region or when confirmed by exploratory surgery in accordance with the suggested grading system by Finnerup et al.<sup>5</sup>

The radiologic opinion was based on the report of the performed MRI in the context of a possible PTN case. The MRI was considered positive when the initial radiology report mentioned the visualization of a lesion of a peripheral trigeminal nerve branch.

### Statistical Analysis

Statistical analysis was conducted in GraphPad Prism 8 software. Univariate analyses (eg, mean and mode) were used for different variables in the total dataset to summarize the patient characteristics in this sample. A contingency table was constructed for the total dataset, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Since there were cells with an expected cell count of less than five, Fisher exact test was conducted between the clinical and radiologic opinions to determine if there was an association between these two dichotomous variables. Further statistical tests to assess the correlation between clinical and radiologic variables were not performed due to the low number of subjects per group.

## Results

### Patient Characteristics

This sample consisted of 41 patients who underwent MRI examination in the context of PTN, comprising 27 women (65.9%) and 14 (34.1%) men. Their mean age was  $42.59 \pm 14.20$  years, with a range between 4 and 70 years (**Table 1**).

*Table 1. Patient and clinical characteristics of all 41 patients with an MRI in the context of PTN. All data are reported as n (%) unless otherwise indicated.*

Mean (SD) age	42.59 (14.20)
Gender	
Men	14 (34.1)
Women	27 (65.9)
Evaluated nerve	
Lingual nerve	13 (31.7)
Inferior alveolar nerve	11 (26.8)
Mandibular nerve	7 (17.1)
Complete trigeminal nerve	6 (14.6)
Maxillary nerve	4 (9.7)
Cause of injury	

Non-wisdom tooth extraction	10 (24.4)
Third molar surgery	9 (21.9)
Orthognathic surgery	5 (12.2)
Local anesthesia	4 (9.8)
Noniatrogenic trauma	4 (9.8)
Implant placement	3 (7.3)
Other iatrogenic trauma	6 (14.6)
Clinical symptoms	
Positive sensory signs	21 (51.2)
Negative sensory signs	11 (26.8)
Positive and negative sensory signs	9 (21.9)
Subgroups based on clinical findings	
Painful neuropathy	30 (73.2)
Nonpainful neuropathy	11 (26.8)
Initial management, n (%)	
Watchful waiting	3 (7.3)
Medication	28 (68.3)
Surgery	10 (24.4)

The majority of patients had a possible cause in their medical history, most frequently being tooth extraction or orthognathic surgery. Nearly 75% of all patients were assigned to the subgroup for painful neuropathy on the basis of physical examination. More than half of the patients (51.2%) presented with positive sensory signs, eleven patients (26.8%) with negative sensory signs, and nine patients (21.9%) with a combination of positive and negative sensory signs. In the diagnostic work-up, dental panoramic radiography and CBCT were almost always added to the MRI examination (**Table 2**).

*Table 2. Added imaging exams next to an MRI, artifacts detected on MRI and use of gadolinium contrast in the study sample (N= 41). All data are reported as n (%). PANO: dental panoramic radiography. CBCT: conebeam CT.*

PANO	35 (85.4)
CBCT	26 (63.4)
Second MRI	1 (2.4)
Artifacts on MRI	10 (24.4)
Use of gadolinium-based contrast agents in MRI	39 (95.1)

## Contingency Table

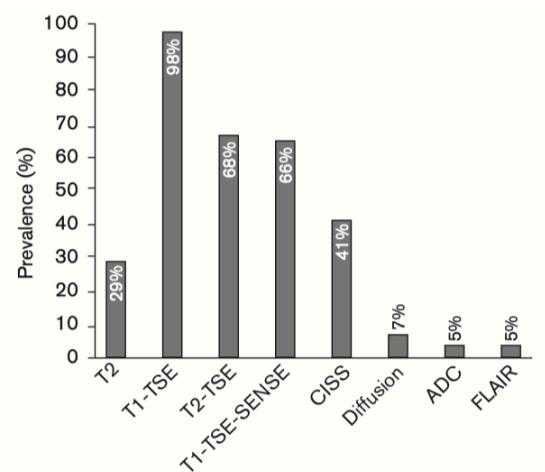
Specificity and PPV were 1 (**Table 3**). Sensitivity and NPV were 0.18 and 0.77, respectively. Fisher exact test showed no significant association ( $P = .067$ ) between clinical and radiologic opinions.

*Table 3. Contingency table of PTN. A positive MRI (MRI +) means that the most plausible cause of PTN could be visualized on MRI. The clinical opinion was defined as the diagnosis based on other radiological modalities or surgical exploration and was positive when the most plausible cause of the trigeminal pain could be demonstrated. Sens: Sensitivity; Spec: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value.*

	Clinical +	Clinical -	Total	
MRI +	2	0	2	<b>PPV: 1</b>
MRI -	9	30	39	<b>NPV: 0,77</b>
Total	11	30	41	
Sens: 0,18		Spec: 1		

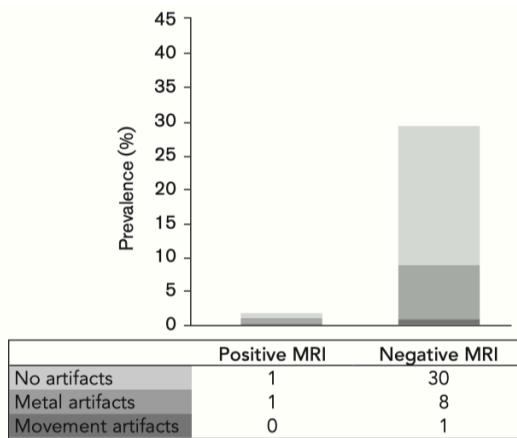
## MRI sequences and artifacts

All 41 MRIs were taken on an Ingenia 3.0T scanner (Philips Healthcare, Best, Netherlands). A total of ten different MRI sequences were used. A T1-TSE sequence was present in 98% of cases (**Figure 1**).



*Figure 1.* MRI sequences used in the study population ( $N = 41$  patients). Only MRI sequences used in  $> 5\%$  of patients are shown. T2 = T2-weighted sequence; T1-TSE = weighted turbo spin echo; T2-TSE = T2-weighted turbo spin echo; T1-TSE-SENSE = T1-weighted turbo spin echo sensitivity encoding; CISS = constructive interference steady state; ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery.

No metal artifact reduction pulse sequences were applied. A gadolinium-based contrast agent was used in 95% of MRIs taken in the context of PTN. An artifact that possibly limited the visualization of a cause was present in 24.4% of the MRIs (Table 2). Nine out of ten artifacts were metal artifacts caused by metal debris originating from the causal procedure (e.g. orthognathic surgery) (Figure 2).



*Figure 2.* The presence of artifacts on MRIs. The MRI was considered positive if the cause of PTN could be identified by the consulting radiologist.

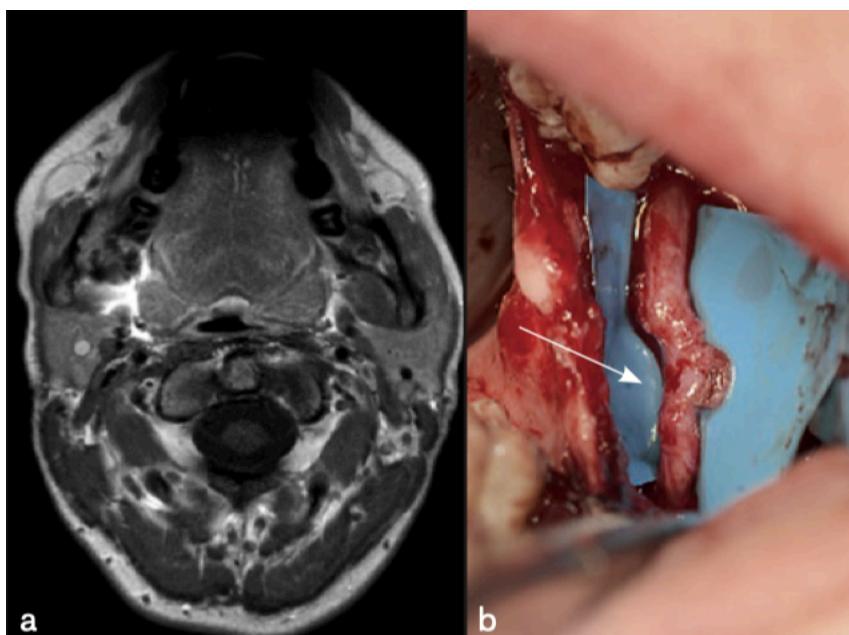
MRI acquisition resulted only once (2.4%) in changed management for the PTN patient. This patient suffered from PTN caused by third molar extraction. Subsequent nerve damage was visualized on T2-TSE. Therefore, a microsurgical repair was performed.

## Discussion

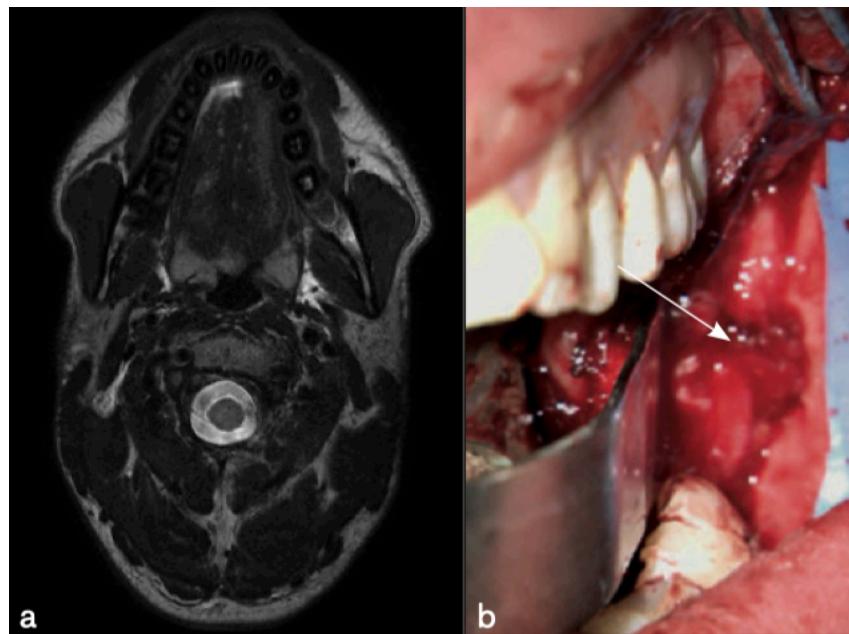
This study provides real-world information from a tertiary referral center about the diagnostic value of non–nerve-selective MRI sequences in the context of PTN. The demographic results and age and sex ratios for PTN patients were in line with the findings of Zuniga et al.<sup>11</sup>

Although MRI has good results for the diagnosis of classical and secondary trigeminal neuralgia and is even included in the guidelines for these two pathologies, the question remains as to whether it can be an asset in the diagnosis and treatment of PTN.<sup>12–14</sup>

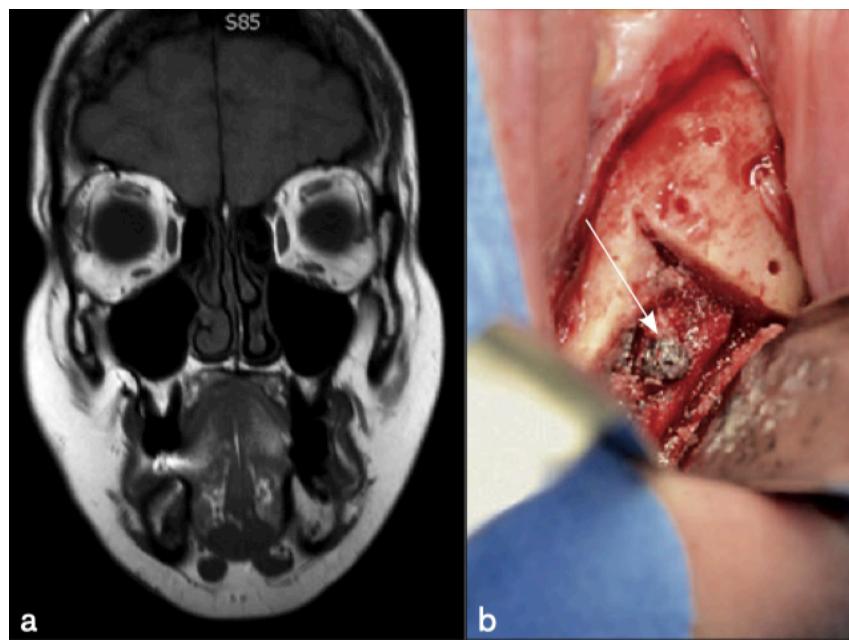
Currently, MRI is not part of the guidelines for the diagnosis of PTN and therefore not used for every patient consulting with a history suggestive of PTN.<sup>2</sup> It is only used in specific cases to provide important information when differentiating between diagnoses or when surgical repair is a therapeutic option. However, the contingency table (**Table 3**) of this study shows that the sensitivity and NPV of MRI for the causal injury of the trigeminal nerve are 0.18 and 0.77, respectively. This means that an MRI examination with non–nerve-selective sequences is not designated for diagnosis of post-traumatic trigeminal injuries; otherwise, too many false negative results will be obtained (**Figures 3 to 5**). Non–nerve-selective MRI sequences are therefore not able to provide an important added value to the diagnostic work-up. Moreover, MRI resulted in changed management for these patients only once (2.4%).



*Figure 3. (a) MRI and (b) surgical images of a patient exhibiting trauma due to crushing of the lingual nerve (third division of the trigeminal nerve) caused by third molar extraction. This lesion could not be visualized on MRI (T1-TSE sequence) due to metal artifacts, but surgery was performed due to a clinical indication. During the surgery, a neuroma-in-continuity of the lingual nerve was found (arrow).*



*Figure 4. (a) MRI and (b) surgical images of a patient reporting trigeminal pain after third molar extraction. The treating physician suspected PTN of the lingual nerve, and an MRI (T2-weighted sequence) was performed. There were no artifacts that limited the reporting of a possible lesion, but the lingual nerve could not be visualized on the MRI. During surgery, a complete transection of the lingual nerve was found (arrow).*



*Figure 5. (a) MRI and (b) surgical images of a patient reporting neuropathic pain after a dental implant placement procedure. There was no clear visualization of the trauma on MRI (T1-TSE sequence), but during surgery, contact between the implant screw and the inferior alveolar nerve was seen (arrow).*

A possible explanation for the low diagnostic value of the current non–nerve-selective MRI sequences is the frequent presence of a metal artifact, which possibly limits the visualization of a lesion. In this study, artifacts possibly interfered with visualization of a cause in 24.4% of MRIs.

However, artifacts alone cannot completely explain the low diagnostic value of MRI in PTN. There was no artifact present in five out of nine false negative MRIs (**Figure 2**). The remaining cause is most probably inherent to non–nerve-selective MRI sequences.

Although MRI is often used to image larger nerves, Cassetta et al. demonstrated that evaluation of the inferior alveolar nerve (IAN) is possible by means of a 3T MRI and that early assessment of relative signal intensity values can be considered a valid predictor for the prognosis of sensory disorders.<sup>15</sup> Recent findings have shown the potential of nerve-selective magnetic resonance techniques in the visualization of the peripheral trigeminal nerve system and injuries of the small trigeminal branches.<sup>10,11,16,17</sup> The capacity to visualize the trigeminal nerve depends on the used sequences, and therefore a nerve-selective MRI protocol needs to be composed of sequences with high resolution and low artifact susceptibility. Specific magnetic resonance neurography (MRN) sequences in previous research articles were most often executed on 3T scanners with T2-weighted gradient echo imaging.<sup>18</sup> To clearly visualize the peripheral trigeminal nerve system, a uniform fat suppression sequence for example, an adiabatic inversion pulse or a chemical shift selective pulse—must be added to this combination.<sup>18–20</sup> Since the presence of a metal artifact often hinders the visualization of a possible lesion in this population, sequences with low artifact susceptibility based on spin echo imaging should be preferred. Newer techniques such as slice encoding for metal artifact correction and view angle tilting sequences could provide added value in a standardized combination of MRI sequences in the context of PTN.<sup>21</sup>

The present study has limitations, including its retrospective nature and the subsequent introduction of selection bias. The retrospective design also implies a large amount of different MRI sequences, depending on the choice of the consulting radiologist. Therefore, this study did not have the purpose of evaluating the diagnostic value of each individual MRI sequence, but rather of illustrating the real-world value of non-nerve-selective MRI sequences. In the future, a single or multicenter prospective study should be performed to evaluate and compare the diagnostic value of different MRI sequences. Quantitative sensory testing was not executed in a standardized way in the diagnostic process of these patients, and therefore clinical opinion

was based on basic neurosensory testing and thorough history-taking. An association between the MRI results and clinical symptoms could not be determined due to the low sample size.

Due to the lack of a golden standard reference test, it was decided to create the contingency table based on the opinions of the clinician and radiologist. Therefore, this table demonstrates the agreement between MRI and clinical evaluation. Subsequently, the definitions of sensitivity, specificity, PPV, and NPV are not aligned with their usual definitions.

## **Conclusions**

This study showed that the diagnostic value of non-nerve-selective MRI sequences for PTN patients is low and has little impact on the clinical management of these patients. Currently, the diagnosis of PTN should rely on a combination of thorough history-taking, clinical examination, and other radiologic modalities, sometimes supplemented with a surgical exploration.<sup>22</sup> However, it is unethical to perform a surgical exploration for every suspected nerve injury, and MRI has the potential to provide a clear indication for surgery with its ability to directly visualize the nerve. Consequently, there is a need for dedicated MRI sequences with high resolution and low artifact susceptibility for visualizing the post-traumatic injuries of the peripheral trigeminal branches in the maxillofacial area.

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## CHAPTER 6

### The 3D CRANI MRN sequence: a proof-of-concept

*This chapter is based on the following manuscript:*

**Van der Cruyssen F, Croonenborghs TM, Hermans R, Jacobs R, Casselman J.** 3D Cranial Nerve Imaging, a Novel MR Neurography Technique Using Black-Blood STIR TSE with a Pseudo Steady-State Sweep and Motion-Sensitized Driven Equilibrium Pulse for the Visualization of the Extraforaminal Cranial Nerve Branches. *American Journal of Neuroradiology*. 2020;42(3):578-580.

## **Abstract**

This study investigated the feasibility of a 3D black blood STIR TSE sequence with a pseudo-steady state sweep and motion-sensitized driven equilibrium (MSDE) pulse for extraforaminal cranial nerve imaging (3D CRANI) on a 3T system. Assessments on healthy volunteers showed near-perfect agreement in nerve visualization with excellent to good visualization of the extraforaminal trigeminal, greater occipital, and facial nerves. Suppression of surrounding tissues was excellent to good. The 3D CRANI can produce nerve-selective imaging of extraforaminal cranial and spinal nerve branches.

## Introduction

Being the largest cranial nerve, the trigeminal nerve—more specifically its inferior alveolar and lingual branches—is frequently damaged during dental, oral, and maxillofacial surgical procedures.<sup>1</sup> Moreover, it can be subject to a myriad of disease entities such as inflammatory, infectious, neoplastic, and congenital pathology. Magnetic resonance imaging has been widely applied to the visualization of cranial nerves.<sup>2</sup> Intracranial trajectories such as nuclear and supranuclear, as well as cisternal segments, can be well depicted on routine MRI sequences. The cisternal segment is typically visualized using constructive interference in steady-state (CISS) and 3D heavily-T2WI.<sup>3</sup> However, visualization of the extracranial peripheral branches on 3D T2WI remains a challenge because of their small diameters, tortuous courses, movement and susceptibility artifacts, and the presence of blood vessels in close proximity, which can all confound nerve visualization.<sup>4</sup> B1 and B0 inhomogeneities further lead to poor fat suppression and low SNR, and the use of multiple echoes to improve water and fat separation increases acquisition times considerably, making patient compliance difficult. Therefore, to address the above-mentioned problems, we developed a novel black blood 3D Short TI Inversion Recovery Turbo Spin Echo (STIR TSE) sequence for extraforaminal cranial nerve imaging (3D CRANI) on a 3T system, and here describe its assessment.

## Description of technique

The 3D CRANI is a 3D TSE STIR black blood sequence that uses a pseudo-steady state (PSS) sweep in combination with a motion-sensitized driven equilibrium (MSDE) pulse. We used STIR in combination with MSDE to ensure that signals from fat, muscle, and blood are suppressed uniformly across the field of view. The PSS sweep is designed such that the signal is smoothly varying during a long TSE shot to keep the signal strength approximately constant. This means that the flip angle sweep is not calculated based on specific tissue parameters (T1, T2). In this manner, it helps us to reduce the T2 decay for a range of tissues, which makes the sequence less sensitive to tissue dependencies. For the PSS functionality, a minimum, middle, and maximum angle need to be defined, and four intermediate flip angles are used to asymptotically approach the minimum flip angle defined within the sequence (**Supplementary Figure 1**). After reaching the minimum angle, non-linear interpolation is used to calculate an optimum sweep according to the PSS principle, while trying to keep the signal constant.<sup>5</sup> The middle angle is defined at the specified effective TE. After definition of the middle angle, the refocusing angles are increased linearly to the maximum defined angle. Finally, compressed

sensing is added to reduce the acquisition time. The sequence was optimized by comparing it to existing nerve-selective sequences until satisfactory and robust results were obtained, with particular attention being paid to artifact reduction (**Supplementary Figure 2**).

### MR imaging procedure

After optimization, six healthy volunteers (three females and three males; average age of 32 years; range 23–48 years) were included in this study. Imaging was performed on a 3T MRI system (Ingenia; Philips, Best, Netherlands) equipped with a 32-channel head coil (INVIVO, Gainesville, USA) without the use of any contrast agent. After acquisition of standard T1WI, T2WI, and gradient echo sequences, the CRANI sequence was acquired using the following parameters: TR = 2300 ms, TE = 150 ms, FOV = 200 × 200 × 100 mm, slice thickness = 0.5 mm, act slice gap = −0.45 mm, matrix = 224 × 222, acquired voxel size = 0.9 × 0.9 × 0.9 mm, reconstructed voxel size = 0.5 × 0.5 × 0.45 mm, slice oversampling = 1.5, compressed sense reduction = 5, number of slices = 200. TSE Nerve STIR included TSE factor = 45 (startup echoes 2), number of acquisitions = 1, black blood pulse = MSDE (mode: nerve), acquisition time = 5:17 min.

### Imaging analysis

Three orthogonal planes, as well as a plane following the course of the nerve trajectory using MPR and MIP, were reconstructed using the Philips Volume post-processing package (Philips, Best, Netherlands). MIP images with a thickness of 5 mm and gap of −0.5 mm (4.5 mm overlap) allowed for the best demonstration of the selected nerve trajectory. The images were analyzed by two fixed and independent observers with expertise in cranial nerve imaging. First, a training session was held to familiarize the observers with the grading scales, then, for the subsequent evaluations, the observers were blinded to each other's scoring. Arterial, venous, and fat suppression were graded on a three-point Likert scale (0: unsuppressed and nondiagnostic; 1: moderately suppressed but diagnostic; 2: excellent suppression). A nerve scoring system using a five-point Likert scale (4, excellent; 3, good; 2, fair; 1, poor; 0, none) was adopted from Fujii et al. to evaluate the signal continuity of the following nerves over a predetermined trajectory. The evaluated trajectory of the inferior alveolar (n. V3) and lingual nerves (n. V3) starts at the oval foramen and stops at the mental foramen and the submandibular duct, respectively. The facial nerve (n. VII) trajectory starts in the labyrinthine portion in the temporal bone and stops at the anterior edge of the parotid. The greater occipital nerve (n. C2-C3) trajectory starts posteriorly of the axis and stops before piercing the trapezius muscle.<sup>6</sup>

## Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA). Interobserver agreement on the Likert scales was tested using weighted kappa statistics with quadratic weights. A P value of less than 0.05 was considered significant.

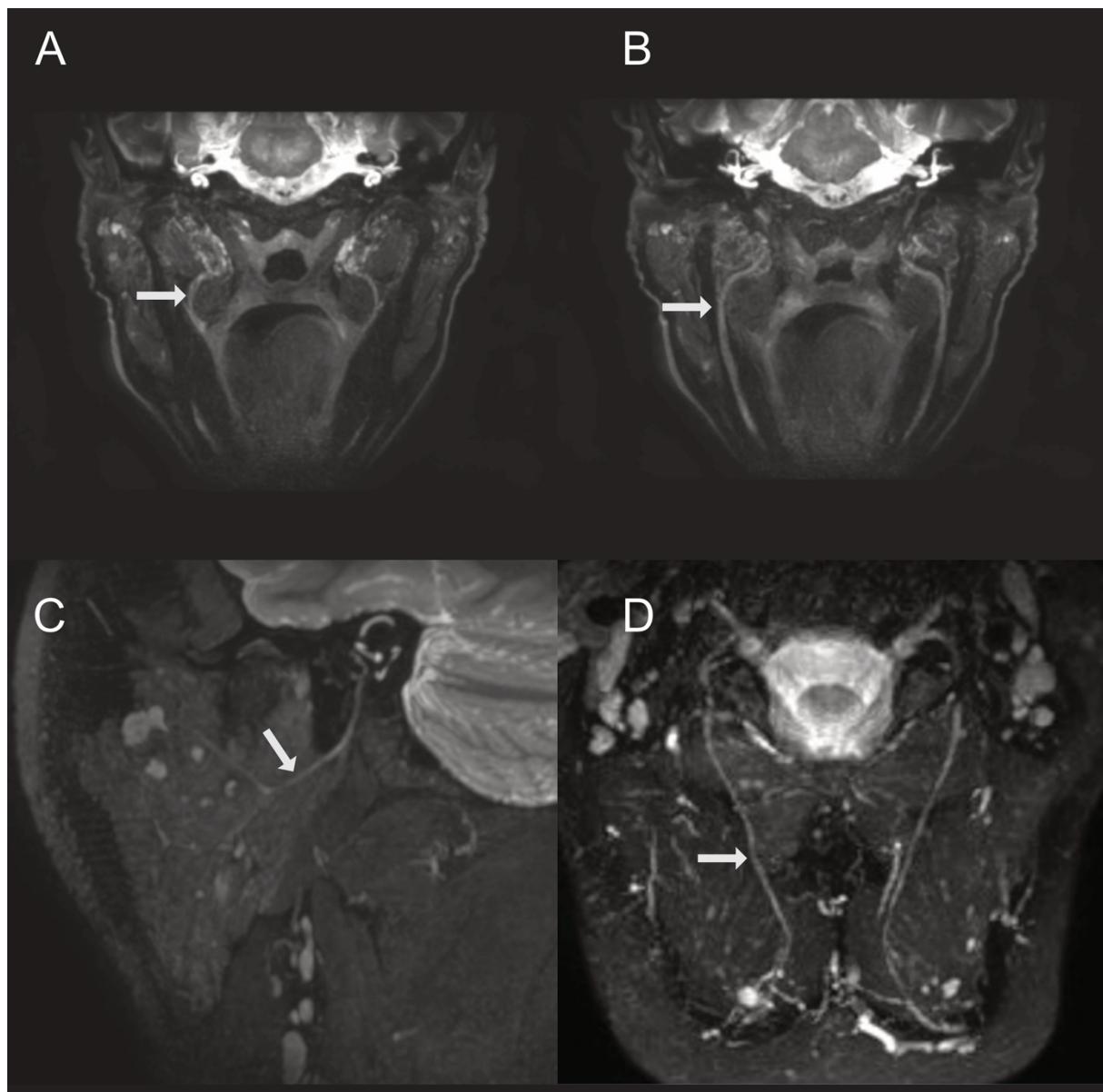
## Results

There was a statistically significant near-perfect agreement between the two observers, except in the visualization of the extracranial portion of the facial nerve, for which the agreement was still considered to be very good (independent observer scores are illustrated in **Supplementary Table 1**). The strength of agreement ranged from very good to excellent for all parameters (**Table 1**).

*Table 1. Weighted kappa scores, confidence intervals, and P values for the interobserver agreement for the observed variables.*

Parameter	Weighted Kappa	95% Confidence Interval	P Value
Arterial suppression	1	1-1	0.014
Venous suppression	1	1-1	0.014
Fat suppression	1	1-1	0.014
Overall nerve visualization	1	1-1	0.014
Inferior alveolar nerve	1	1-1	0.014
Lingual nerve	1	1-1	0.014
Facial nerve	0.933	0.79-1.10	0.020
Greater occipital nerve	1	1-1	0.014

Venous suppression was evaluated as excellent, except in two cases where it was considered “moderately suppressed”. These two cases also had the lowest scores for the other variables observed. When the independent nerve scoring results were evaluated, the facial nerve had the lowest scores. The visualizations of the trigeminal and greater occipital nerve branches were rated as good to excellent. **Figure 1** illustrates the nerve-selective sequence with examples of the evaluated structures.



*Figure 1. The evaluated cranial and spinal nerve branches acquired using the 3D CRANI sequence. A, Lingual nerve (arrow) on MIP after MPR. B, Inferior alveolar nerve (arrow) after MIP MPR on a coronal oblique reconstruction. C, Extraforaminal facial nerve (arrow) after sagittal oblique MIP MPR, illustrating the intraparotid nerve course. D, Greater occipital nerve (arrow) extending between the semispinalis muscles on MIP MPR.*

## Discussion

This technical note successfully demonstrates the use of 3D CRANI, a modified black blood STIR TSE sequence for nerve-selective imaging of peripheral cranial and spinal nerve branches. Diffusion-weighted pre-pulsing by MSDE for magnetic resonance neurography (MRN) purposes was first described by Yoneyama et al., and further demonstrated for brachial

plexus imaging by Klupp et al.<sup>7,8</sup> This study is innovative in the sense that an MSDE pulse was applied in combination with a PSS sweep to further optimize nerve-enhanced imaging within clinically feasible acquisition times. The results from our study indicate excellent inter-observer agreement. Moreover, the scoring of the images indicates moderate to excellent suppression of surrounding tissues. Chhabra et al. published several papers on cranial nerve imaging and advocate several sequences for clinical evaluations, including a STIR TSE sequence when magnetic field inhomogeneities are expected.<sup>9–12</sup> However, their main imaging method for MRN involves diffusion-weighted reversed fast imaging with steady state free precession (PSIF), which is applied using gradient echo imaging. In the past, gradient echo imaging was preferred because of its short acquisition times. However, with new techniques such as those illustrated in this study, STIR sequences with reasonable acquisition times, low artifact susceptibility, and excellent fat suppression have become possible. The current limitations appear to be similar signal intensities for nerve and (intraparotid) lymphoid tissue, unpredictable visualization of nerves with a diameter less than 0.9 mm, and imperfect venous suppression of the pterygoid plexus. A future large prospective study will be designed to validate this sequence in both healthy and patient populations, comparing 3D CRANI with existing protocols.

## Conclusion

The 3D CRANI can produce nerve-selective imaging of the trigeminal, facial, and greater occipital extraforaminal nerve branches, with excellent interobserver agreement, and within clinically feasible acquisition times. Prospective studies are needed to further evaluate and validate its clinical use.

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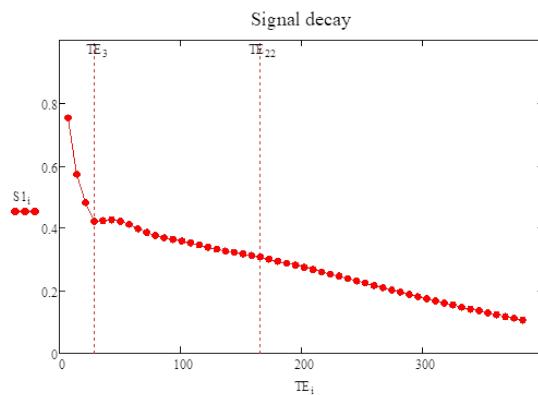
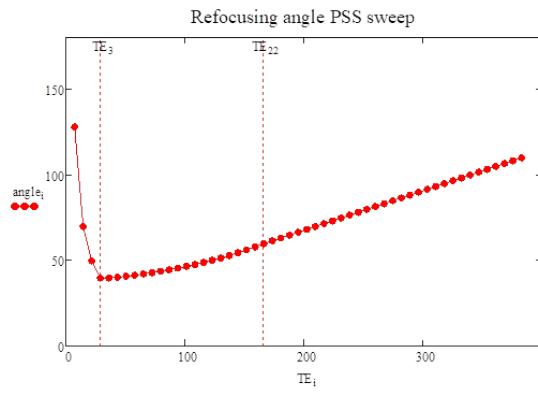
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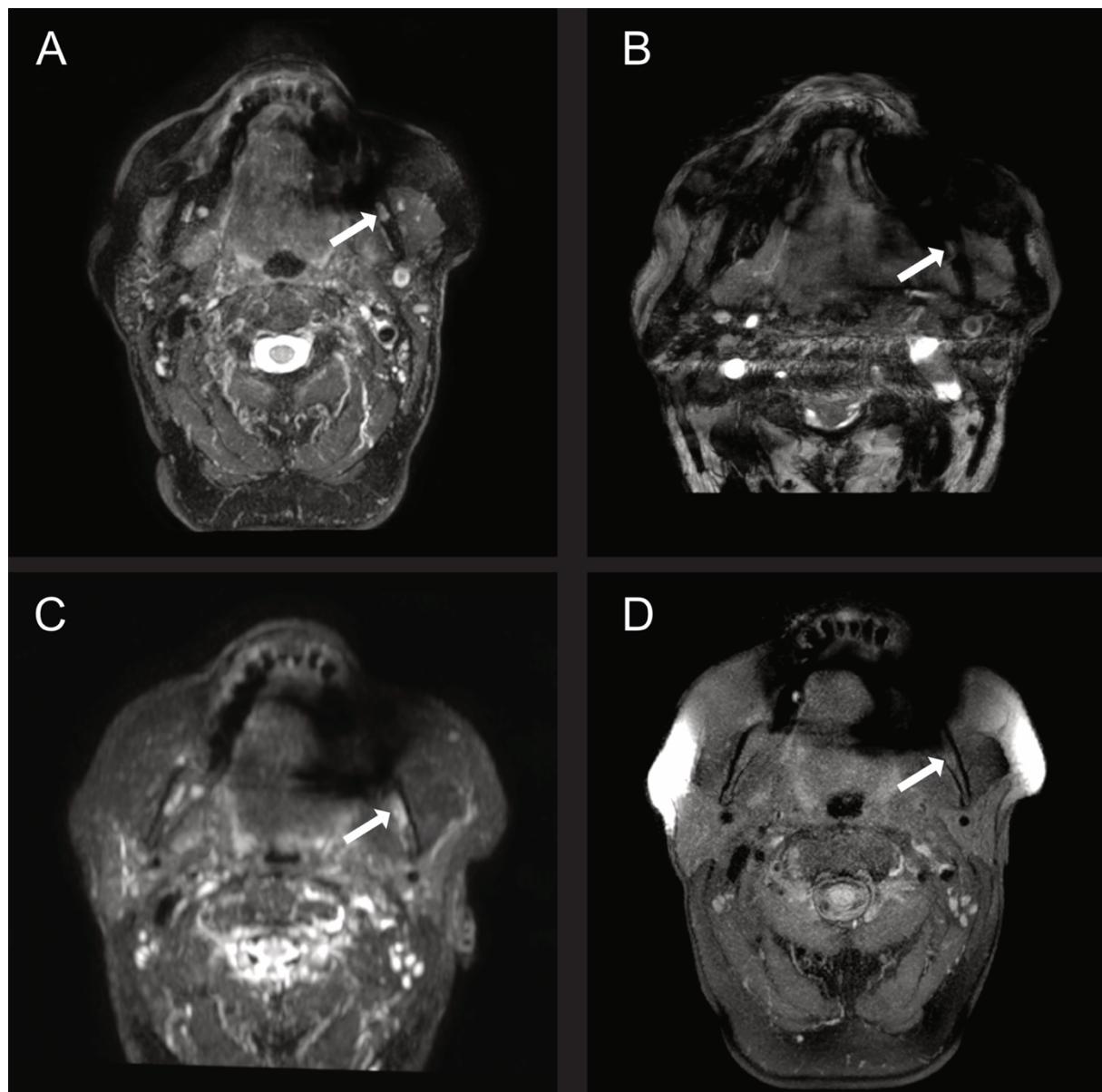
## Supplementary data

*Supplementary Table 1. Scores by the two independent observers for arterial, venous, and fat suppression of the 3D CRANI sequence. Suppression was scored using a three-point Likert scale (0: un suppressed and nondiagnostic; 1: moderately suppressed but diagnostic; 2: excellent suppression). A nerve scoring system using a five-point Likert scale was adopted from Fuji et al. (4: excellent; 3: good; 2: fair; 1: poor; 0: none). F: female; M: male.*

Case number	Sex	Age	Observer 1							Observer 2								
			Arterial suppression	Venous suppression	Fat suppression	Overall nerve visualization	Inferior alveolar nerve	Lingual nerve	Facial nerve	Greater occipital nerve	Arterial suppression	Venous suppression	Fat suppression	Overall nerve visualization	Inferior alveolar nerve	Lingual nerve	Facial nerve	Greater occipital nerve
1	F	25	2	1	2	1	3	3	3	4	2	1	2	1	3	3	3	4
2	M	28	2	2	1	2	4	4	1	4	2	2	2	2	4	4	1	4
3	M	25	2	1	2	1	3	3	3	3	2	1	2	1	3	3	2	3
4	M	23	2	2	2	2	4	4	4	4	2	2	2	2	4	4	4	4
5	F	48	2	2	1	2	4	4	4	4	2	2	2	2	4	4	4	4
6	F	44	2	2	2	2	4	4	4	4	2	2	2	2	4	4	4	4



*Supplementary Figure 1.* Pseudo-steady state (PSS) sweep curves indicating the minimum, middle, and maximum angles. After reaching the minimum angle, non-linear interpolation is used to calculate an optimum sweep, while trying to keep the signal constant.



*Supplementary Figure 2. Comparison of some contemporary magnetic resonance sequences and the newly introduced 3D CRANI sequence in a subject with titanium osteosynthesis material in the left mandible. Notice the artifact reduction when the 3D CRANI sequence is applied. The inferior alveolar nerve is indicated (white arrow). A: 3D CRANI sequence. B: 3D PSIF (reverse fast imaging with steady-state free precession). C: 3D Brainview (Philips, Best, The Netherlands). D: 3D THRIVE (T1 high-resolution isotropic volume excitation).*

## CHAPTER 7

### MRN: state of the art, anatomy, pathology, future

*This chapter is based on the following manuscript:*

**Van der Cruyssen F**, Croonenborghs TM, Renton T, Hermans R, Politis C, Jacobs R, Casselman J. Magnetic resonance neurography of the head and neck: state of the art, anatomy, pathology and future perspectives. *The British Journal of Radiology*. 2021;94(October):20200798.

## **Abstract**

Magnetic resonance neurography allows for the selective visualization of peripheral nerves and is increasingly being investigated. Whereas in the past the imaging of the extracranial cranial and occipital nerve branches was inadequate, more and more techniques are now available that do allow nerve imaging. This basic review provides an overview of the literature with current state of the art, anatomical landmarks and future perspectives. Furthermore, we illustrate the possibilities of the 3D CRANI MR-sequence by means of a few case studies.

## **Introduction**

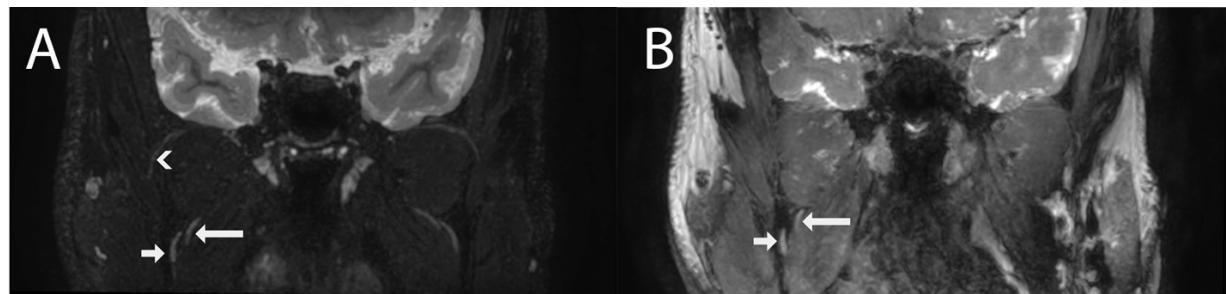
Magnetic resonance neurography (MRN) refers to dedicated MRI sequences that selectively enhance the visualization of peripheral nerves. Several techniques have been described in the literature including 2D and 3D T2 weighted fat suppressed and diffusion weighted imaging.<sup>1</sup> The first reports on MRN date from 1992 by Howe and Filler and have much evolved since then.<sup>2</sup> At present, MRN is gaining importance due to the introduction of high-field MRI devices and improved imaging techniques.

The skull base course of cranial nerve MRI anatomy has been extensively reviewed.<sup>3–6</sup> In this article we will review the state of the art and relevant MRN anatomy of the extracranial cranial and occipital nerve branches with illustrative pathologic cases. The author's 3D CRANI MRN sequence will be shared together with its clinical application. This sequence makes use of the latest technical developments in MRI research such as compressed sensing and black blood imaging. Assessment methods and benchmark values are cited. Finally, we will discuss some future directions.

## **State of the art**

Although there is well supported literature on MRN in musculoskeletal imaging, the original research articles are rather limited for the head-neck area. There are several factors why MRN is more difficult to implement in this region. First, the cranial nerves have small calibers and have a complex tortuous course, passing tissues with very different physical properties. The close proximity of fat pads, sinuses and vessels with slow and fast flows require more performant sequences. Ideally a cranial nerve MRN sequence has a large FOV with three-dimensional thin slice thickness, high signal- (SNR) and contrast-to-noise ratios (CNR), with uniform fat, venous and arterial suppression and minimal magic angle artifacts. All these requirements should be met within reasonable acquisition times and minimum chance for motion artifacts. Also, when considering nerve-related pathology we can expect surgical and pathology induced susceptibility artifacts such as edema, increased vascularity and metal particles, which should be accounted for when possible. Previous reports described cranial nerve anatomy using various MRI sequences such as 3D bFFE (3D balanced fast-field echo sequences), T2w TSE (turbo spin echo), STIR (short tau inversion recovery) and CISS (constructive interference in steady state).<sup>3–5,7</sup> Although these sequences nicely demonstrate the anatomy, they are not nerve-specific as surrounding structures are not suppressed. In true MRN sequences we try to obtain a heavily T2 weighted image to achieve high soft tissue contrast

with homogenous fat, arterial and venous suppression. Several authors published on available techniques for inferior alveolar, lingual, as well as occipital nerve imaging mainly based on 3D PSIF (reversed fast imaging in steady-state free precession).<sup>8,9</sup> PSIF combines a steady state with a water excitation pulse and fat suppression, selectively enhancing neural anatomy with excellent vascular suppression. A disadvantage of PSIF is the lower SNR and risk for susceptibility artifacts compared to STIR sequences (**Figure 1**).



*Figure 1. Coronal thick slab (5 mm) MIP/MPR images in the same subject comparing two magnetic resonance neurography techniques. Short arrow: lingual nerve (V3); long arrow: inferior alveolar nerve (V3); arrowhead: masseteric nerve (V3). A: 3D CRANI sequence. B: 3D PSIF sequence.*

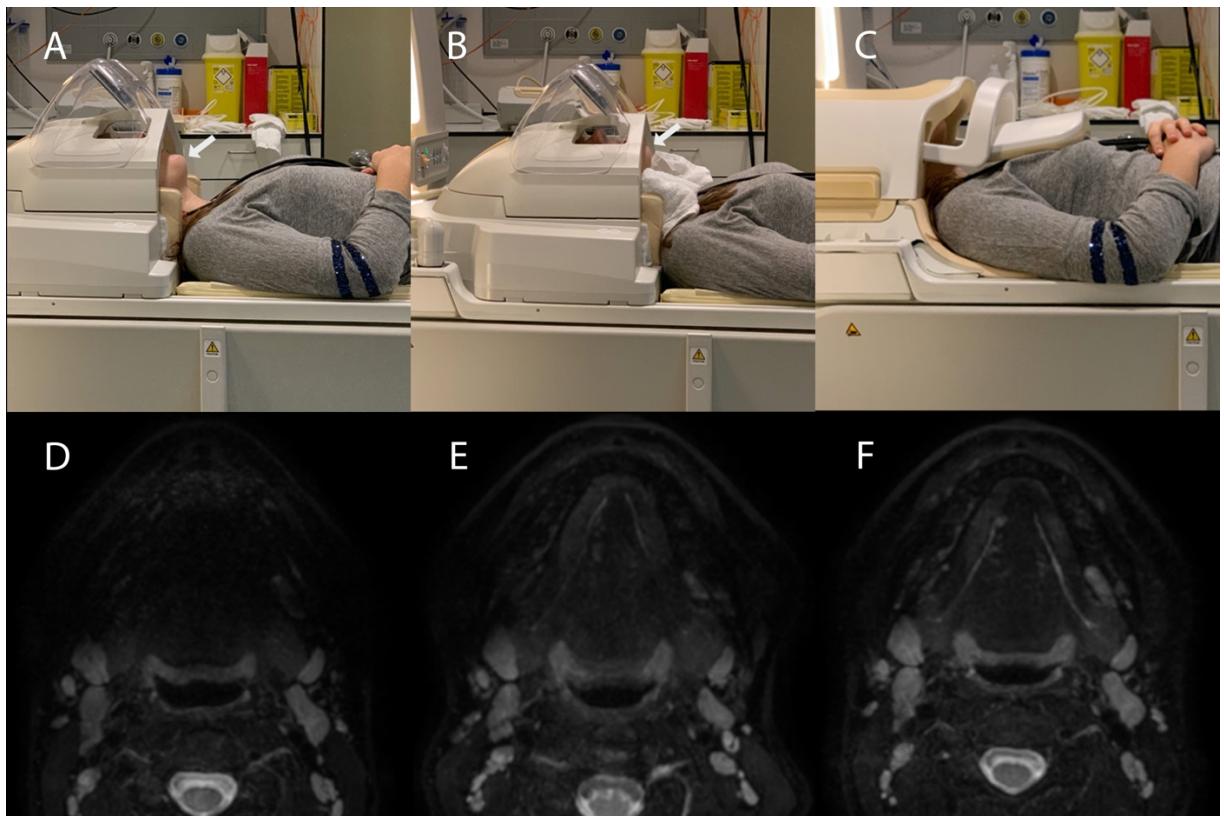
A protocol suggested by Chhabra et al. is further complemented by STIR, CISS, bFFE and DTI (diffusion tensor imaging).<sup>9</sup> By adding multiple sequences, one reduces the risk of non-diagnostic images but loses time and cost efficiency, which are becoming increasingly important in a healthcare environment under financial pressure and with increasing demand for MRI. The authors apply the 3D CRANI (CRAnial Nerve Imaging) sequence which is based on contrast enhanced black blood 3D STIR TSE preceded by an MSDE (motion-sensitized driven equilibrium) pulse in combination with a pseudo steady state sweep and compressed sensing.<sup>10,11</sup> Advantages of 3D CRANI are high SNR and CNR and less susceptibility artifacts. By combining 3D PSIF and 3D CRANI, a cranial MRN examination can be performed in a total acquisition time of 12 minutes. **Table 1** describes in detail the author's MRN protocol including 3D PSIF and 3D CRANI sequences.

*Table 1. Magnetic resonance neurography sequences for a 3T Philips system (Philips, Best, Netherlands). 3D CRANI (CRAnial Nerve Imaging) and 3D PSIF (reversed fast imaging in steady-state free precession) sequences. These can be further supplemented with routine brain T1w, T2w, CISS and FLAIR images. TSE: turbospin echo; GE: gradient echo; TE: echo time;*

*TR: repetition time, FOV: field-of-view, STIR: short tau inversion recovery; FFE: fast field echo; N/A: not applicable; MSDE: motion-sensitized driven equilibrium; MIP: maximum-intensity-projection; MPR: multiplanar reformatting.*

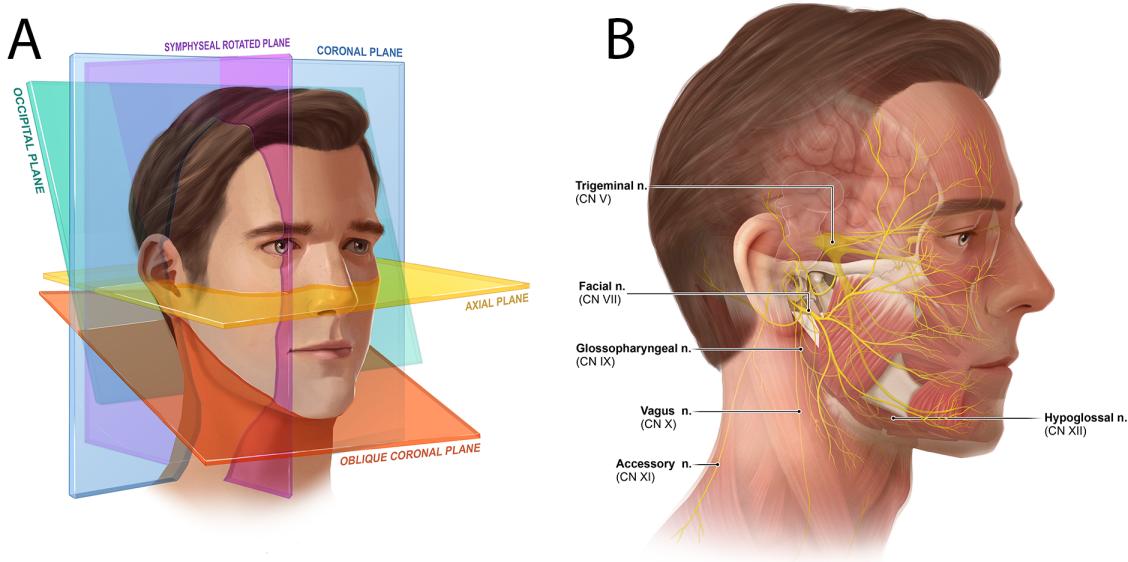
	<b>3D CRANI</b>	<b>3D PSIF</b>
<b>Basic MRI technique</b>	3D STIR (TSE)	3D FFE (GE)
<b>TR/TE (msec)</b>	2300/188	12/2.5
<b>FOV (AP/RL/FH mm)</b>	200/200/100	200/164/200
<b>Acquired voxel size (AP/RL/FH mm)</b>	0.9/0.9/0.9 (isotropic)	0.9/0.9/0.9 (isotropic)
<b>Reconstructed voxel size (AP/RL/FH mm)</b>	0.5/0.5/0.45	0.45/0.4/0.4
<b>Slice thickness (mm)</b>	0.5	0.45
<b>Slice oversampling</b>	1.5	1.4
<b>Acquisition time (min:sec)</b>	5:17	6:45
<b>Compressed sensing (acceleration rate)</b>	Yes (3)	No
<b>Flip angle</b>	N/A	35°
<b>Fat suppression technique</b>	STIR	Proset
<b>TSE factor</b>	43 (Startup echoes: 2, linear in Y direction)	N/A
<b>Additional techniques</b>	MSDE “Black blood” pulse Pseudo-steady state sweep	
<b>Post-processing</b>	MIP/MPR	
<b>Multiplanar reformatting</b>	<u>Orthogonal plane:</u> 5 mm slab thickness with 4.5 mm overlap <u>Curved/oblique planes:</u> 9 mm slab thickness with 8.5 mm overlap	

Routine T1, T2w and 3D FLAIR (fluid attenuated inversion recovery) brain sequences could be added as well to exclude intracranial pathology. DTI is increasingly being used but, for the time being, mostly remains of scientific value.<sup>10,12,13</sup> In order to obtain a diagnostic MRN acquisition, adequate patient positioning and coil selection is necessary.<sup>6</sup> Thorough patient fixation in mild hyperextension using a 32-channel head coil plays an important role in optimization of the SNR (**Figure 2**).



*Figure 2.* A: patient positioning in a standard 32-channel head coil without additional measures. Note the anterior mandible is located outside the coil. B: patient positioning after fixation by means of an inflatable pillow with the head in slight hyperextension using a towel roll. The mandible is now well positioned within the coil. C: alternative coil, being a 16-channel neck coil. D: imaging output after patient positioning as in example A. Signal loss is seen at the anterior segment. E: imaging output after slight hyperextension and thorough fixation as in example B. F: imaging output using a neck coil after patient positioning as in example C.

Others have advocated the use of a 16-channel head neck spine coil.<sup>14</sup> Finally, post-processing using maximum intensity projection (MIP) and multiplanar reformatting (MPR) renders the necessary viewing windows to evaluate the attenuation-enhanced cranial nerves along their trajectory or in non-axial planes according to the radiologist's discretion (**Figure 3**).<sup>15,16</sup>



*Figure 3. A: orthogonal and additional planes constructed in evaluating the cranial and occipital peripheral nerves. Multiplanar reformatting and maximum-intensity-projection post-processing is applied to visualize the tortuous nerves in the necessary viewing planes. B: overall nerve anatomy discussed in this review.*

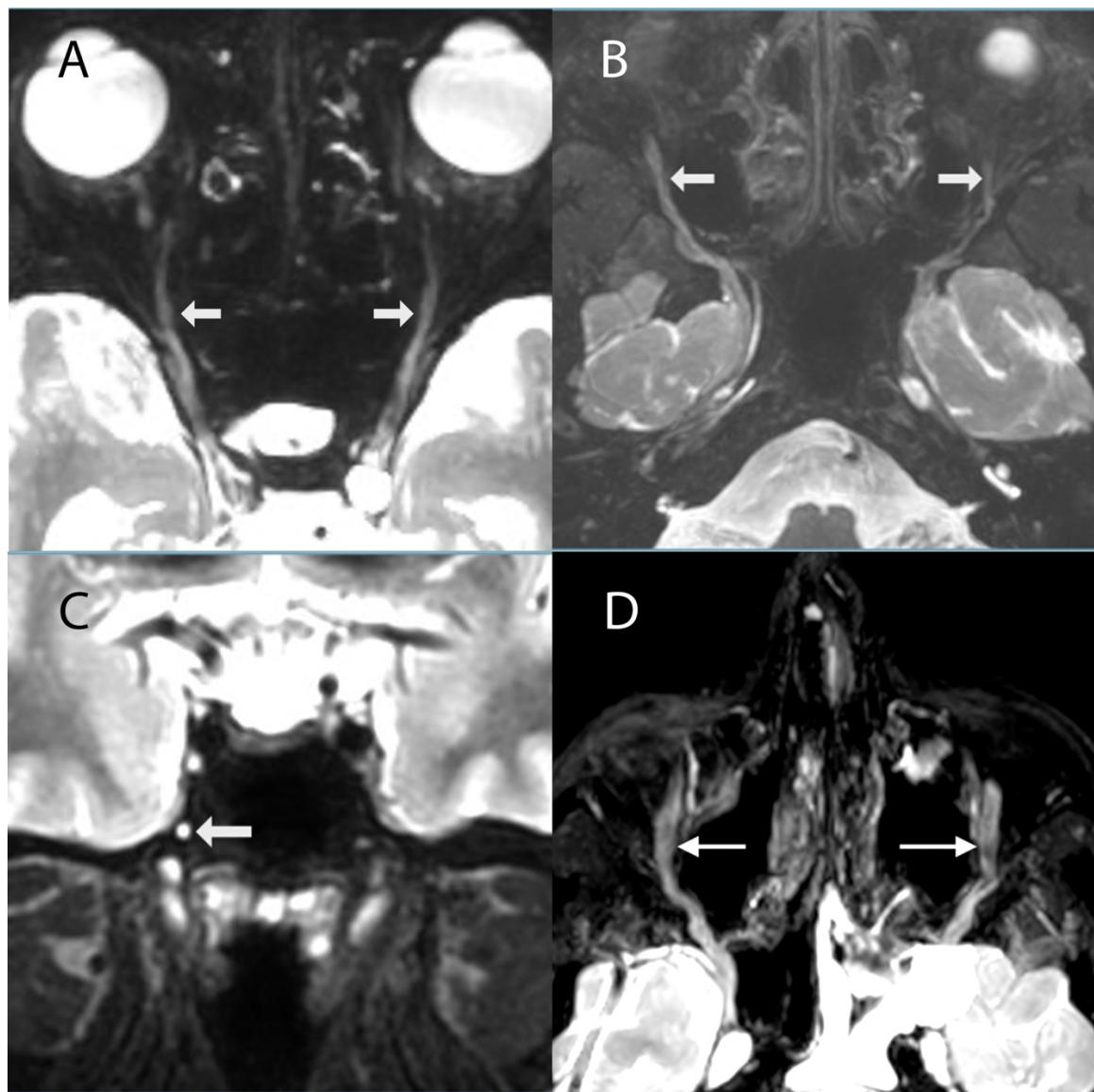
Routine post-processing software packages allow the necessary reformatting to be carried out such as Philips Volume post-processing package (Philips, Best, Netherlands). Freeware software, e.g. Horos (Nimble Co LLC, Annapolis, USA), offers MPR and MIP tools as well. In the next paragraphs the cranial and occipital nerve imaging anatomy is described and further illustrated by a **supplementary video**.

## Trigeminal Nerve

### Anatomy

The trigeminal nerve has extensive sensory, motor and (para-)sympathetic functions in the orofacial area. The nerve splits into three main divisions before it leaves the skull: ophthalmic nerve ( $V_1$ ), maxillary nerve ( $V_2$ ) and mandibular nerve ( $V_3$ ). The ophthalmic division ( $V_1$ ) splits into three branches (lacrimal, frontal and nasociliary nerve) which enter the orbit via the superior orbital fissure. The maxillary division ( $V_2$ ) leaves the cranial cavity via the foramen rotundum and reaches the pterygopalatine fossa. It innervates the teeth of the upper jaw and part of the nasal mucosa. Its dermal branches, the zygomatic nerves and infraorbital nerve, enter via the inferior orbital fissure. The infraorbital nerve runs over the floor of the orbit, it passes

through the infraorbital foramen to the skin of the lower eyelid, the side of the nose and part of the upper lip (**Figure 4**).

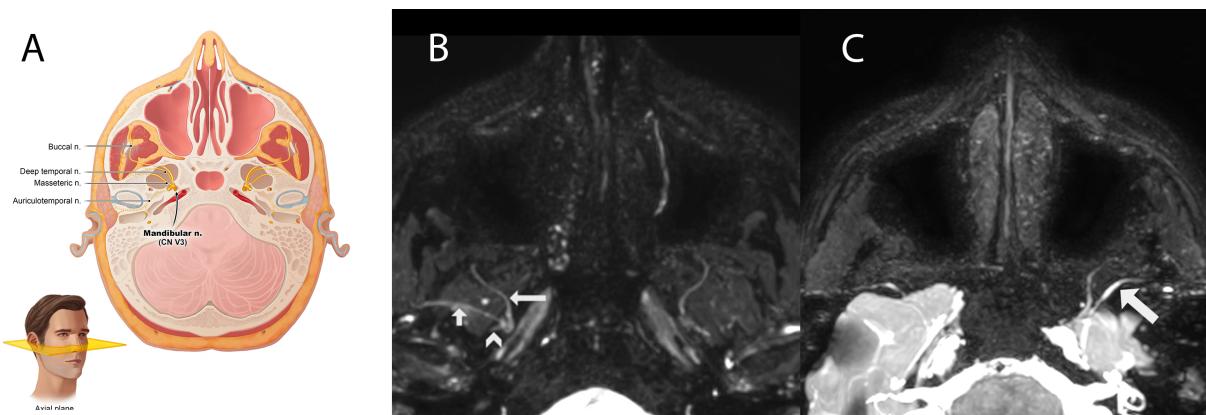


*Figure 4.* A: ophthalmic division of the trigeminal nerve (V1) using the 3D CRANI sequence. B: 3D CRANI sequence. Increased caliber of the right infra-orbital nerve (V2) in a patient with SUNCT (Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing rhinorrhea and forehead sweating). C: 3D CRANI sequence. Increased signal intensity is noted of the Vidian nerve (V2) in the same patient as seen in B. D: 47-year-old male diagnosed with empty nose syndrome after repeated sinonasal procedures. Marked increase of caliber and signal intensity of both maxillary and infraorbital nerves (arrows) is seen.

The mandibular nerve ( $V_3$ ) runs through the oval foramen from the middle cranial fossa to the infratemporal fossa. Three of its four large branches (buccal nerve, inferior alveolar nerve and

auriculotemporal nerve) reach the lower skin of the face and are responsible for the cutaneous innervation of the face but it also carries the smaller motor part (radix motoria) which supplies the muscles of mastication. Approximately one centimeter below the oval foramen, the trunk of the mandibular nerve splits into an anterior and a posterior division. Its branches are described in three groups (trunk, anterior and posterior division). Branches of the trunk of the mandibular nerve include: the medial pterygoid nerve for the chewing muscle of the same name and meningeal rami.

Branches of the anterior division are all motoric except the buccal nerve which appears between the two heads of lateral pterygoid muscle (**Figure 5**).

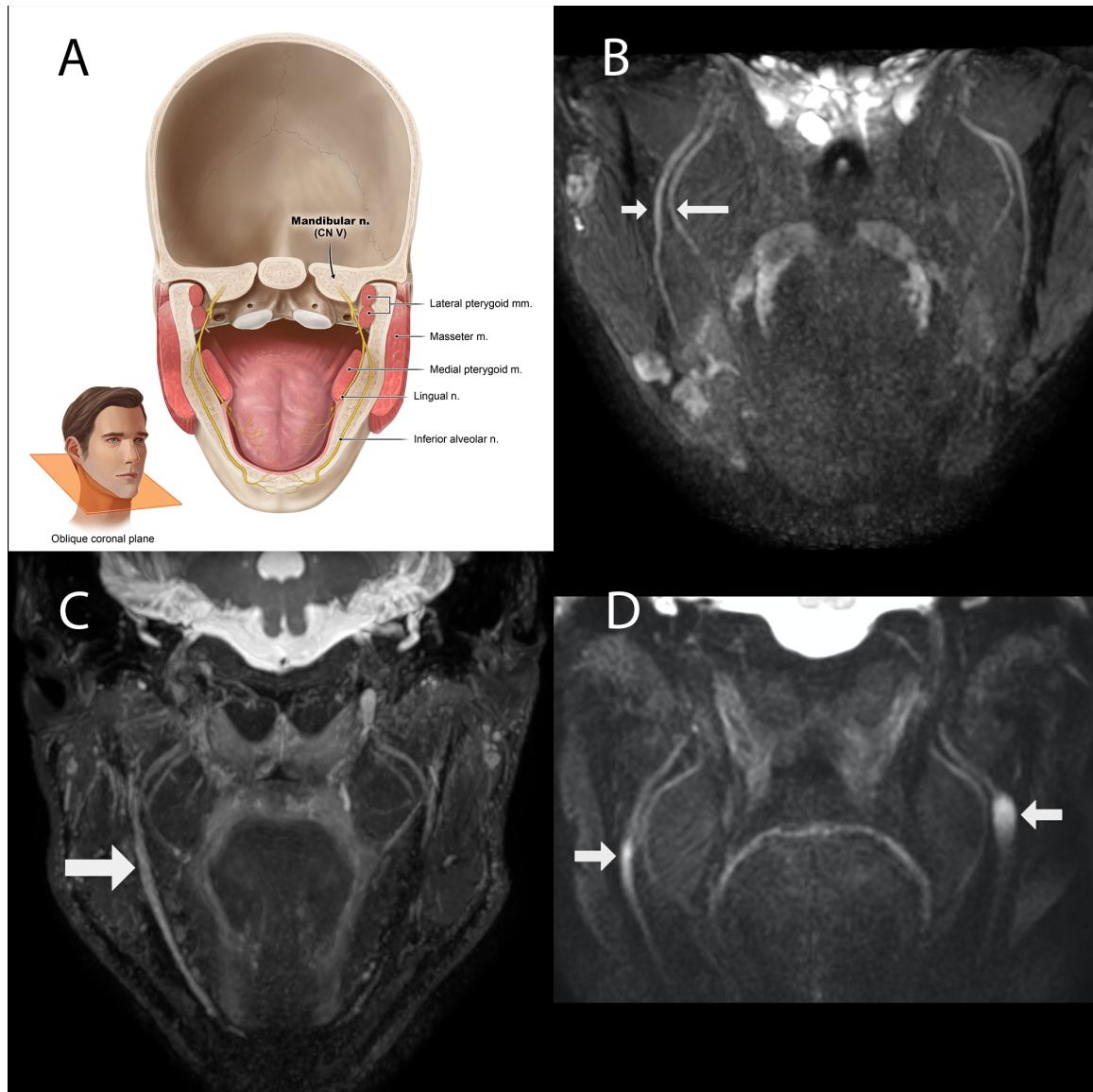


*Figure 5. A: anatomic relation of the anterior division of the mandibular nerve (V3) best seen in the axial plane. B: 3D CRANI sequence illustrating the buccal nerve (long arrow), the masseteric nerve (short arrow) and the stem of the auriculotemporal nerve (arrowhead). C: 3D CRANI sequence in a patient with post-traumatic trigeminal neuropathy of the mandibular division after placement of a titanium temporomandibular joint prosthesis. The left masseteric nerve is thickened and shows an increased signal intensity.*

The masseteric nerve runs superior from the lateral pterygoid muscle. It passes between the tendon of temporal muscle and the temporomandibular joint (TMJ) and reaches the masseter muscle via the mandibular incisura. On the way, it supplies small branches towards the TMJ. The deep temporal branches, two or three in number, run over the lateral pterygoid muscle to innervate the temporal muscle. The lateral pterygoid nerve innervates the muscle of the same name.

The posterior division of the mandibular nerve constitutes the auriculotemporal, lingual, inferior alveolar and mylohyoid nerve (**Figure 5, 6**). The auriculotemporal nerve innervates

most of the temporal region and a small part of the auricle (leading edge) and the outer ear canal.



*Figure 6. A: anatomic overview of the posterior division of the mandibular nerve (V3) on a coronal oblique plane. B: normal appreciation of the lingual (long arrow) and inferior alveolar (short arrow) nerve running between the pterygoid muscles. C: right-sided post-traumatic trigeminal neuropathy of the inferior alveolar nerve after ramus bone grafting. D: patient with neurofibromatosis type 1, showing bilateral neurofibromas of the inferior alveolar nerve at the level of the mandibular foramen.*

The lingual nerve, providing sensory and gustatory innervation to the tongue, appears in the infratemporal fossa between both pterygoid muscles and runs antero-inferiorly over the lateral

side of medial pterygoid muscle. The inferior alveolar nerve also ends up between the two pterygoid muscles in the infratemporal fossa. There, it lies behind the lingual nerve. Together with the artery of the same name it runs between the sphenomandibular ligament towards the inferior alveolar canal or mandibular canal. Just before it enters the mandibular foramen, it releases the mylohyoid nerve that innervates the mylohyoid muscle and anterior belly of the digastric muscle. The inferior alveolar nerve innervates all the teeth of the lower jaw, the adjacent gums and, via its end branch (mental nerve), the skin of the chin and the skin and mucosa of the lower lip.<sup>17–19</sup>

### *Imaging*

The brainstem, cisternal and cavernous trigeminal segments can be imaged using conventional brain sequences including CISS and balanced FFE sequences and have been extensively reviewed in the past.<sup>6,19</sup> The peripheral trigeminal nerve branches are best viewed in multiple planes after thick-slab MIP. The first ( $V_1$ ), second ( $V_2$ ) and anterior division of the third division ( $V_3$ ) can be well depicted on axial views whereas the lingual and inferior alveolar nerve are best seen in a coronal oblique direction (**Figure 4, 5, 6**).

In addition to the neurovascular conflict seen in trigeminal neuralgia cases, more and more neurological abnormalities are becoming detectable. The branches that are mostly involved in pathological conditions are the lingual and inferior alveolar nerve. Their course makes these nerves vulnerable to numerous dental and oro-maxillofacial procedures. MRN techniques can aid in grading and clinical decision making if trauma has occurred.<sup>20</sup> Interested readers are referred to a recent systematic review summarizing the available knowledge base on MRN in post-traumatic trigeminal neuropathies.<sup>21</sup> There is also increasing interest for the use of MRN in orofacial pain patients and more specifically in migraine and trigeminal autonomic cephalgias (**Figure 4**).<sup>22</sup>

## **Facial Nerve**

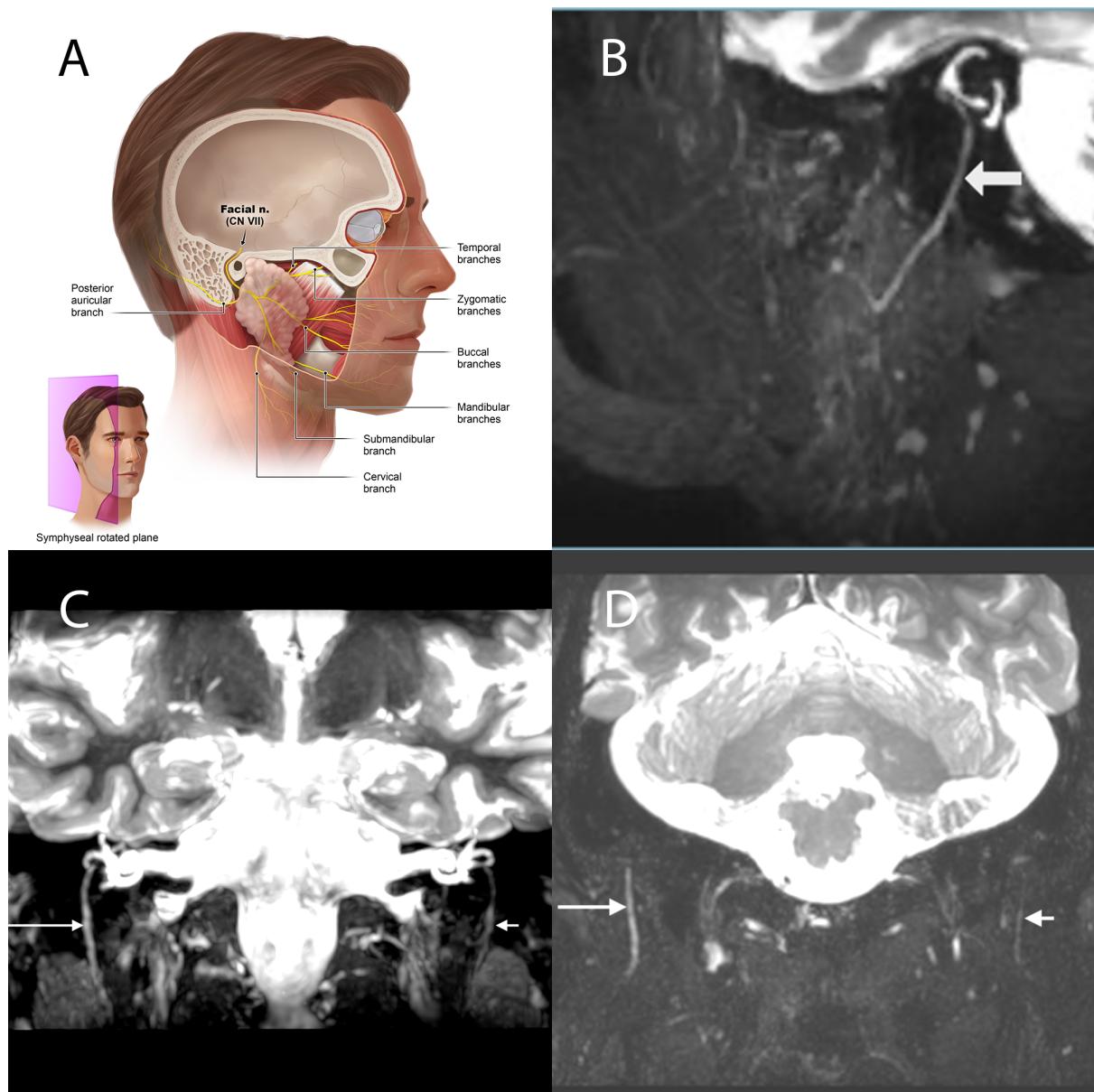
The facial nerve consists out of motor, sensory and parasympathetic fibers. The sensory fibers innervate a part of the inner ear and the special sensory fibers transport the taste stimuli from the anterior two thirds of the tongue via the chorda tympani. The parasympathetic fibers innervate the submandibular, sublingual and minor salivary glands, as well as the lacrimal glands. The motor fibers innervate the muscles responsible for the facial expression.

The primary or cisternal segment of the facial nerve leaves the brainstem close to the dorsal pons, transverses the cerebellopontine angle and enters the temporal bone by the porus acusticus in proximity to the vestibulocochlear nerve branches: superior to the cochlear nerve and anterior to the superior and inferior vestibular nerves. The trajectory through the temporal bone is subdivided in a meatal, labyrinthine, tympanic and mastoid segment. The sensory fibers, coming from the intermediate nerve, give on the one hand sensibility to the posterior concha and external auditory canal, on the other hand the special sensory fibers will form the chorda tympani.

The main trunk of the facial nerve leaves skull base via the stylomastoid foramen, it immediately releases the smaller posterior auricular r. auricularis. Subsequently, the nerve enters the craniomedial part of the parotid gland. The intraglandular nerve subdivides into five branches, which appear separately at the upper, front and lower edges of this gland. These end branches spread from here to the facial mimic muscles like the spread fingers of a hand resting on the parotid area (temporal, zygomatic, buccal, marginal mandibular and cervical, **Figure 6).**<sup>23,24</sup>

## Imaging

When considering MRI-imaging of the facial nerve, two segments need to be distinguished from each other: the skull base and the extracranial nerve segments. The intracranial and the temporal facial nerve segment is best visualized using 3D CISS, axial T1-weighted and fat-suppressed T2-weighted images.<sup>25</sup> Visualization of the facial nerve within the stylomastoid canal, the extracranial and intraparotid part of the VII cranial nerve can be made using thick-slab MIP/MPR reconstructions of 3D PSIF, and in case of extensive artifacts a black blood 3D-STIR such as 3D CRANI.<sup>9</sup> In case of nerve pathology, an increase of signal intensity and nerve caliber changes can be identified (**Figure 7**).



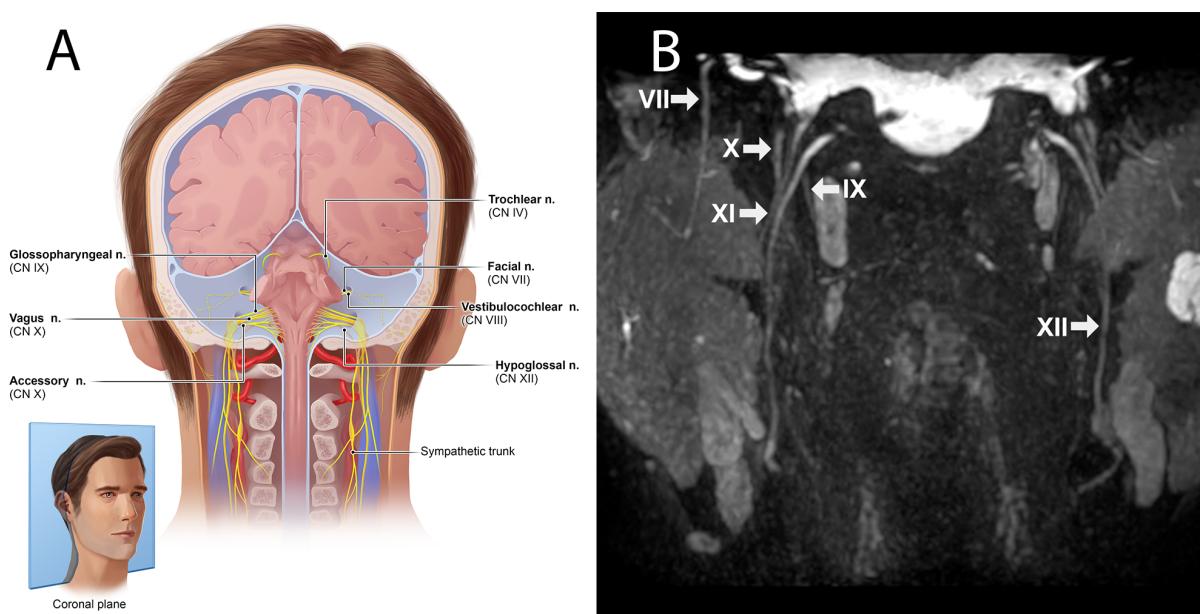
*Figure 7. A:* anatomic overview of the facial nerve and its branches which are best seen on a sagittal slightly rotated or coronal plane. *B:* sagittal view of a normal extracranial facial nerve entering the parotid gland on a 3D CRANI thick-slab MIP/MPR-image. *C:* coronal image with bilateral visualization of the intratemporal and extraforaminal facial nerve after iatrogenic damage on the right side. A slowly recuperative facial nerve paresis occurred after an infiltration with local anesthesia. *D:* 60-year-old male with a right sided Bell's palsy. The right extracranial facial (long arrow) nerve shows increased caliber and signal intensity compared to the contralateral facial nerve (short arrow). Discrepancies are noted all the way to the intraparotid course.

The use of a 3D PSIF sequence in combination with microsurface coils resulted in superior visualization of the peripheral facial nerve branches, in comparison to a standard head and neck

coil, as was reported by Chu et al.<sup>26</sup> The 3D-DESS-WE (double-echo steady state with water excitation) sequence is another established option to be considered for peripheral facial nerve neurography.<sup>27–29</sup>

## Cranial nerves IX to XII

The trajectory of the IX, X and XII cranial nerves is anatomically closely intercalated, moreover a lot of imaging characteristics are similar and therefore they are discussed together (**Figure 8**).



*Figure 8. A: anatomic overview of the facial (VII), hypoglossal (XII), glossopharyngeal (IX), vagus (X) and accessory (XI) nerves which can be seen in close relation to each other on a coronal plane. B: coronal view after a 3D CRANI sequence indicating the aforementioned peripheral nerves without pathological characteristics.*

### Glossopharyngeal nerve anatomy

The glossopharyngeal nerve or IX cranial nerve is composed of a combination of motor, sensory and parasympathetic fibers. Firstly, the sensory, gustatory and visceral stimuli are transported via afferent fibers from the retroauricular region, the posterior third of the tongue, the pharynx wall and the tonsils, the soft palate and the eardrum. Secondly, the motor efferents innervate the stylopharyngeus muscle. Thirdly, the parasympathetic fibers stimulate the production of saliva within the parotid gland.<sup>30</sup>

The origin of the IX cranial nerve is strongly associated with the vagus nerve, sharing three functional nuclei in the upper medulla oblongata. The nerve branches from the medulla oblongata within the cerebellomedullary cistern, slightly superior to the vagus nerve. The 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> cranial nerves course in an anterolateral direction through the cistern to the jugular foramen, exiting the foramen anteriorly from the internal jugular vein. Within the foramen the glossopharyngeal nerve is known for two focal expansions: a superior node handling general sensible information and a lower node handling visceral sensory, taste and carotid innervations. The extratemporal course of the IX cranial nerve continues in a caudal direction within the carotid space and disperses in five major branches. Firstly, the tympanic nerve branches from the inferior node, carrying sensory information from the external and middle ear and parasympathetic stimuli to the parotid gland via the lesser petrosal nerve. Secondly, the stylopharyngeus branch gives motor input to the stylopharyngeus muscle. Thirdly, the pharyngeal branches associate with branches from the vagus nerve, forming the pharyngeal plexus. Fourthly, the carotid sinus branch mediates parasympathetic information to the carotid body. Finally, the lingual branch conveys general and gustatory sensory input from the posterior third of the tongue.<sup>30,31</sup>

### Vagus nerve Anatomy

The n. X forms the pharyngeal plexus and mediates the motor function of the soft palate. The parasympathetic fibers of the dorsal motor core of the n. X innervate pharynx, esophagus, trachea, bronchi, lungs, heart, intestines, liver and pancreas.

Multiple rootlets exiting the ventrolateral sulcus, formed by the olive and interior cerebellar peduncle, fuse together in the vagus nerve. The vagus and glossopharyngeal nerve progress closely intercalated through the cerebellopontine angle. Noteworthy, is the small meningeal branch coming from the vagus nerve, innervating the dura within the posterior cranial fossa. Subsequently, the vagus nerve travels through the center of the jugular foramen: superficial to the internal jugular vein and caudal to the glossopharyngeal nerve. Caudally progressing within the carotid space between, however slightly posterior to the internal carotid artery and internal jugular vein. The internal jugular vein remains lateral and superficial to the vagus nerve; the common carotid artery travels medial and slightly anterior to the nerve.

There are four major extracranial branches leaving the vagus nerve in the head and neck area. Firstly, the auricular branch or Arnold nerve, exiting from the main nerve when passing through

the jugular foramen, this nerve receives sensory input coming from the external auditory canal and tympanic membrane. Secondly, the pharyngeal branches leave the vagus nerve below the skull base and form, together with the IX cranial nerve, the pharyngeal plexus innervating the muscles of the soft palate and pharynx. Besides the motor function, the plexus conveys sensory stimuli coming from the epiglottis, trachea and esophagus. Thirdly, the superior laryngeal nerve has a sensory, as well as a motor component. The internal sensory branch conducts sensory input from the hypopharynx, larynx and vocal cords, the external motor branch innervates the cricothyroid and inferior pharyngeal constrictor muscles. And finally, the recurrent laryngeal nerve (RLN) is identified with its renowned asymmetrical anatomical morphology. Bilaterally the RLN branches from the vagus nerve, it loops around the subclavian artery on the right side and on the left side around the aortic arch. The RLN mediates somatic and visceral sensory input coming from below the vocal cords, moreover, conveying motor output to all laryngeal musculature with exception of the cricothyroid muscle. Hereafter, the vagus nerve continues the trajectory into the thorax.<sup>6,32,33</sup>

### **Accessory nerve anatomy**

The accessory nerve solely contains motor fibers, innervating the sternocleidomastoid as well as the trapezius muscle. The accessory nerve is composed of both cranial and spinal (C1-5) rootlets. The main trunk of the accessory nerve subsequently travels in a lateral direction, before the nerve leaves the skull via the jugular foramen wherein connections with the vagus nerve can be found. The extracranial accessory nerve runs through the center of the carotid space between the medial internal carotid artery and laterally positioned internal jugular vein (IJV). Subsequently, the nerve divides again in the cranial and spinal roots. The cranial rootlets or internal branches fuse together with the vagus nerve and the spinal rootlets or external branches laterally cross the IJV, passing the transverse process of atlas mostly anteriorly and advancing medially from the styloid process and digastric and stylohyoid muscles. Further progression of the nerve follows an anterolateral direction before reaching the sternocleidomastoid muscle and subsequent formation of a nerve plexus with the ventral rami of C2 to C4, mediating the innervation of the trapezius muscle.<sup>34-36</sup>

### **Hypoglossal nerve anatomy**

The hypoglossal nerve is a purely motor nerve, innervating the extrinsic and intrinsic musculature of the tongue, with exception of the palatoglossus muscle. The XII cranial nerve is formed by two bundles of 10-15 rootlets coming from the ventrolateral sulcus at the medulla

oblongata. The bundles pierce through the dura mater separately and fuse together after passing through the hypoglossal canal. The extracranial hypoglossal nerve is joined by efferent C1 motor fibers and progresses laterally and inferiorly to the vagus nerve and internal carotid artery, initially closely associated with the carotid space. Subsequently, after passing the occipital artery the hypoglossal nerve will turn and mostly pass through the space between carotid arteries and internal jugular vein. After progressing medially to the hyoid tendon of the digastric muscle, the nerve will enter the submandibular space medial to the submandibular gland and hyoglossus muscle (**Figure 9**). Some of the C1-fibers branch off more cranially and innervate the superior root of the ansa cervicalis, however other C1 nerve fibers conveying motor input for the geniohyoid and thyrohyoid muscles will remain associated with the XII cranial nerve.<sup>31,37,38</sup>

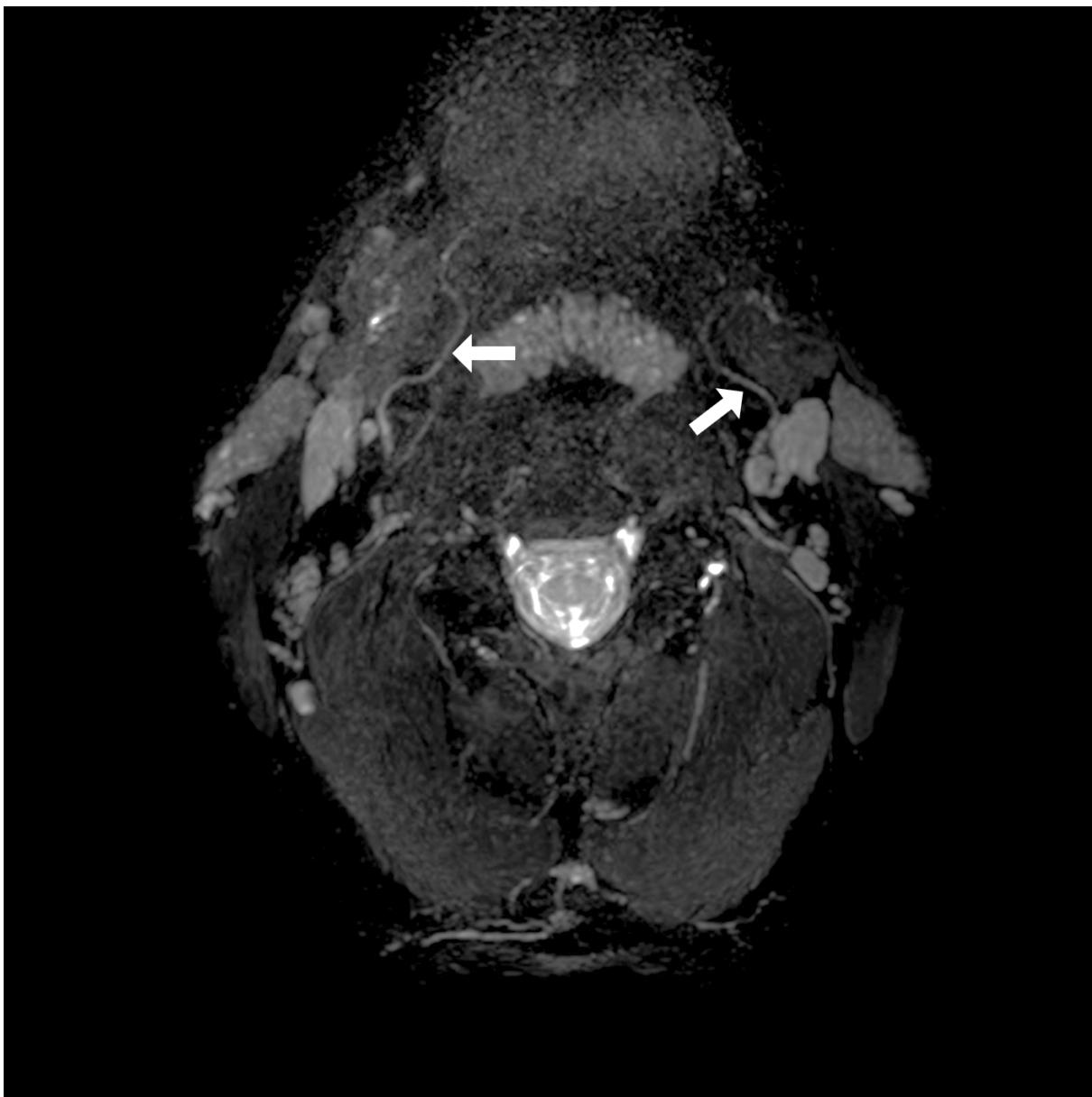


Figure 9. Bilateral normal appreciation of the peripheral hypoglossal nerve (white arrows) on an axial 3D CRANI image after MIP/MPR showing its course around the great vessels before innervating the tongue.

#### Glossopharyngeal, vagus, accessory and hypoglossal nerve imaging

Evaluation of the cisternal IX, X and XI cranial nerve segments is preferably performed using heavily T2-weighted steady-state free precession imaging sequences.<sup>25</sup> However, these 2-D sequences have mainly been replaced by 3D DRIVE, 3D B-FFE, 3D CISS and 3D FIESTA.<sup>3</sup> The distinct foraminal nerve segments are identified using conventional 3D FIESTA, or CE-MRA (contrast-enhanced magnetic resonance angiograph) as described by Linn et al.<sup>5,39</sup> The below-skull-base related nerve segments can be nicely differentiated on the MIP/MPR-

reformatted 3D CRANI images (**Figure 8,9**). They are conveniently identified on coronal and axial planes. As discussed by Chhabra and colleagues, 3D PSIF is also a valuable technique for neurography of these closely intercalated cranial nerves.<sup>20</sup> The typical nerve trajectories can be distinguished as follows, the extracranial vagus nerve is positioned between the medial IX and lateral XII nerve and has the largest diameter.

# Occipital Nerves

## Anatomy

The greater occipital nerve (GON) ensues from the fusion of nerve fibers coming from the medial branch of the dorsal ramus of the second and, to a lesser degree, the third spinal nerve. At the level of the C1-C2 vertebrae the nerve travels in the occipital direction between the medial inferior capitis oblique and lateral semispinal muscles. Important anatomical variation is described concerning the penetration of the trapezius, semispinalis capitis and inferior capitis oblique muscles which are pierced by GON in respectively, 45%, 7,5% and 90% of cases.<sup>40</sup> Next, the nerve loops upwards, joins the occipital artery and subdivides in a medial and lateral branch before terminal branches ensue.<sup>40-43</sup>

The lesser occipital nerve (LON) typically originates from the ventral rami of spinal nerves C2 and C3. The nerve loops around the sternocleidomastoid muscle (SCM). Its trajectory is parallel to the posterior border of the SCM, piercing the superficial lamina of the cervical fascia, in direction of the occipital area. Finally, the LON divides into medial and lateral branches in the middle between the intermastoid line and the external occipital protuberance (EOP). Interconnections or overlap of GON and LON twigs are frequently present.<sup>42-44</sup>

The third occipital nerve (TON) derives from the superficial medial branch of the dorsal ramus of the third spinal nerve. The nerve courses on top of the dorsolateral surface of the C2-C3 facet joint. The TON travels deeply to the semispinalis capitis muscle in a posterior direction when a communicating branch to GON exits. The overlying musculature will be pierced by TON before progressing subcutaneously.<sup>33,40,42,43</sup>

Functionally, GON, LON and TON receive somatic sensory input from the occipital region. The semispinalis muscle will receive motor output via GON, and to a lesser degree from TON (**Figure 10**).<sup>33,42,43</sup>

## Imaging

The occipital nerves are easily visualized on a slightly oblique axial plane using 3D PSIF or 3D CRANI sequences and are of increasing interest to neurologists and pain specialists. Pathological thickening and signal alterations can be noted in cases of occipital neuralgia also referred to as occipital migraine.<sup>22</sup> Occasionally one can also detect pathological changes after trauma or surgery in this region (**Figure 10**).

## MRN assessment

The evaluation of the extraforaminal cranial nerves and possible abnormalities is best performed systematically. A proposal is presented in **Table 2**. At present, large series with benchmark values for each nerve segment are lacking in order to distinguish pathology from normal. Studies are under way to report these normal values.<sup>45–47</sup> However, internal validation is always possible with the contralateral side. When bilateral abnormalities occur, a possible problem arises, but in combination with the clinical picture and focal changes, there is usually no diagnostic problem. **Table 2** includes anatomical benchmark values for the discussed cranial and occipital nerves. We should remain cautious with external validation of nerve thickness and signal intensity as MR sequences are not actual anatomical representations but representations of signal intensity. Therefore, caution should be exercised when comparing MR parameters with published reference values. For the time being, internal comparison with the non-pathological side is the most reliable method. Interested readers are referred to the excellent review papers by Chhabra et al.<sup>5,9,48</sup>

*Table 2. Assessment of normal MRN findings and anatomical benchmark nerve diameters (Attention: this does not necessarily correspond to MRN nerve diameters which reflect signal intensities).*

Assessment of normal MRN findings			
Nerve	Site of measurement	Mean diameter (mm) ± standard deviation	Reference
<b>Anatomical benchmark nerve diameters</b>			
Trigeminal nerve			
V1: Ophthalmic division	Middle cranial fossa	1.7 ± 0.1	49
V2: Maxillary division	Middle cranial fossa	4.01 ± 0.52	50
V2: Infraorbital nerve	Infraorbital foramen	3.30 ± 0.52	50
V3: Mandibular division	Middle cranial fossa	7.41 ± 1.41	51
V3: Inferior alveolar nerve	Mandibular foramen	2.2 ± 0.4	52
V3: Mental nerve	Mental foramen	1.68–2.37	53
V3: Lingual nerve	Third molar region	3.0 ± 0.5	54
V3: Auriculotemporal	After fusion of rootlets	3.18 ± 0.84	55
Facial nerve			
Segment	Labyrinth	1.13 ± 0.39	56
	Tympanic	1.09 ± 0.57	56
	Mastoid	1.33 ± 0.65	56

	Average between stylomastoid foramen and intraparotid branching	$1.4 \pm 0.2$	57
Peripheral branch	Intraparotid	$0.5 \pm 0.1$	58
	Temporal branch	$0.94 \pm 0.33$	59
	Zygomatic	$1.00 \pm 0.46$	59
	Buccal	$0.99 \pm 0.40$	59
	Mandibular	$0.80 \pm 0.34$	59
	Cervical	$0.83 \pm 0.15$	59
<b>IX-X-XI nerves</b>			
Glossopharyngeal nerve	Midcervical	Not available	
Vagus nerve	Midcervical	$5.1 \pm 1.5$	60
Accessory nerve	Midcervical	Not available	
Hypoglossal nerve			
Segment	Proximal	$1.41 \pm 1.01$	61
	Above greater horn of hyoid	$1.23 \pm 0.77$	61
	Cervical loop	$0.48 \pm 0.26$	61
<b>Occipital nerves</b>			
Greater occipital nerve	After exiting the semispinalis capitis muscle	$3.8 \pm 1.6$	62
Lesser occipital nerve	Posterior border of sternocleidomastoid muscle	$1.2 \pm 1.6$	62
Third occipital nerve	After exiting the trapezius muscle	$1.5 \pm 0.3$	63

## Future perspectives

MRN performance and applications are evolving rapidly. Where 0.5T systems were available twenty years ago, we are now seeing the arrival of clinical 7T and higher. The introduction of these high-field MRI devices can further improve spatial resolution and soft tissue contrast. However, there is also a risk of increasing susceptibility artifacts as they increase with increasing field strength and thus, they should not be considered the holy grail in MRN imaging. Rather a combination of high-field systems, specialized coils, improved post-processing and contrast agents will likely evolve this field in the next phase.<sup>26,64,65</sup> First, there is a need to further define anatomical benchmarks for the cranial nerves. Several authors have described reference values for the trigeminal nerve or provided classifications to define degree of nerve injury.<sup>14,47</sup> Next, there is a whole field of research left to obtain functional information by means of DTI and diffusion tensor tractography (DTT). These techniques are based on differences in diffusion of protons along nerve tracts and allow quantification of diffusion restriction by means of the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values. In combination with morphological changes a more detailed description of neural dysfunction and neuroregeneration becomes reality.<sup>66</sup> Additionally, they allow for a multiparametric and standardized approach towards nerve injuries and pathology, which is currently lacking. Several studies described the successful application of DTI and DTT in extraforaminal cranial nerve

imaging.<sup>12,67–70</sup> But, most reports only describe DTT of the proximal nerve branches with varying reference values.<sup>68,71</sup> DTT of the small distal cranial nerve branches remains challenging and, for the time being, is mostly of scientific value.<sup>13,72</sup> In addition to strong diagnostic value, MRN also offers applications for planning of surgical procedures. Current indications are summarized in **Table 3**.

*Table 3. Possible MRN indications in the head and neck area.*

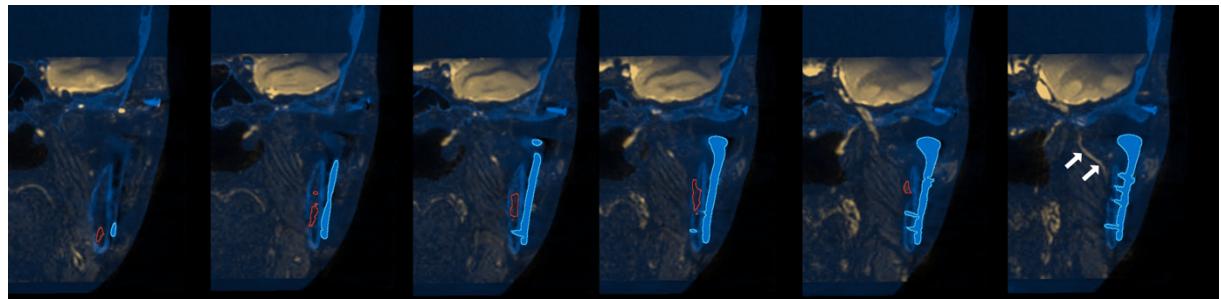
Indication	Reference
Chronic demyelinating neuropathies	Own experience, unpublished
Cranial neuralgias	Hwang et al. <sup>22</sup>
Follow-up of regeneration (e.g. after nerve surgery)	Not available
Traumatic neuropathies	
Maxillofacial trauma	Burian et al. <sup>73</sup> Dessouky et al. <sup>20</sup> ,
Post-traumatic cranial neuropathies	Zuniga et al. <sup>47</sup>
Nerve sheath tumors	Chhabra et al. <sup>74</sup>
Surgical planning involving cranial nerves	Dessouky et al. <sup>20</sup>
Viral, bacterial neuritis (e.g. Bell's palsy)	Own experience, unpublished

The surgeon could check in advance where the nerve is located in relation to the neoplasia or when the anatomy deviates from the normal.<sup>68</sup> Panoramic reconstructions can aid in dental surgery planning (**Figure 11**).<sup>75</sup>



*Figure 11. Panoramic curved reconstruction and MIP of the inferior alveolar nerve using a 3D CRANI sequence allowing a full evaluation at a glance.*

Fusion with computed tomography images could help with the placement of a temporomandibular joint prosthesis near these peripheral nerve branches (**Figure 12**) and it is only a matter of time before artificial intelligence aids find their way to the clinic.<sup>76,77</sup>



*Figure 12. 3D fusion of CT and MRN images which can be valuable in planning the placement of a custom made temporomandibular joint prosthesis (blue outline). The inferior alveolar nerve is segmented (red outline) and indicated (white arrows) before entering the mandibular canal.*

The current paper is based on only a handful studies published by a limited number of centers. Large studies on MRN applications in the head and neck area are lacking. Most studies are still in a feasibility phase. There is a need for more high-quality research to further validate these techniques for the various applications in the coming years. In conclusion, the field of MRN is still in its infancy but a wide range of applications are already under development. It is therefore important that radiologists and anyone involved in cranial nerve pathology become familiar with these techniques and their possibilities.

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## **Supplemental data**

*Illustrative video indicating the peripheral cranial nerve anatomy using the 3D CRANI sequence on a 3T Ingenia system with a 32-channel head coil (Philips, Best, Netherlands).*

Online access:

[https://www.birpublications.org/doi/suppl/10.1259/bjr.20200798/suppl\\_file/bjr.20200798.suppl-01.mp4](https://www.birpublications.org/doi/suppl/10.1259/bjr.20200798/suppl_file/bjr.20200798.suppl-01.mp4)

# CHAPTER 8

## 3D CRANI Validation in healthy subjects

*This chapter is based on the following manuscript:*

Casselman J\*, **Van der Cruyssen F\***, Vanhove F, Peeters R, Hermans R, Politis C, Jacobs R. 3D CRANI, a novel MR neurography sequence, can reliable visualise the extraforaminal cranial and occipital nerves. *Eur Radiol.* Published online November 26, 2022.

\*Shared first authorship

## **Abstract**

### **Objectives**

We aim to validate 3D CRANI, a novel high field STIR TSE, MR neurography sequence in the visualisation of the extraforaminal cranial and occipital nerve branches on a 3T system. Furthermore, we wish to evaluate the role of gadolinium administration and calculate nerve benchmark values for future reference.

### **Methods**

Eleven consecutive patients underwent MR imaging including the 3D CRANI sequence before and immediately after intravenous gadolinium administration. Two observers rated suppression quality and nerve visualisation using Likert-scales before and after contrast administration. Extraforaminal cranial and occipital nerves were assessed. Nerve calibers and signal intensities were measured at predefined anatomical landmarks, and apparent signal intensity ratios were calculated.

### **Results**

The assessed segments of the cranial and occipital nerves could be identified in most cases. The overall intrarater agreement was 79.2% and interrater agreement was 82.7% (intrarater  $\kappa=.561$ ,  $p < .0001$ ; interrater  $\kappa=.642$ ,  $p < .0001$ ). After contrast administration, this significantly improved to an intrarater agreement of 92.7% and interrater agreement of 93.6% (intrarater  $\kappa=.688$ ,  $p < .0001$ ; interrater  $\kappa=.727$ ,  $p < .0001$ ).

Contrast administration improved suppression quality and significant changes in nerve caliber and signal intensity measurements. Nerve diameter and signal intensity benchmarking values were obtained.

### **Conclusion**

3D CRANI is reliable for the visualization of the extraforaminal cranial and occipital nerves. Intravenous gadolinium significantly improves MR neurography when applying this sequence. Benchmarking data are published to allow future assessment of the 3D CRANI sequence in patients with pathology of the extraforaminal cranial and occipital nerves.

## **Introduction**

MR neurography (MRN) in the head and neck region is attracting increasing attention in the literature.<sup>1</sup> This novel MRI technique already showed promise to diagnose peripheral and trigeminal neuropathies.<sup>2-4</sup> MRN may localize the neuropathy and even grade the severity of these neuropathies.<sup>5</sup> The obtained information can be useful in diagnosing and treatment planning of patients with neuropathies. Given the recent introduction of MRN in the head and neck area, only a limited number of validation studies are available. The studies by Chabarra and by Burian illustrated feasibility of MR neurography of the mandibular nerve and its terminal branches.<sup>6,7</sup> But no studies are available that validate MR neurography for all extraforaminal cranial or occipital nerves. The purpose of this study was to validate the use of the previously published 3D CRANI (CRAnial Nerve Imaging)<sup>8</sup>, a novel high field STIR TSE, sequence in extraforaminal cranial and occipital nerve visualisation on a 3T system. Secondary aims were to assess the role of gadolinium administration on imaging quality and to obtain benchmarking values of signal intensities, apparent signal-to-noise (aSNR) and apparent nerve-muscle contrast-to-noise ratios (aNMCNR), and nerve diameters for the evaluated nerve branches.

## **Materials and methods**

### **Subjects**

This study was conducted according to the Guidelines for Reporting Reliability and Agreement Studies (GRASS)<sup>9</sup>, additionally, we adhered to the STROBE checklist for observational studies.<sup>10</sup> Retrospectively, 3D CRANI sequencing data was retrieved from consecutive patients visiting the radiology department of Bruges, Belgium and who underwent head and neck MR imaging. Patients were included whenever the senior radiologist (JC) could not identify pathology along the extraforaminal cranial and occipital nerve branches and when a 3D CRANI sequence was present before and after gadolinium contrast administration. Thus, no pathology was present along the course of the observed nerve branches on both sides. Moreover, none of the patients received radiotherapy in the head and neck area nor did they receive chemotherapy. The reason for MRI referral is addressed in supplemental table 1. Ethical committee approval was waived due to the retrospective nature of this study.

### **MRI Imaging Procedure**

Imaging was performed on a 3.0 Tesla (T) MRI system (Ingenia; Philips, Best, Netherlands) equipped with 32-channel head coil (INVIVO, Gainesville, USA). A previously published MR

neurography sequence, 3D CRANI, was performed.<sup>1,8</sup> 3D CRANI is a 3D TSE STIR sequence which uses a PSS (pseudo-steady state) sweep in combination with MSDE (Motion Sensitized Driven Equilibrium) Pulse. We used STIR in combination with MSDE to ensure the signal from fat, muscle and blood are suppressed uniformly across the field of view.

Following parameters were applied: TR = 2300 ms, TE = 188 ms, FOV = 200x200x90 mm, slice thickness = 0.9 mm, act slice gap = -0.45 mm, matrix = 224 x 222 mm, acquired voxel size = 0.9x0.9x0.9 mm, reconstructed voxel Size = 0.6x0.6x0.45 mm, slice oversampling = 1.5, compressed sense, (reduction 2), number of slices = 200. TSE Nerve STIR, TSE factor = 43 (startup echoes 2), number of acquisitions = 1, scanning time 8:08 min, BB pulse = MSDE (flow ghost suppression). The 3D CRANI sequence was repeated immediately after administration of gadolinium.

### **Imaging analysis**

Three orthogonal planes, as well as a plane following the course of the mandibular nerve using multiplanar reformation (MPR) and maximum intensity projection (MIP), were reconstructed using the Philips Volume post-processing package. A reformatted slab thickness of 5 mm and gap of -0.5 mm allowed for the best demonstration of the nerve trajectory. The images were analysed by two trained observers (FVDC with five years of experience in head and neck imaging, FV with five years of radiology experience and two years in head and neck imaging). After a calibration session, initial evaluations were made independently and blinded from each other using a scoring form (**Table 1**).

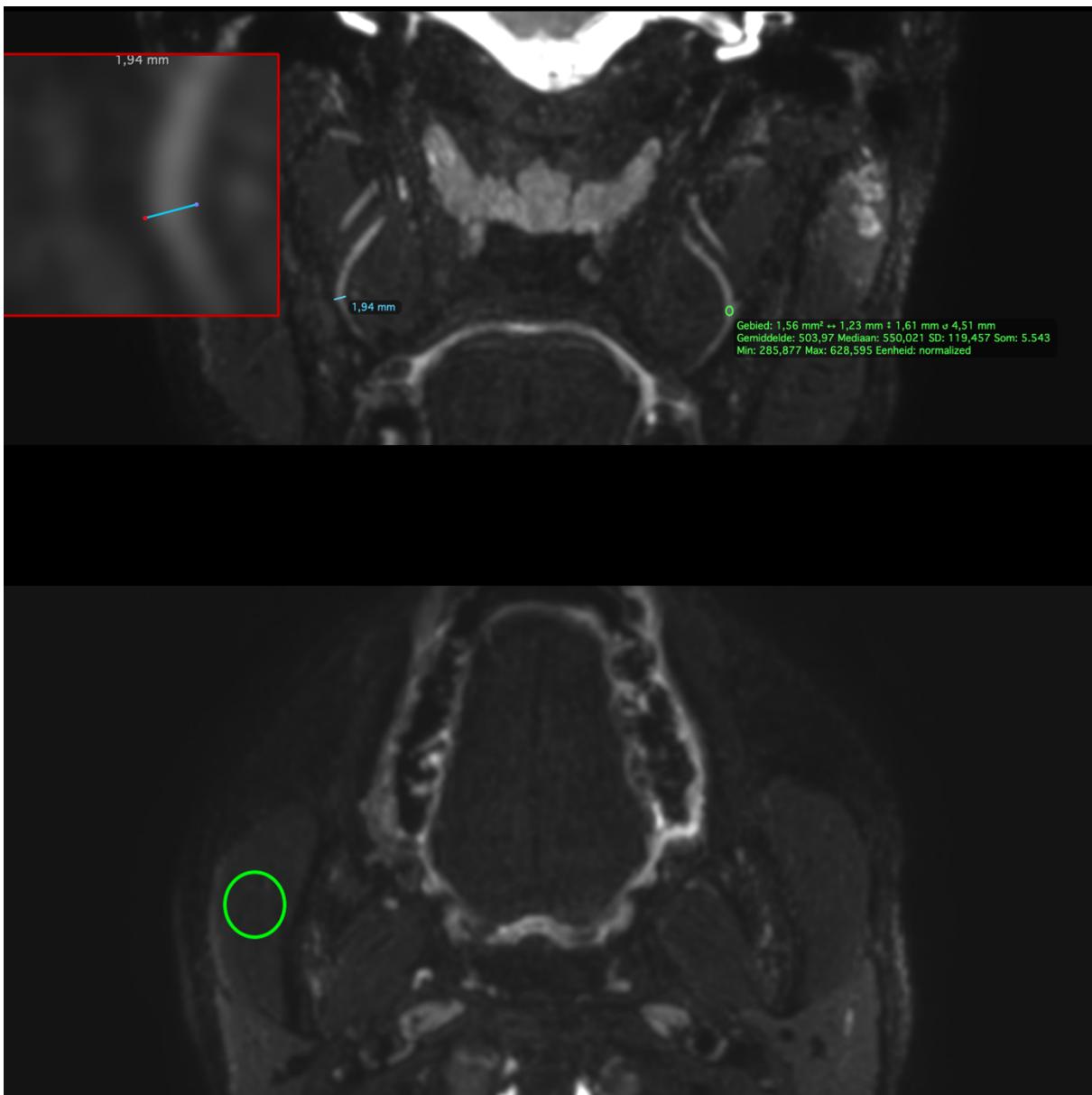
*Table 1. Assessment form illustrating qualitative Likert-scales to rate suppression quality and nerve visualization. The landmarks used for evaluation of suppression quality and calculation of nerve dimensions and signal intensity are also listed. The maximum convex point was defined as the peak or the highest point of the convex curve of the extraforaminal nerve after which it arches away from this point to distal.*

<b>Suppression quality score</b>	
1	Not suppressed, not diagnostically usable
2	Not suppressed, but diagnostically usable
3	Moderately suppressed, diagnostically usable
4	Excellent suppression, diagnostically usable
<b>Suppression quality landmarks</b>	
Arterial	Internal carotid artery
Venous	Pterygoid plexus

Fat	Subcutaneous fat plane		
Lymph nodes	Lymph nodes in neck level II/III		
<b>Nerve identification</b>			
0	Not identified		
1	Identified		
<b>Nerve visualisation score</b>			
0	Nerve not identified		
1	Poor - Only proximal portion identified but not continuous		
2	Fair - Only proximal portion identified		
3	Good Fair - Both portions identified but not continuous		
4	Excellent - Both proximal and distal portion identified		
99	Nerve not within field of view		
<b>Nerve landmarks</b>			
Proximal	Midpoint	Distal	Viewing plane for evaluation
V1 Ophthalmic nerve	Meckel's Cave	Entry of orbit	Axial
V2 Infraorbital nerve	Meckel's Cave	Posterior wall of maxillary sinus	Axial
V3 Inferior alveolar nerve	Skullbase	Mandibular foramen	Coronal oblique
V3 Lingual nerve	Skullbase	Maximum convex point	Coronal oblique
V3 Buccal nerve	Skull base	Maximum convex point	Axial
V3 Masseteric nerve	Skull base	Medial border of lateral pterygoid muscle	Entry of masseter muscle Axial
V3 Deep temporal nerve	Skull base	Medial border of lateral pterygoid muscle	Entry of temporal muscle Axial
V3 Auriculotemporal nerve	Skull base	Midway between skull base and TMJ	Medial condylar surface Axial
VII Facial nerve	Styломastoid foramen	Entry of parotid gland	Coronal
IX Glossopharyngeal nerve	Skull base	Posterior wall of carotid	Pharyngeal wall Coronal
X Vagus nerve	Skull base	Posterior wall of carotid	Exit of field-of-view Coronal
XI Accessory nerve	Skull base	Posterior wall of carotid	Trapezius muscle Coronal
XII hypoglossal nerve	Skull base	Posterior wall of carotid	Anterior border of submandibular gland Coronal/Axial
Greater occipital nerve	Cervical vertebrae	Semispinal muscle	Trapezius muscle Axial
Lesser occipital nerve	Cervical vertebrae	Obliquus capitis inferior muscle	Skin Axial

The observers first scored the suppression quality for arteries, veins, fat, and lymph nodes before and after contrast administration on the 3D CRANI sequence. Next, all cranial nerves were assessed and scored for visualization before and after contrast administration. The following nerves were evaluated on both sides: trigeminal nerve branches, facial nerve, glossopharyngeal nerve, vagus and accessory nerve, hypoglossal nerve and the greater and lesser occipital nerves. We defined a midpoint for each cranial nerve resulting in a proximal

and distal segment (**Table 1**). Both observers were asked if they could identify each nerve before and after contrast administration. Next, a nerve visualisation score was adopted using a 5-point scale (4, excellent: both proximal and distal portion identified; 3, good: both portions identified but not continuous; 2, fair: only proximal portion identified; 1, poor: only proximal portion identified but not continuous; 0, nerve could not be identified).<sup>11</sup> If the nerve was not located in the field-of-view, this could also be indicated. The observers were allowed to consider the proximal portion of cranial nerves IX-X-XI as one and the same given their close anatomical location and in accordance with a previously published study.<sup>11</sup> The measurements were repeated after one month by both observers and after randomizing all cases. After this qualitative analysis, each nerve was analysed quantitatively to obtain benchmark values before and after contrast administration during the first observation session. Both observers measured signal intensities of the cranial nerves by placing circular region of interests (ROI) within the identified cranial nerves (iROI) at the predefined landmarks. Similarly, a 1 cm<sup>2</sup> ROI was drawn within the masseter muscle (mROI) and in air (aROI) (**Figure 1**).



*Figure 1. Illustration of ROI measurements on the 3D CRANI sequence of the midpoint of the lingual nerve. Using the magnifying tool (red box at top inset) the nerve diameter (blue ROI line) can be accurately measured in a coronal view. To measure signal intensity, a ROI is placed at predefined landmarks within the nerve contour (upper green ROI circle). A 1 cm<sup>2</sup> ROI circle is used to measure muscle signal intensity in an axial view (right masseter muscle: lower green ROI circle) and air signal intensity within the right maxillary sinus (not illustrated here).*

The apparent signal-to-noise ratio (aSNR), the apparent nerve-muscle contrast-to-noise ratio (aNMCNR) and nerve diameter were measured for each cranial nerve. aSNR and aNMCNR were calculated by normalising with the standard deviation of air ( $SD_{air}$ ).<sup>4</sup> Equations used to calculate aSNR and aNMCNR:

$$aSNR = \frac{iROI}{SD_{air}}$$

$$aNMCNR = \frac{iROI - mROI}{SD_{air}}$$

## Statistical analysis

All statistical analyses were done by a certified statistician (FVDC) with RStudio Team (2020) (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA). Descriptive statistics were carried out after pooling of left and right sides as scored by the observers. Confidence intervals of 95% were calculated where suited. A Pearson's Chi-squared test was used to assess independence of nerve identification and suppression quality scores and Fleiss' kappa statistics to assess inter- and intra-rater agreement on the ordinal outcome measures (nerve identification and suppression quality). Group differences between continuous measurements were compared using a Student's T-test or ANOVA test in case of multiple groups. Intraclass correlation coefficients were calculated to determine agreement on the quantitative continuous measurements. A P-value of less than 0.05 was considered significant. There was no missing data in the final dataset.

## Results

### Nerve identification and visualization score

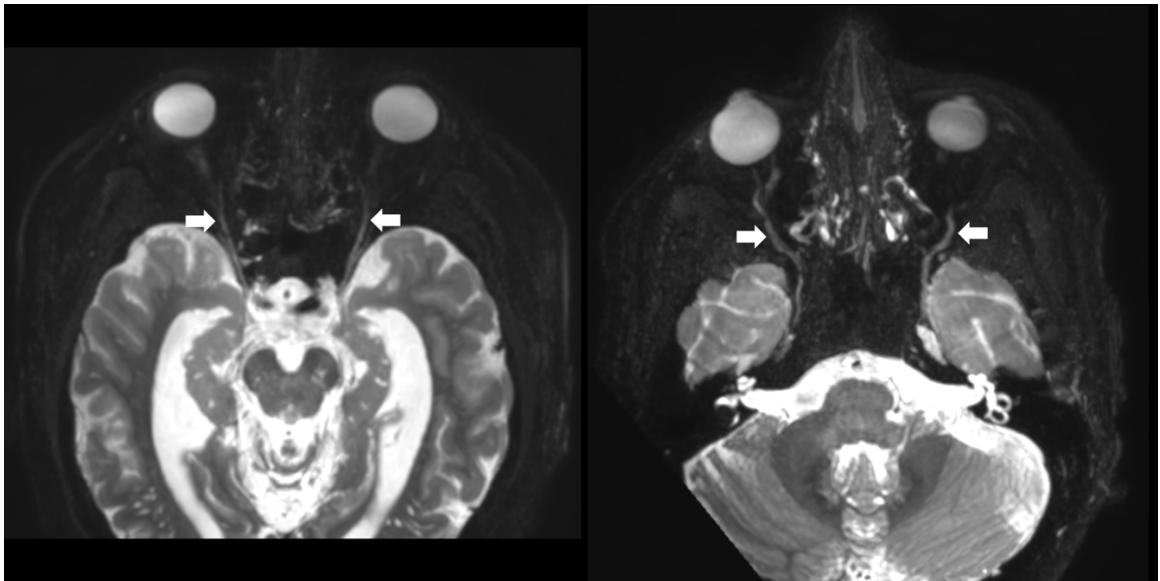
Data from eleven patients were included in this study between January and September 2020 (**Supplemental table 1**): six males and five females with an average age of 47 (range: 14-83). Most extraforaminal cranial nerve branches could be identified in all subjects by both observers after administration of gadolinium contrast agent, except for the lesser occipital and ophthalmic division of the trigeminal nerve where detection rates were considerably lower (**Table 2**).

*Table 2. Nerve identification scores (nerve identified: yes or no) as assessed by both observers before and after contrast administration. This is expressed as a percentage where one hundred percent means that the nerve could be detected in all cases. A significant improvement in detection rates is established after contrast administration.*

Percentage detected (%)	Without Gd contrast	With Gd contrast
Nervus ophthalmicus (V1)	29.5	36
Nervus maxillaris - infraorbitalis (V2)	98.9	100
Nervus alveolaris inferior (V3)	100	100
Nervus lingualis (V3)	100	100
Nervus buccalis (V3)	38.6	100
Nervus auriculotemporalis (V3)	28.4	97.7
Nervus massetericus (V3)	37.5	96.6
Nervi temporalis profundi (V3)	8	72.7
Nervus facialis (VII)	100	100
Nervus glossopharyngeus (IX)	43.2	89.8
Nervus vagus (X)	51.1	85.2
Nervus accessorius (XI)	75.9	94.3
Nervus hypoglossus (XII)	88.5	95.5
Nervus occipitalis major	70.8	72.7
Nervus occipitalis minor	54.5	56.8

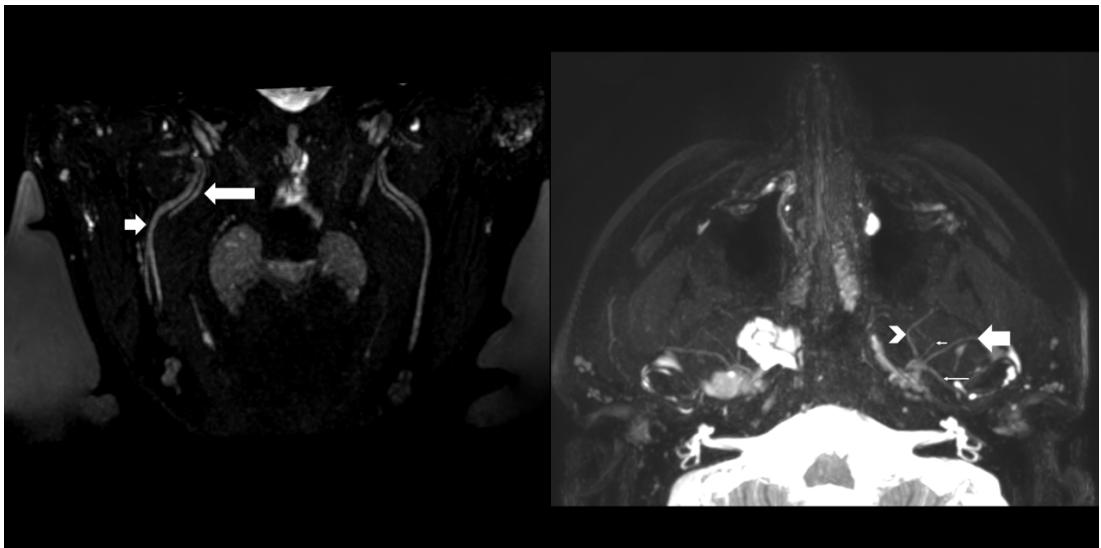
Pearson's Chi-squared test,  $p < 0.001$ ; Gd: gadolinium

The use of gadolinium contrast significantly improved nerve detection rates on the 3D CRANI sequence when comparing combined detection rates before and after contrast administration ( $p < 0.001$ ). 3D CRANI allowed us to obtain high spatial resolution (**Figures 2-5**).



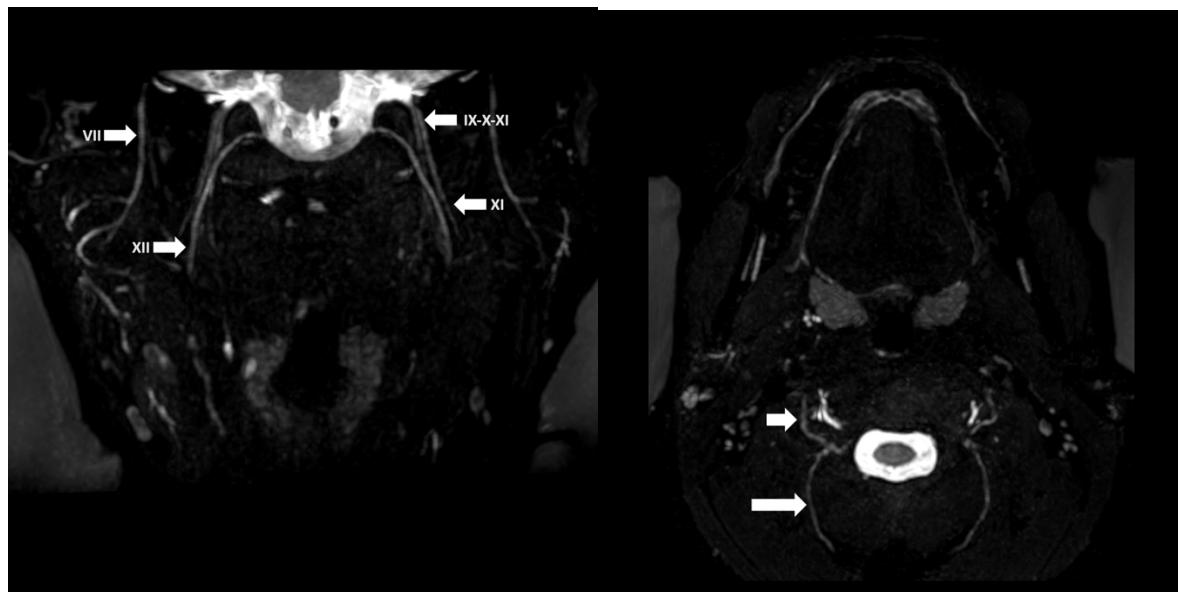
*Figure 2a.* Axial view of the 3D CRANI sequence immediately after contrast administration illustrating the ophthalmic division of the trigeminal nerve (white arrows) entering the orbit.

*Figure 2b.* Axial view of the 3D CRANI sequence immediately after contrast administration illustrating the maxillary nerve (second division of the trigeminal nerve) starting at Meckel's cave and its infraorbital branch coursing inferior to the optic nerve towards the infraorbital foramen.



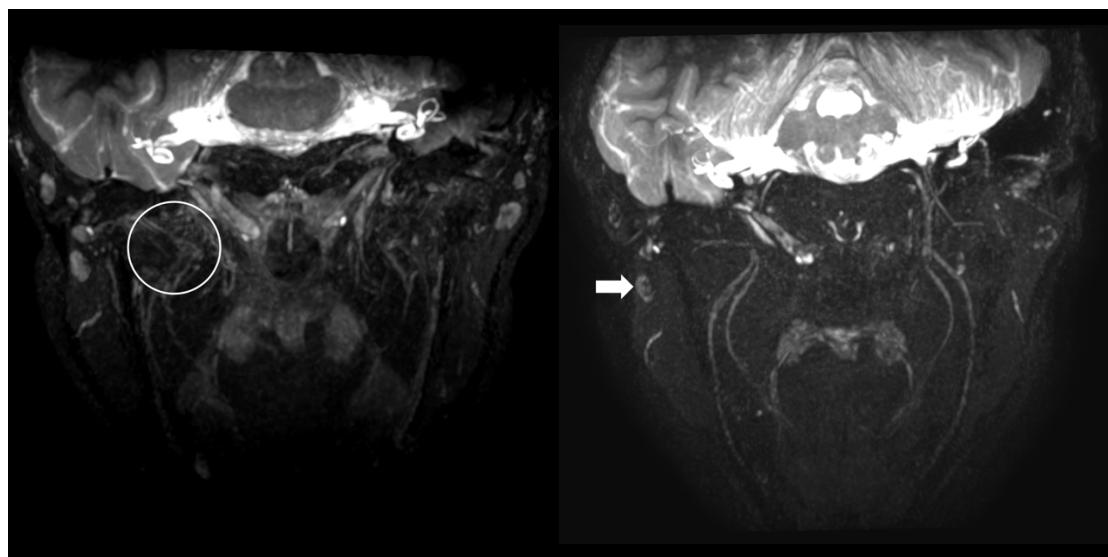
*Figure 3a.* Oblique coronal view of the 3D CRANI sequence immediately after contrast administration illustrating the lingual nerve (long arrow) and inferior alveolar nerve (short arrow) running lateral to the pterygoid muscles on an oblique coronal viewing plane. Barium filled bags were used to fixate the patient head and further improve suppression quality of surrounding tissues.

*Figure 3b.* Third division of the trigeminal nerve in an axial view. This illustrates the ability of the 3D CRANI sequence to visualize the buccal (arrowhead), deep temporal (small short arrow), auriculotemporal (small long arrow) and masseteric (large arrow) nerves.



*Figure 4a.* Visualization of facial (VII), hypoglossal (XII), accessory (XI) and glossopharyngeal-vagus (IX-X) nerves on a coronal 3D CRANI sequence immediately after contrast administration.

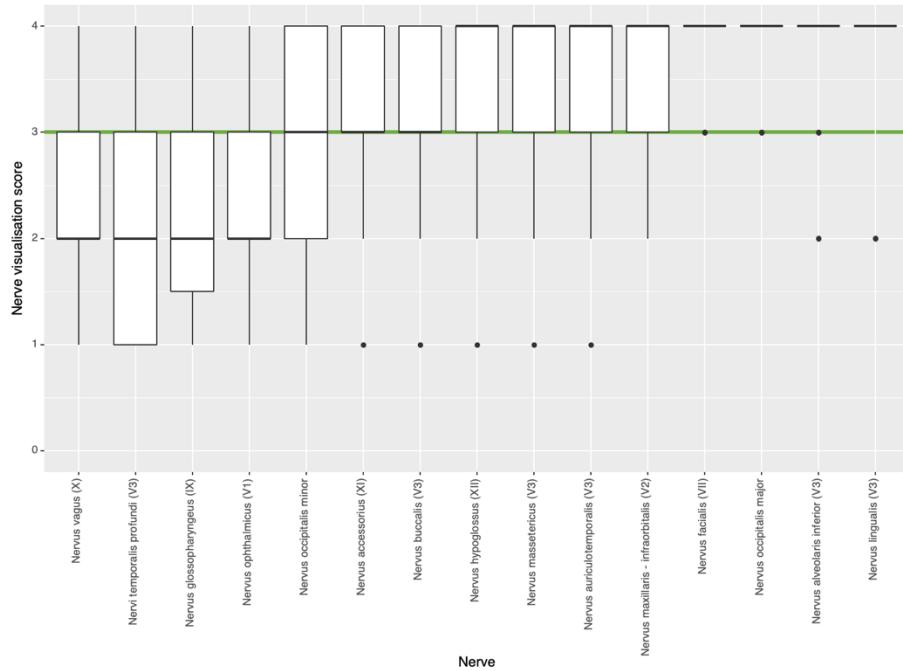
*Figure 4b.* Greater occipital (long arrow) and lesser occipital nerves on an axial 3D CRANI viewing plane.



*Figure 5a.* Venous plexus artifacts before contrast administration limiting the visualization of the third division of the trigeminal nerve in the area of the pterygoid muscles and plexus.

*Figure 5b.* Same patient as in figure 5-1 after gadolinium contrast administration. Remarkable improvement in suppression quality and nerve visualization. Some lymph nodes remain poorly suppressed (white arrow).

The ophthalmic trigeminal branch and the occipital nerve branches were most difficult to distinguish as illustrated by lower identification scores. A similar pattern was seen when nerve visualisation scores were evaluated (**Figure 6**).



*Figure 6.* Qualitative nerve visualization scores as assessed by both observers using a 5-point scale (4, excellent: both proximal and distal portion identified; 3, good: both portions identified but not continuous; 2, fair: only proximal portion identified; 1, poor: only proximal portion identified but not continuous; 0, nerve could not be identified). Most nerves were rated as good to excellent visualization (green cut-off line).

On average, the visualisation of most cranial nerve branches was scored as good to excellent, except for the glossopharyngeal and vagus nerves and the smaller nerve branches such as the deep temporal and ophthalmic nerves which still received a fair score meaning the proximal portion of these branches could be identified. Nerve identification before contrast administration showed an overall intrarater agreement of 79.2% and interrater agreement of 82.7% (intrarater  $\kappa=.561$ ,  $p < .0001$ ; interrater  $\kappa=.642$ ,  $p < .0001$ ). After contrast administration, this improved to an overall intrarater agreement of 92.7% and interrater agreement of 93.6% (intrarater  $\kappa=.688$ ,  $p < .0001$ ; interrater  $\kappa=.727$ ,  $p < .0001$ ).

## Suppression quality of surrounding structures

The arterial and fat suppression quality was moderate to excellent both before and after contrast administration. Venous and lymph node suppression quality was scored non-suppressed to excellently suppressed, with an improvement in suppression quality after contrast administration (**Table 3, Figure 5**).

*Table 3. Suppression quality scores before and after contrast administration. A significant improvement in suppression quality is seen after contrast administration. Lymph nodes remain not to moderately suppressed immediately after contrast administration.*

Suppression quality score	Without Gd contrast	With Gd contrast
<b>Arterial</b>		
1: Not suppressed, not diagnostically usable	0 (0%)	0 (0%)
2: Not suppressed, but diagnostically usable	0 (0%)	0 (0%)
3: Moderately suppressed, diagnostically usable	0 (0%)	0 (0%)
4: Excellent suppression, diagnostically usable	44 (100%)	44 (100%)
<b>Venous</b>		
1: Not suppressed, not diagnostically usable	1 (2%)	0 (0%)
2: Not suppressed, but diagnostically usable	20 (46%)	0 (0%)
3: Moderately suppressed, diagnostically usable	22 (50%)	14 (32%)
4: Excellent suppression, diagnostically usable	1 (2%)	30 (68%)
<b>Fat tissue</b>		
1: Not suppressed, not diagnostically usable	0 (0%)	0 (0%)
2: Not suppressed, but diagnostically usable	0 (0%)	0 (0%)
3: Moderately suppressed, diagnostically usable	18 (41%)	3 (7%)
4: Excellent suppression, diagnostically usable	26 (59%)	41 (93%)
<b>Lymphatic tissue</b>		
1: Not suppressed, not diagnostically usable	0 (0%)	0 (0%)
2: Not suppressed, but diagnostically usable	38 (86%)	15 (34%)
3: Moderately suppressed, diagnostically usable	4 (9%)	26 (59%)
4: Excellent suppression, diagnostically usable	2 (5%)	3 (7%)

Pearson's Chi-squared test, p < 0.001; Gd: gadolinium

Excellent agreement was seen for arterial and fat suppression. Venous and lymph node suppression quality scores showed varying agreement between and within observers. Kappa statistics varied from poor to moderate (**Supplemental table 2**).

### **Quantitative analysis: benchmarking values and reliability**

Nerve benchmarking values were calculated before and after contrast administration (**Supplemental table 3**). Excellent aSNR ( $M = 36.2$ ,  $SD = 14.5$ ) and aNMCNR ( $M = 24.1$ ,  $SD = 14.7$ ) were seen along nerve trajectories post contrast administration, with a decrease in aSNR, aNMCR and diameter from proximal to distal for all nerve branches (**Supplemental figures**).

Nerve branches as small as 0.5 millimeters could be identified. A significant decrease in nerve diameter measurements and aSNR was observed after contrast administration ( $p < .05$ ). aNMCNR did not significantly differ before and after contrast administration. The intraclass correlation coefficients (ICC) showed high concordance for all measurements with decreasing ICC values from proximal to distal (**Table 4**).

*Table 4. Intraclass correlation coefficients (ICC) and confidence intervals for quantitative apparent signal-to-noise ratios (aSNR) and nerve-muscle contrast-to-noise-ratios (aNMCNR) before and immediately after contrast administration measured by both observers during the first session.*

	Without Gd contrast			With Gd contrast		
	ICC	ICC, Lower limit	ICC, Upper limit	ICC	ICC, Lower limit	ICC, Upper limit
aSNR, proximal	0.7346	0.6805	0.7807	0.7316	0.6771	0.7781
aSNR, mid	0.689	0.6277	0.7418	0.6265	0.556	0.688
aSNR, distal	0.6725	0.6086	0.7277	0.5922	0.5173	0.6581
diameter, proximal	0.773	0.7255	0.8132	0.7144	0.6572	0.7635
diameter, mid	0.7461	0.6941	0.7904	0.7274	0.6721	0.7746
diameter, distal	0.71	0.6519	0.7598	0.6503	0.5832	0.7085
aNMCNR, proximal	0.7317	0.6772	0.7783	0.6157	0.5439	0.6786
aNMCNR, mid	0.6165	0.5447	0.6794	0.5734	0.4961	0.6417
aNMCNR, distal	0.6608	0.5952	0.7177	0.4679	0.3791	0.5482

Gd: gadolinium; ICC: intraclass correlation coefficient; aSNR: apparent signal-to-noise ratio; aNMCNR: apparent nerve-muscle contrast-to-noise ratio

## Discussion

This study confirms that the novel MR neurography sequence, also denoted as 3D CRANI<sup>8</sup>, is a reliable and reproducible MR neurography technique for the visualisation of the extraforaminal cranial and occipital nerves. Previous studies already evaluated the feasibility of heavily T2 weighted MR imaging for nerve specific visualization of the mandibular nerve<sup>2,12</sup> but this is the first study to expand on this topic and evaluate reliability of MRN in cranial and occipital nerve evaluation. Reliable imaging techniques are necessary when dealing with cranial nerve disorders, as electrophysiological and sensory examinations in the head and neck area have their own limitations.<sup>13</sup> Some already described the advantageous role of MRN in diagnosing trigeminal nerve injuries and impact on clinical management.<sup>2,5</sup> Within other domains such as brachial plexus imaging, MRN established its role and showed substantial therapeutic impact in over one third of patients.<sup>14</sup>

This is the first study to assess the role of contrast administration in MR neurography. We illustrated improved suppression quality of surrounding structures as well as improved nerve visualisation after gadolinium administration. This probably results from a short-lasting change

in susceptibility of the contrast filled vessels resulting in faster blood dephasing and thus a better suppression quality.

A significant decrease in signal intensities and nerve diameters immediately after contrast administration was noticed. A possible explanation could be the improved suppression of the surrounding tissues and vasa nervorum. As a result, true MR neurography is achieved. This further implies that benchmarking of signal intensity, but also spatial dimensions, depends on contrast administration. Current literature does not allow unequivocal comparison of benchmarking values as each study applies its own MR sequences, relative signal calculations, with or without contrast administration.<sup>4-6</sup> One study by Burian et al. evaluating the lingual and inferior alveolar nerves did produce similar nerve diameters.<sup>6</sup> However, aSNR and aMNCNR do not seem to correspond. Perhaps because different formulas for signal calculation were applied. Publishing all relevant data may overcome this hurdle for future comparison. Furthermore, future studies could compare pathological nerve thickening found on MRN with surgical findings, as exemplified by the work of Zuniga et al.<sup>3</sup>

A signal intensity drop moving from proximal to distal along the nerve trajectory was seen. And, as one would expect, the nerve diameter also decreased in the distal direction. This is an important fact if we want to be able to make statements about pathological abnormalities in cranial and occipital neuropathy in the future. Others found similar signal changes in both healthy volunteers and neuropathy cases.<sup>4</sup> In case of traumatic neuropathies, an increase in focal signal intensity and caliber correlates with histological changes such as endoneurial edema, vascular congestion, onset of endoneurial fibrosis and demyelination.<sup>15</sup> Bendszus and colleagues further identified temporal MR changes in the weeks following sciatic nerve lesions in a rat model that correlated with electrophysiological findings.<sup>15</sup>

This study had some limitations including its retrospective nature, a small sample size and limited number of observers. However, a wide age distribution and near equal female-male ratio was achieved. Both observers anticipated in a calibration session to limit method bias. Future studies should confirm these findings on a larger cohort. The large number of measurements could have resulted in measurement errors. Automatic segmentation and signal intensity calculation would be a next step forward in determining benchmarking values for any anatomical location, limiting this bias. The occipital nerves showed a surprisingly low overall visualisation score, probably this was related due to patient positioning resulting in suboptimal suppression quality in the occipital area and not due to inherent flaws in the MRN technique, however this must be verified in a future study. Suppression quality scores showed varying

results both between and within observers. This could be due to several factors such as the use of a limited 4-point Likert scale to score suppression quality and small sample size. Finally, a case-control study will be needed to address the reliability of 3D CRANI in patients with cranial or occipital nerve disorders.

## **Conclusion**

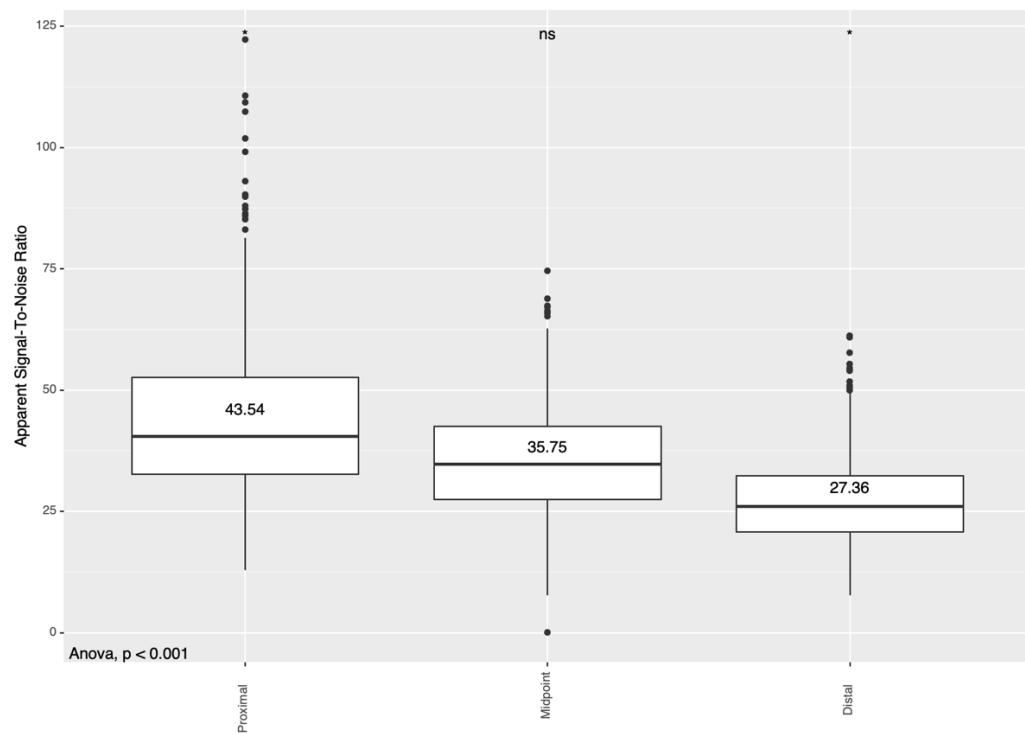
This study confirms the reliability of the novel 3D CRANI sequence for MR neurography of the extraforaminal cranial and occipital nerves in healthy subjects. Intravenous gadolinium administration improves suppression quality and nerve visualisation but alters signal intensities and nerve calibers. Quantitative measurements are reproducible and may serve as benchmarking for future case-control studies on cranial nerve disorders.

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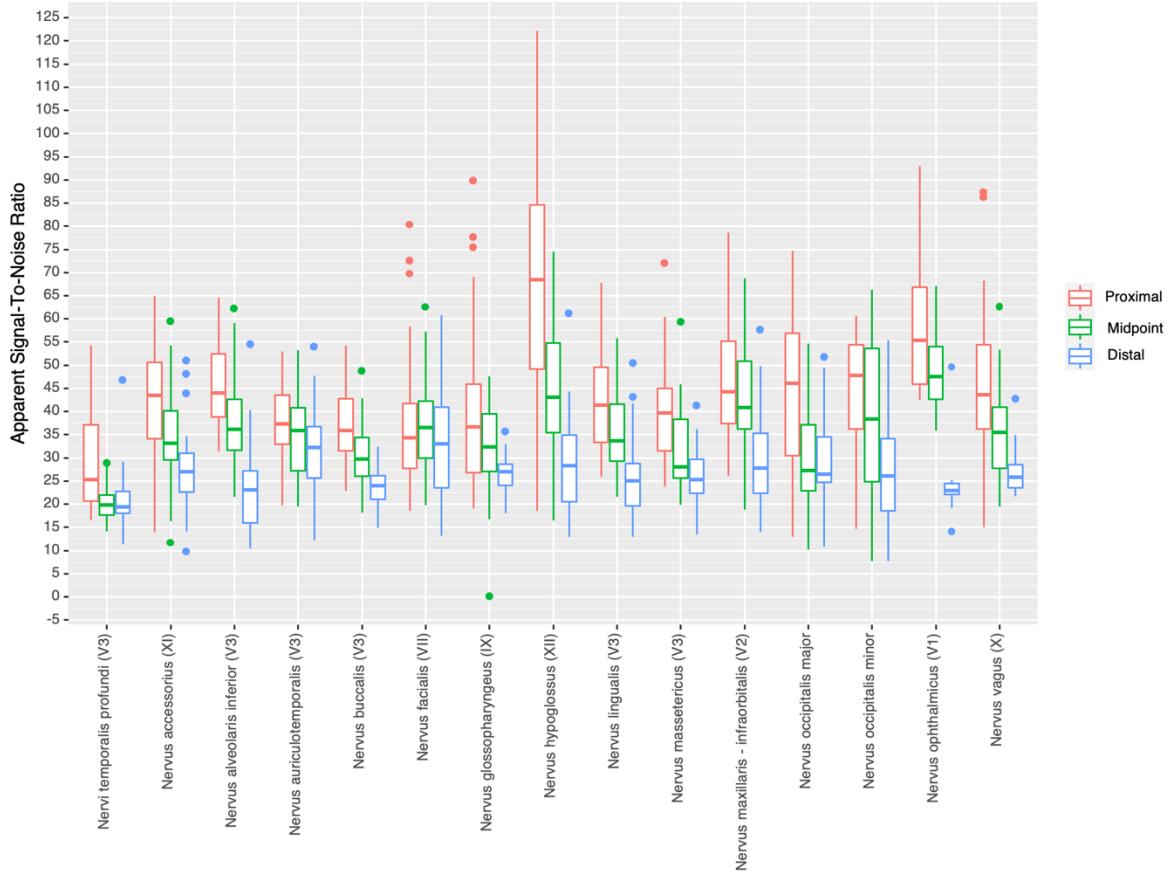
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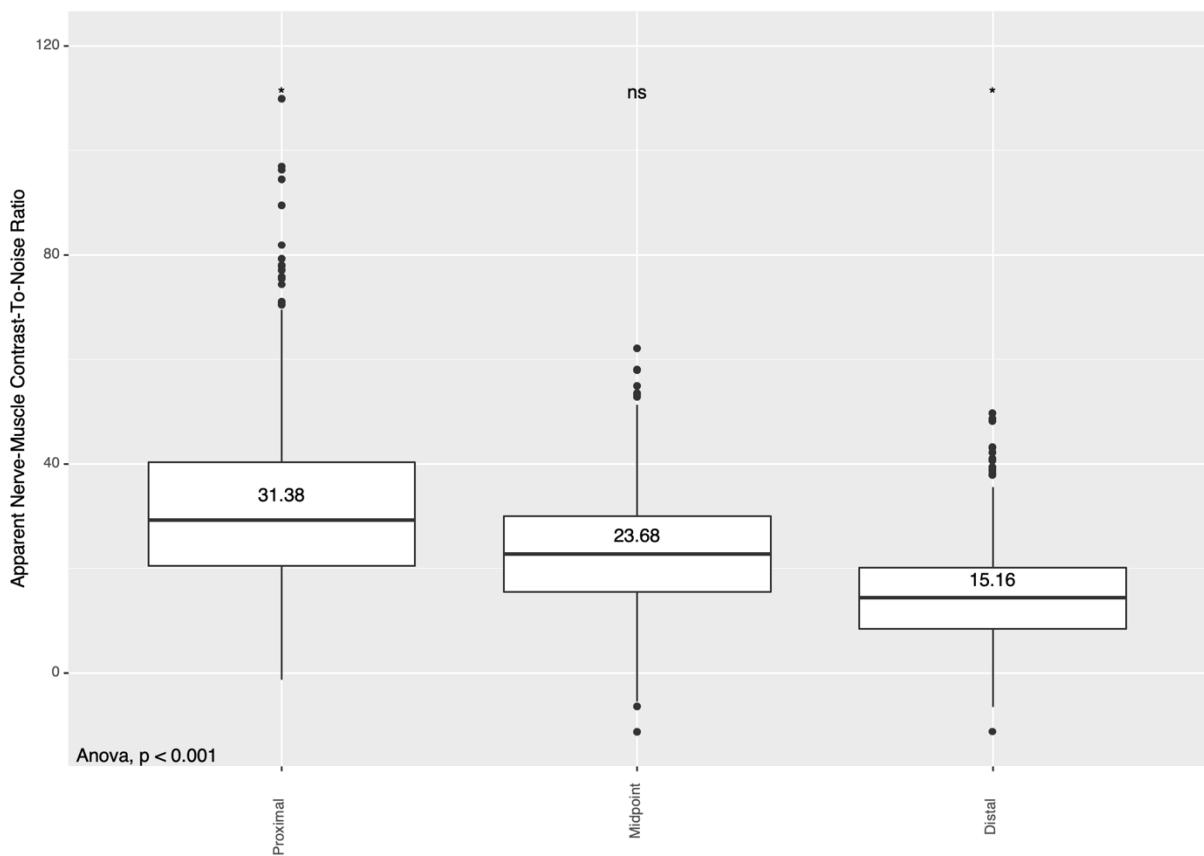
## Supplemental data



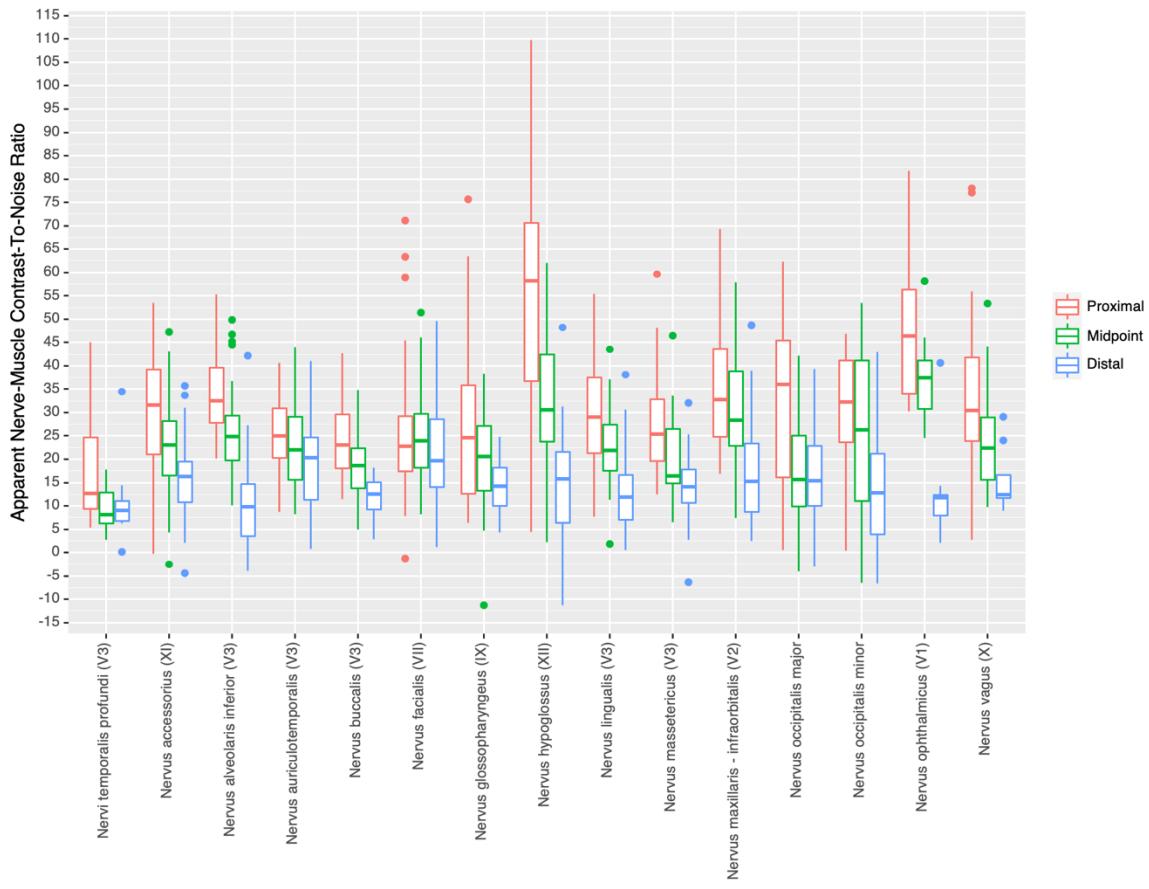
*Supplemental figure 1a. Apparent signal-to-noise ratio (aSNR) boxplots comparing overall proximal, middle and distal aSNR. ns: not significant, \* $p < 0.001$ .*



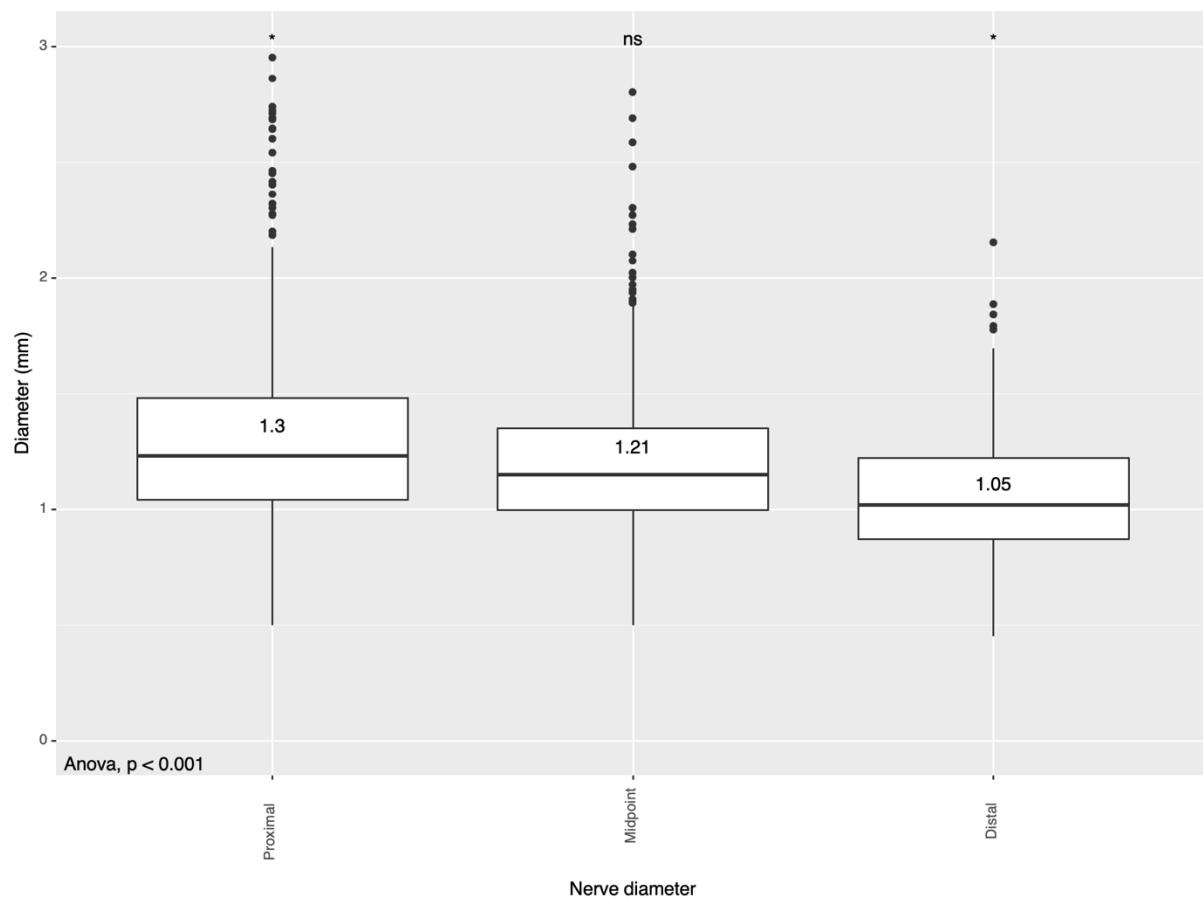
*Supplemental figure 1b. Apparent signal-to-noise ratio (aSNR) boxplots comparing proximal, middle and distal aSNR, stratified according to the observed nerves.*



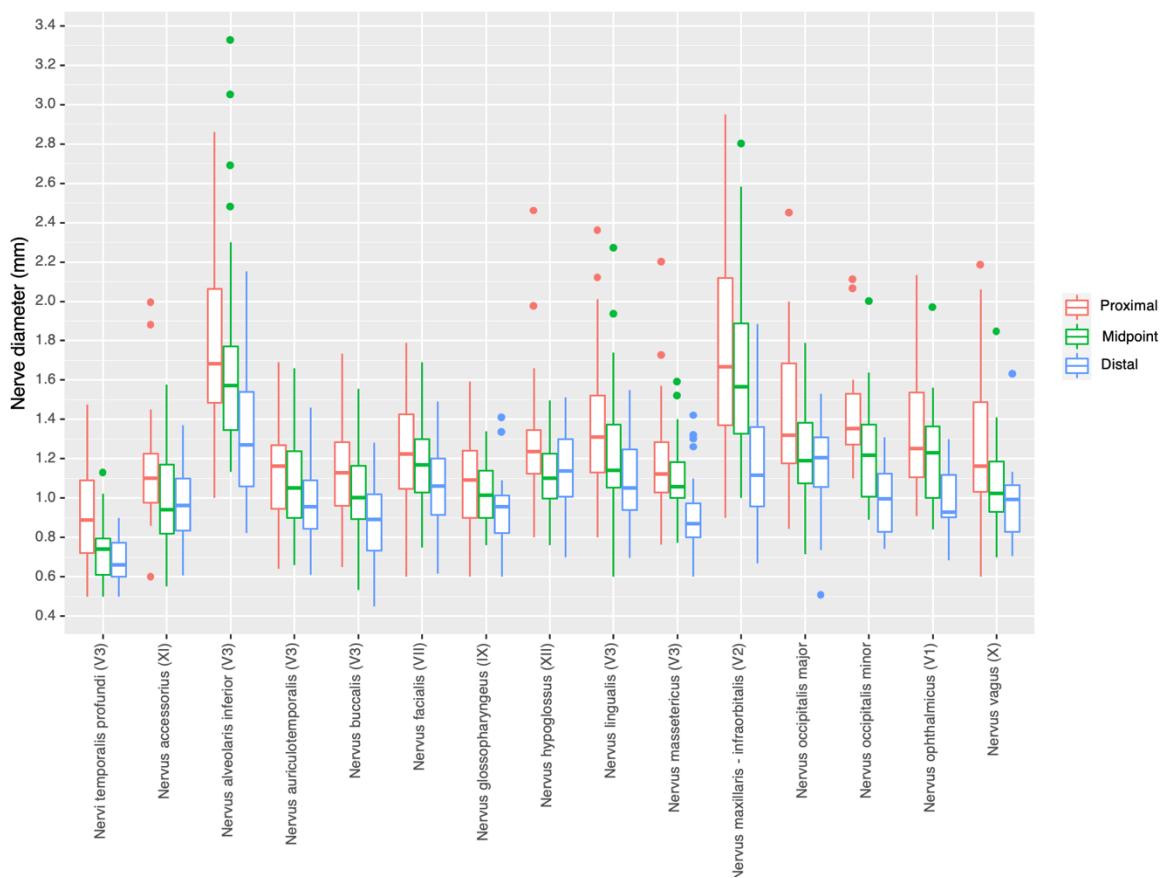
*Supplemental figure 2a. Apparent nerve-muscle contrast-to-noise ratio (aNMCNR) boxplots comparing overall proximal, middle and distal aNMCNR. ns: not significant, \*  $p < 0.001$ .*



*Supplemental figure 2b. Apparent nerve-muscle contrast-to-noise ratio (aNMCNR) boxplots comparing proximal, middle and distal aNMCNR, stratified according to the observed nerves.*



*Supplemental figure 3a.* Nerve diameter boxplots comparing overall proximal, middle and distal nerve diameters. ns: not significant, \*  $p < 0.001$ .



*Supplemental figure 3b. Nerve diameter boxplots comparing proximal, middle and distal nerve diameters, stratified according to the observed nerves.*

*Supplemental table 1. Patient characteristics and reason for MRI referral.*

ID	Gender	Age	Reason for MRI referral
1	M	65	Suspected trigeminal neuralgia
2	F	57	Suspected trigeminal neuralgia
3	M	53	Persistent tension headache
4	M	49	Suspected trigeminal neuralgia
5	M	24	Suspected occipital neuralgia
6	F	55	Infraorbital weakness after facelift
7	M	66	Suspected parotid tumor
8	F	35	Pineal cyst
9	F	14	Inexplainable sudden drop attack
10	M	83	Hearing loss
11	F	16	Suspected lingual nerve deficit

*Supplemental table 2. Suppression quality inter- and intrarater agreement and kappa statistics before and immediately after contrast administration.*

	Contrast administration	% agreement, inter-rater	Inter-rater kappa	Inter-rater kappa, CI	% agreement, rater 1	Intra-rater kappa rater 1	Intra-rater kappa, CI	% agreement, rater 2	Intra-rater kappa rater 2	Intra-rater kappa, CI	% agreement, rater 1 and 2	Intra-rater kappa, rater 1 and 2	Intra-rater kappa, rater 1 and 2, CI		
Arterial	No	1	1		1	1		1	1		1	1	1		
Arterial	Yes	1	1		1	1		1	1		1	1	1		
Venous	No	0.5	0.1619	[−0.207;0.5308]	0.7	0.4054	[−0.1094;0.9202]	0.4	-0.2941	[−0.8132;0.225]	0.5	0.1619	[−0.207;0.5308]		
Venous	Yes	0.8	0.581	[0.1631;0.9989]	0.5	-0.0476	[−0.6386;0.5434]	0.7	0.3714	[−0.2196;0.9624]	0.6	0.1619	[−0.256;0.5798]		
Fat tissue	No	0.8	0.6239	[0.206;1.0418]	0.3	-0.5714	[−1.1624;0.0196]	0.5	-0.1	[−0.691;0.491]	0.4	-0.3162	[−0.7341;0.1017]		
Fat tissue	Yes	0.9	-0.05	[−0.4777;0.3777]	0.9	-0.0526	[−0.6724;0.5672]	0.9	-0.0476	[−0.6386;0.5434]	0.9	-0.05	[−0.4777;0.3777]		
Lymphatic tissue	No	0.7	-		0.1186	[−0.4528;0.2156]	0.7	0.12	[−0.3685;0.6085]	0.8	-0.0732	[−0.5338;0.3874]	0.8	0.0678	[−0.2664;0.402]
Lymphatic tissue	Yes	0.8	0.5712	[0.2199;0.9225]	0.5	0.12	[−0.402;0.642]	0.5	0.1603	[−0.3162;0.6368]	0.5	0.1423	[−0.209;0.4936]		

CI: confidence interval

*Supplemental table 3. Benchmarking values describing nerve visualization scores, diameters, signal intensities (SI), apparent signal to noise ratio (aSNR), apparent nerve-muscle contrast-to-noise ratio (aNMCNR) measured at a proximal, mid and distal landmark for each evaluated cranial and occipital nerves. Values are given before and after gadolinium contrast administration.*

Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (V3), N = 88	Nervus facialis (VII), N = 88	Nervus glossopharyngeus (IX), N = 88	Nervus hypoglossus (XII), N = 88	Nervus lingualis (V3), N = 87	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
<b>Before gadolinium contrast administration</b>														
<b>Nerve visualization score</b>														
0 Not identified														
81 (92%)	14 (16%)	0 (0%)	63 (72%)	54 (61%)	0 (0%)	44 (50%)	3 (3.4%)	0 (0%)	55 (62%)	0 (0%)	1 (1.1%)	15 (17%)	1 (1.1%)	37 (42%)
1 Poor	5 (5.7%)	31 (36%)	0 (0%)	12 (14%)	21 (24%)	9 (10%)	21 (24%)	27 (31%)	2 (2.3%)	11 (12%)	2 (2.3%)	11 (12%)	11 (12%)	21 (24%)
2 Fair	0 (0%)	8 (9.2%)	6 (6.9%)	7 (8.0%)	9 (10%)	21 (24%)	14 (16%)	29 (33%)	18 (21%)	8 (9.1%)	20 (23%)	7 (7.9%)	17 (19%)	13 (15%)
3 Good	2 (2.3%)	20 (23%)	20 (23%)	6 (6.8%)	4 (4.5%)	42 (48%)	2 (2.3%)	18 (21%)	31 (36%)	12 (14%)	35 (40%)	39 (44%)	11 (12%)	1 (1.1%)
4 Excellent	0 (0%)	7 (8.0%)	61 (70%)	0 (0%)	0 (0%)	16 (18%)	1 (1.1%)	3 (3.4%)	36 (41%)	2 (2.3%)	30 (34%)	15 (17%)	9 (10%)	1 (1.1%)
Not within FOV	0 (0%)	7 (8.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (6.8%)	7 (8.0%)	0 (0%)	0 (0%)	1 (1.1%)	25 (28%)	25 (28%)	61 (69%)
<b>SI proximal</b>														
N	3	30	43	10	13	44	7	36	43	15	43	31	17	14
Mean (SD)	642 (293)	685 (176)	623 (130)	621 (201)	545 (130)	557 (122)	645 (351)	974 (300)	584 (128)	581 (124)	664 (168)	598 (228)	611 (194)	663 (186)
Median (IQR)	598 (485, 776)	670 (549, 778)	634 (518, 693)	625 (527, 672)	545 (460, 585)	562 (473, 618)	562 (405, 903)	935 (815, 1,200)	558 (504, 646)	626 (490, 667)	651 (529, 790)	583 (431, 747)	557 (489, 724)	706 (526, 829)
Range	373, 954	339, 1,159	298, 864	264, 1,042	344, 816	297, 854	210, 1,126	424, 1,564	279, 878	346, 774	267, 961	267, 1,353	308, 980	356, 917
<b>SI mid</b>														
N	1	16	42	7	1	38	0	15	39	8	39	29	10	6
Mean (SD)	735 (NA)	535 (224)	538 (167)	682 (252)	599 (NA)	545 (139)	NA (NA)	655 (263)	519 (153)	435 (130)	626 (146)	460 (172)	466 (178)	546 (182)
Median (IQR)	735 (735, 735)	542 (434, 593)	533 (451, 618)	684 (549, 738)	599 (599, 599)	537 (437, 636)	NA (NA, NA)	693 (494, 786)	517 (408, 593)	415 (344, 529)	632 (550, 710)	427 (381, 529)	451 (369, 611)	558 (443, 665)
Range	735, 735	0, 933	224, 1,137	373, 1,143	599, 599	289, 990	Inf, -Inf	1, 1,041	269, 946	270, 648	192, 1,057	0, 906	125, 699	278, 779
<b>SI distal</b>														
N	2	12	39	4	1	32	0	11	31	8	36	25	8	2
Mean (SD)	254 (360)	510 (152)	337 (132)	581 (208)	382 (NA)	584 (164)	NA (NA)	432 (191)	446 (146)	386 (96)	443 (141)	401 (114)	377 (126)	245 (60)

	Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (V3), N = 88	Nervus facialis (VII), N = 88	Nervus glossopharyngeus (IX), N = 88	Nervus hypoglossus (XII), N = 88	Nervus lingualis (V3), N = 87	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
Median (IQR)	254 (127, 382)	474 (429, 536)	339 (226, 447)	633 (471, 743)	382 (382, 382)	560 (467, 701)	NA (NA, NA)	415 (383, 511)	445 (342, 528)	416 (303, 427)	419 (349, 549)	368 (316, 473)	407 (331, 450)	245 (223, 266)	361 (315, 422)
Range	0, 509	334, 813	148, 672	310, 745	382, 382	280, 966	Inf, -Inf	0, 782	195, 778	256, 547	64, 758	183, 684	112, 511	202, 287	0, 507
<b>Diameter proximal</b>															
N	3	30	43	10	13	44	7	35	43	15	43	30	17	14	13
Mean (SD)	1.17 (0.36)	1.17 (0.25)	1.64 (0.42)	1.32 (0.25)	1.23 (0.23)	1.17 (0.20)	1.09 (0.20)	1.27 (0.24)	1.27 (0.30)	1.20 (0.25)	1.81 (0.53)	1.32 (0.31)	1.40 (0.47)	1.21 (0.26)	1.34 (0.20)
Median (IQR)	1.10 (0.98, 1.33)	1.10 (1.00, 1.32)	1.68 (1.34, 1.94)	1.19 (1.12, 1.56)	1.20 (1.08, 1.42)	1.16 (1.02, 1.36)	1.03 (0.96, 1.14)	1.22 (1.12, 1.37)	1.21 (1.08, 1.39)	1.21 (0.97, 1.36)	1.70 (1.48, 2.13)	1.34 (1.12, 1.55)	1.28 (1.02, 1.64)	1.19 (1.02, 1.33)	1.30 (1.20, 1.51)
Range	0.86, 1.56	0.85, 1.90	0.91, 2.80	1.06, 1.76	0.87, 1.57	0.80, 1.49	0.91, 1.48	0.90, 2.10	0.80, 2.40	0.86, 1.60	0.89, 3.00	0.68, 2.06	0.88, 2.57	0.80, 1.74	1.08, 1.78
<b>Diameter mid</b>															
N	1	15	42	7	1	38	0	14	39	8	39	27	10	6	5
Mean (SD)	1.20 (NA)	1.06 (0.18)	1.96 (0.41)	1.20 (0.43)	1.01 (NA)	1.12 (0.24)	NA (NA)	1.26 (0.25)	1.23 (0.33)	1.20 (0.30)	1.64 (0.40)	1.17 (0.43)	1.20 (0.27)	1.14 (0.36)	1.23 (0.18)
Median (IQR)	1.20 (1.20, 1.20)	1.01 (0.93, 1.16)	2.00 (1.72, 2.22)	1.20 (1.16, 1.28)	1.01 (1.01, 1.01)	1.16 (0.94, 1.27)	NA (NA, NA)	1.29 (1.10, 1.43)	1.15 (0.99, 1.56)	1.15 (0.96, 1.44)	1.67 (1.34, 1.89)	1.09 (0.92, 1.26)	1.12 (1.00, 1.31)	1.17 (0.89, 1.21)	1.33 (1.22, 1.33)
Range	1.20, 1.20	0.81, 1.52	1.18, 2.90	0.43, 1.90	1.01, 1.01	0.70, 1.80	Inf, -Inf	0.82, 1.70	0.60, 1.75	0.82, 1.65	0.82, 2.37	0.81, 3.03	0.90, 1.70	0.75, 1.76	0.91, 1.33
<b>Diameter distal</b>															
N	1	12	39	4	1	32	0	10	31	8	36	25	8	2	4
Mean (SD)	1.10 (NA)	0.95 (0.20)	1.73 (0.43)	1.16 (0.49)	1.03 (NA)	0.97 (0.23)	NA (NA)	1.20 (0.29)	1.02 (0.23)	0.94 (0.19)	1.32 (0.41)	1.13 (0.22)	1.11 (0.28)	0.65 (0.08)	1.29 (0.58)
Median (IQR)	1.10 (1.10, 1.10)	0.97 (0.85, 1.10)	1.59 (1.42, 2.04)	1.21 (0.96, 1.42)	1.03 (1.03, 1.03)	0.91 (0.77, 1.16)	NA (NA, NA)	1.07 (1.00, 1.34)	1.04 (0.85, 1.19)	0.92 (0.81, 1.02)	1.34 (1.02, 1.55)	1.15 (0.97, 1.30)	1.08 (0.88, 1.32)	0.65 (0.63, 0.68)	1.18 (0.84, 1.64)
Range	1.10, 1.10	0.58, 1.22	1.11, 3.02	0.52, 1.70	1.03, 1.03	0.64, 1.47	Inf, -Inf	0.92, 1.79	0.45, 1.48	0.70, 1.29	0.59, 2.51	0.75, 1.54	0.80, 1.54	0.60, 0.71	0.80, 2.01
<b>aSNR proximal</b>															
N	3	30	43	10	13	44	7	36	43	15	43	31	17	14	13
Mean (SD)	48 (22)	51 (13)	47 (10)	46 (15)	41 (10)	42 (9)	48 (26)	73 (22)	44 (10)	43 (9)	50 (13)	45 (17)	46 (15)	50 (14)	45 (13)
Median (IQR)	45 (36, 58)	50 (41, 58)	47 (39, 52)	47 (39, 50)	41 (34, 44)	42 (35, 46)	42 (30, 68)	70 (61, 90)	42 (38, 48)	47 (37, 50)	49 (40, 59)	44 (32, 56)	42 (37, 54)	53 (39, 62)	47 (33, 54)
Range	28, 71	25, 87	22, 65	20, 78	26, 61	22, 64	16, 84	32, 117	21, 66	26, 58	20, 72	20, 101	23, 73	27, 69	20, 65
<b>aSNR mid</b>															
N	1	16	42	7	1	38	0	15	39	8	39	29	10	6	5
Mean (SD)	55 (NA)	40 (17)	40 (12)	51 (19)	45 (NA)	41 (10)	NA (NA)	49 (20)	39 (11)	33 (10)	47 (11)	34 (13)	35 (13)	41 (14)	30 (9)

	Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (VII), N = 88	Nervus facialis (IX), N = 88	Nervus glossopharyngeus (XII), N = 88	Nervus hypoglossus (VIII), N = 87	Nervus lingualis (V3), N = 88	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
Median (IQR)	55 (55, 55)	41 (32, 44)	40 (34, 46)	51 (41, 55)	45 (45, 45)	40 (33, 48)	NA (NA, NA)	52 (37, 59)	39 (30, 44)	31 (26, 40)	47 (41, 53)	32 (29, 40)	34 (28, 46)	42 (33, 50)	26 (25, 35)
Range	55, 55	0, 70	17, 85	28, 85	45, 45	22, 74	Inf, -Inf	0, 78	20, 71	20, 48	14, 79	0, 68	9, 52	21, 58	20, 42
<b>aSNR distal</b>															
N	2	12	39	4	1	32	0	11	31	8	36	25	8	2	5
Mean (SD)	19 (27)	38 (11)	25 (10)	43 (16)	29 (NA)	44 (12)	NA (NA)	32 (14)	33 (11)	29 (7)	33 (11)	30 (9)	28 (9)	18 (4)	24 (14)
Median (IQR)	19 (10, 29)	35 (32, 40)	25 (17, 33)	47 (35, 56)	29 (29, 29)	42 (35, 52)	NA (NA, NA)	31 (29, 38)	33 (26, 39)	31 (23, 32)	31 (26, 41)	27 (24, 35)	30 (25, 34)	18 (17, 20)	27 (24, 32)
Range	0, 38	25, 61	11, 50	23, 56	29, 29	21, 72	Inf, -Inf	0, 58	15, 58	19, 41	5, 57	14, 51	8, 38	15, 21	0, 38
<b>aNMCNR proximal</b>															
N	3	30	43	10	13	44	7	36	43	15	43	31	17	14	13
Mean (SD)	34 (20)	34 (13)	30 (9)	31 (14)	25 (9)	25 (9)	32 (25)	56 (21)	27 (9)	27 (8)	33 (12)	28 (17)	29 (15)	33 (17)	28 (13)
Median (IQR)	29 (23, 42)	34 (25, 40)	30 (22, 37)	32 (27, 35)	26 (18, 29)	25 (20, 30)	26 (15, 50)	54 (44, 73)	26 (20, 33)	30 (22, 33)	32 (24, 40)	29 (16, 38)	26 (21, 35)	38 (23, 48)	32 (18, 35)
Range	17, 56	10, 69	11, 49	9, 62	14, 45	6, 42	0, 67	16, 93	10, 48	11, 41	9, 57	3, 86	6, 59	1, 54	4, 47
<b>aNMCNR mid</b>															
N	1	16	42	7	1	38	0	15	39	8	39	29	10	6	5
Mean (SD)	39 (NA)	23 (16)	23 (11)	35 (19)	29 (NA)	24 (10)	NA (NA)	33 (19)	22 (11)	16 (9)	30 (11)	18 (12)	19 (12)	27 (14)	13 (7)
Median (IQR)	39 (39, 39)	23 (16, 31)	23 (17, 30)	36 (26, 40)	29 (29, 29)	24 (16, 29)	NA (NA, NA)	35 (25, 44)	22 (13, 28)	15 (11, 22)	29 (25, 36)	16 (13, 23)	22 (12, 27)	26 (17, 35)	9 (9, 18)
Range	39, 39	-16, 49	5, 68	12, 68	29, 29	6, 54	Inf, -Inf	-17, 61	7, 54	4, 31	3, 62	-16, 48	-6, 34	10, 47	5, 22
<b>aNMCNR distal</b>															
N	2	12	39	4	1	32	0	11	31	8	36	25	8	2	5
Mean (SD)	2 (29)	21 (10)	8 (9)	28 (16)	13 (NA)	26 (11)	NA (NA)	16 (14)	16 (10)	13 (7)	17 (11)	14 (8)	13 (10)	2 (4)	8 (14)
Median (IQR)	2 (-9, 12)	19 (15, 24)	6 (1, 15)	31 (19, 40)	13 (13, 13)	26 (19, 34)	NA (NA, NA)	16 (13, 21)	15 (7, 23)	14 (8, 15)	16 (11, 23)	12 (9, 19)	14 (9, 17)	2 (0, 4)	11 (8, 14)
Range	-19, 22	8, 43	-5, 33	7, 41	13, 13	5, 54	Inf, -Inf	-16, 41	3, 40	3, 24	-15, 45	0, 33	-6, 29	-1, 5	-16, 21
<b>After gadolinium contrast administration</b>															
<b>Nerve visualization score</b>															
0 Not identified	24 (27%)	2 (2.3%)	0 (0%)	2 (2.3%)	0 (0%)	0 (0%)	7 (8.0%)	0 (0%)	0 (0%)	3 (3.4%)	0 (0%)	0 (0%)	2 (2.3%)	0 (0%)	11 (12%)

	Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (VII), N = 88	Nervus facialis (IX), N = 88	Nervus glossopharyngeus (XII), N = 88	Nervus hypoglossus (V3), N = 87	Nervus lingualis (V3), N = 88	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
1 Poor	26 (30%)	10 (11%)	0 (0%)	2 (2.3%)	2 (2.3%)	0 (0%)	20 (23%)	1 (1.1%)	0 (0%)	2 (2.3%)	0 (0%)	0 (0%)	3 (3.4%)	5 (5.6%)	17 (19%)
2 Fair	10 (11%)	8 (9.1%)	2 (2.3%)	7 (8.0%)	9 (10%)	0 (0%)	22 (25%)	13 (15%)	2 (2.3%)	7 (8.0%)	7 (8.0%)	0 (0%)	11 (12%)	12 (13%)	34 (39%)
3 Good	18 (20%)	28 (32%)	4 (4.5%)	28 (32%)	36 (41%)	11 (12%)	32 (36%)	24 (27%)	0 (0%)	31 (35%)	25 (28%)	6 (6.8%)	16 (18%)	8 (9.0%)	23 (26%)
4 Excellent	10 (11%)	37 (42%)	82 (93%)	49 (56%)	41 (47%)	77 (88%)	5 (5.7%)	46 (52%)	85 (98%)	45 (51%)	56 (64%)	58 (66%)	20 (23%)	7 (7.9%)	1 (1.1%)
Not within FOV	0 (0%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.3%)	4 (4.5%)	0 (0%)	0 (0%)	0 (0%)	24 (27%)	36 (41%)	57 (64%)	2 (2.3%)
<b>SI proximal</b>															
N	31	41	44	43	44	44	38	42	43	42	44	32	22	15	35
Mean (SD)	392 (143)	563 (164)	619 (125)	506 (106)	493 (117)	506 (183)	529 (231)	921 (322)	562 (146)	530 (147)	632 (170)	592 (242)	593 (176)	769 (187)	614 (207)
Median (IQR)	337 (277, 497)	580 (456, 677)	588 (519, 701)	499 (440, 583)	479 (421, 572)	458 (371, 559)	489 (359, 614)	916 (658, 1,132)	553 (446, 664)	530 (422, 603)	592 (501, 738)	616 (408, 761)	638 (484, 727)	741 (614, 894)	582 (485, 728)
Range	222, 727	188, 870	420, 865	264, 709	306, 727	248, 1,075	256, 1,202	249, 1,635	346, 907	319, 963	350, 1,051	173, 1,000	196, 812	569, 1,244	200, 1,168
<b>SI mid</b>															
N	14	32	44	40	40	44	21	39	43	42	42	32	18	12	16
Mean (SD)	278 (61)	462 (139)	507 (124)	467 (124)	409 (101)	495 (130)	423 (148)	590 (173)	469 (105)	428 (117)	571 (147)	392 (136)	518 (242)	647 (120)	479 (152)
Median (IQR)	265 (237, 295)	444 (395, 537)	484 (424, 571)	479 (364, 545)	397 (348, 460)	489 (401, 566)	433 (363, 528)	576 (474, 556)	450 (392, 556)	375 (344, 512)	546 (485, 682)	364 (306, 496)	512 (332, 718)	635 (571, 723)	475 (371, 548)
Range	189, 387	156, 796	289, 832	261, 712	244, 652	265, 836	1, 637	221, 997	289, 747	266, 794	253, 920	136, 731	103, 886	479, 897	261, 837
<b>SI distal</b>															
N	10	32	41	40	38	44	14	35	41	39	40	31	16	9	8
Mean (SD)	299 (130)	370 (115)	301 (111)	411 (136)	320 (58)	444 (150)	357 (66)	371 (155)	337 (110)	346 (84)	387 (136)	386 (134)	367 (168)	332 (132)	375 (96)
Median (IQR)	259 (241, 304)	361 (303, 416)	307 (214, 364)	431 (343, 492)	320 (281, 351)	440 (315, 549)	361 (322, 384)	352 (272, 386)	334 (263, 386)	338 (298, 397)	370 (299, 472)	353 (331, 463)	348 (248, 457)	307 (296, 326)	346 (315, 382)
Range	152, 626	131, 681	139, 729	163, 722	199, 435	177, 813	241, 477	0, 818	174, 674	180, 553	188, 772	146, 692	103, 741	189, 663	290, 572
<b>Diameter proximal</b>															
N	31	41	44	43	44	44	37	42	43	42	44	32	22	15	35
Mean (SD)	0.93 (0.27)	1.13 (0.26)	1.78 (0.44)	1.13 (0.24)	1.14 (0.24)	1.24 (0.25)	1.08 (0.23)	1.28 (0.29)	1.38 (0.34)	1.18 (0.25)	1.78 (0.56)	1.42 (0.37)	1.42 (0.26)	1.37 (0.38)	1.25 (0.36)
Median (IQR)	0.89 (0.72, 1.09)	1.10 (0.98, 1.23)	1.68 (1.48, 2.06)	1.16 (0.95, 1.27)	1.13 (0.96, 1.28)	1.22 (1.05, 1.43)	1.09 (0.90, 1.24)	1.23 (1.12, 1.35)	1.31 (1.13, 1.52)	1.12 (1.03, 1.29)	1.67 (1.37, 2.12)	1.32 (1.18, 1.69)	1.35 (1.27, 1.53)	1.25 (1.10, 1.54)	1.16 (1.03, 1.49)
Range	0.50, 1.48	0.60, 2.00	1.00, 2.86	0.64, 1.69	0.65, 1.74	0.60, 1.79	0.60, 1.59	0.80, 2.46	0.80, 2.36	0.76, 2.20	0.90, 2.95	0.84, 2.45	1.10, 2.11	0.91, 2.13	0.60, 2.18

	Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (VII), N = 88	Nervus facialis (IX), N = 88	Nervus glossopharyngeus (XII), N = 88	Nervus hypoglossus (V3), N = 87	Nervus lingualis (V3), N = 88	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
<b>Diameter mid</b>															
N	14	32	44	40	40	44	20	39	43	42	42	32	18	12	16
Mean (SD)	0.75 (0.17)	0.98 (0.23)	1.68 (0.49)	1.10 (0.25)	1.02 (0.22)	1.18 (0.21)	1.04 (0.17)	1.12 (0.17)	1.22 (0.30)	1.09 (0.18)	1.62 (0.40)	1.22 (0.23)	1.24 (0.29)	1.25 (0.31)	1.10 (0.28)
Median (IQR)	0.74 (0.61, 0.80) 1.17	0.94 (0.82, 1.57 (1.35, 1.77)	1.05 (0.90, 1.24) 1.16	1.00 (0.90, 1.30)	1.17 (1.03, 1.23)	1.01 (0.90, 1.14) 1.38)	1.10 (1.00, 1.38)	1.14 (1.06, 1.38)	1.06 (1.00, 1.18) 1.56 (1.33, 1.89)	1.06 (1.00, 1.18) 1.56 (1.33, 1.89)	1.19 (1.08, 1.38)	1.22 (0.23) 1.24 (0.29)	1.24 (0.29) 1.25 (0.31)	1.25 (0.31) 1.26 (0.32)	1.10 (0.28) 1.19
Range	0.50, 1.13	0.55, 1.58	1.14, 3.33	0.66, 1.66	0.54, 1.55	0.75, 1.69	0.76, 1.34	0.76, 1.50	0.60, 2.27	0.78, 1.59	1.00, 2.80	0.72, 1.79	0.89, 2.00	0.84, 1.97	0.70, 1.85
<b>Diameter distal</b>															
N	10	32	41	40	38	44	14	34	41	39	40	32	16	9	7
Mean (SD)	0.69 (0.13)	0.97 (0.19)	1.31 (0.30)	0.97 (0.21)	0.89 (0.22)	1.05 (0.20)	0.95 (0.23)	1.15 (0.20)	1.08 (0.21)	0.90 (0.19)	1.15 (0.28)	1.16 (0.23)	1.00 (0.18)	1.00 (0.18)	1.02 (0.31)
Median (IQR)	0.66 (0.60, 0.77) 1.10	0.96 (0.84, 1.27 (1.06, 1.54)	0.96 (0.85, 1.09) 1.02	0.89 (0.73, 1.20)	1.06 (0.91, 1.30)	0.96 (0.82, 1.01) 1.25)	1.14 (1.01, 1.30)	1.05 (0.94, 1.25)	0.87 (0.80, 0.97) 1.12 (0.96, 1.36)	0.87 (0.80, 0.97) 1.12 (0.96, 1.36)	1.21 (1.06, 1.31)	1.15 (0.28) 1.16 (0.23)	1.16 (0.23) 1.00 (0.18)	1.00 (0.18)	1.02 (0.31) 1.09
Range	0.50, 0.90	0.61, 1.37	0.82, 2.15	0.61, 1.46	0.45, 1.28	0.62, 1.49	0.60, 1.41	0.70, 1.51	0.70, 1.55	0.60, 1.42	0.67, 1.89	0.51, 1.53	0.74, 1.31	0.68, 1.30	0.71, 1.63
<b>aSNR proximal</b>															
N	31	41	44	43	44	44	38	42	43	42	44	32	22	15	35
Mean (SD)	29 (11)	42 (12)	46 (9)	38 (8)	37 (9)	38 (14)	40 (17)	69 (24)	42 (11)	40 (11)	47 (13)	44 (18)	44 (13)	57 (14)	46 (15)
Median (IQR)	25 (21, 37)	43 (34, 51)	44 (39, 52)	37 (33, 44)	36 (31, 43)	34 (28, 42)	37 (27, 46)	68 (49, 85)	41 (33, 50)	40 (32, 45)	44 (37, 55)	46 (30, 57)	48 (36, 54)	55 (46, 67)	44 (36, 54)
Range	17, 54	14, 65	31, 65	20, 53	23, 54	19, 80	19, 90	19, 122	26, 68	24, 72	26, 79	13, 75	15, 61	43, 93	15, 87
<b>aSNR mid</b>															
N	14	32	44	40	40	44	21	39	43	42	42	32	18	12	16
Mean (SD)	21 (5)	35 (10)	38 (9)	35 (9)	31 (8)	37 (10)	32 (11)	44 (13)	35 (8)	32 (9)	43 (11)	29 (10)	39 (18)	48 (9)	36 (11)
Median (IQR)	20 (18, 22)	33 (30, 40)	36 (32, 43)	36 (27, 41)	30 (26, 34)	37 (30, 42)	32 (27, 39)	43 (35, 55)	34 (29, 42)	28 (26, 38)	41 (36, 51)	27 (23, 37)	38 (25, 54)	47 (43, 54)	36 (28, 41)
Range	14, 29	12, 60	22, 62	19, 53	18, 49	20, 63	0, 48	16, 75	22, 56	20, 59	19, 69	10, 55	8, 66	36, 67	20, 63
<b>aSNR distal</b>															
N	10	32	41	40	38	44	14	35	41	39	40	31	16	9	8
Mean (SD)	22 (10)	28 (9)	23 (8)	31 (10)	24 (4)	33 (11)	27 (5)	28 (12)	25 (8)	26 (6)	29 (10)	29 (10)	27 (13)	25 (10)	28 (7)
Median (IQR)	19 (18, 23)	27 (23, 31)	23 (16, 27)	32 (26, 37)	24 (21, 26)	33 (24, 41)	27 (24, 29)	26 (20, 35)	25 (20, 29)	25 (22, 30)	28 (22, 35)	26 (25, 35)	26 (19, 34)	23 (22, 24)	26 (24, 29)
Range	11, 47	10, 51	10, 54	12, 54	15, 32	13, 61	18, 36	0, 61	13, 50	13, 41	14, 58	11, 52	8, 55	14, 50	22, 43

	Nervi temporalis profundi (V3), N = 88	Nervus accessorius (XI), N = 88	Nervus alveolaris inferior (V3), N = 88	Nervus auriculotemporalis (V3), N = 88	Nervus buccalis (VII), N = 88	Nervus facialis (IX), N = 88	Nervus glossopharyngeus (XII), N = 88	Nervus hypoglossus (V3), N = 87	Nervus lingualis (V3), N = 88	Nervus massetericus (V3), N = 88	Nervus maxillaris - infraorbitalis (V2), N = 88	Nervus occipitalis major, N = 88	Nervus occipitalis minor, N = 88	Nervus ophthalmicus (VI), N = 89	Nervus vagus (X), N = 88
<b>aNMCNR proximal</b>															
N	31	41	44	43	44	44	38	42	43	42	44	32	22	15	35
Mean (SD)	17 (11)	30 (12)	34 (9)	26 (8)	25 (9)	26 (14)	27 (17)	57 (24)	30 (11)	28 (11)	35 (13)	32 (18)	31 (13)	46 (15)	34 (16)
Median (IQR)	13 (9, 25)	32 (21, 39)	32 (28, 40)	25 (20, 31)	23 (18, 30)	23 (17, 29)	24 (13, 36)	58 (37, 71)	29 (21, 38)	25 (20, 33)	33 (25, 44)	36 (16, 45)	32 (24, 41)	46 (34, 56)	30 (24, 42)
Range	5, 45	0, 54	20, 55	9, 41	11, 43	-1, 71	6, 76	4, 110	8, 55	12, 60	17, 69	1, 62	0, 47	30, 82	3, 78
<b>aNMCNR mid</b>															
N	14	32	44	40	40	44	21	39	43	42	42	32	18	12	16
Mean (SD)	9 (4)	23 (11)	26 (9)	23 (9)	19 (7)	25 (9)	19 (11)	32 (13)	23 (8)	20 (9)	31 (11)	17 (10)	25 (19)	37 (9)	24 (12)
Median (IQR)	8 (6, 13)	23 (17, 28)	25 (20, 29)	22 (16, 29)	19 (14, 22)	24 (18, 30)	21 (13, 27)	31 (24, 42)	22 (18, 27)	16 (15, 26)	28 (23, 39)	16 (10, 25)	26 (11, 41)	37 (31, 41)	22 (16, 29)
Range	3, 18	-3, 47	10, 50	8, 44	5, 35	8, 51	-11, 38	2, 62	2, 43	7, 46	7, 58	-4, 42	-7, 54	24, 58	10, 53
<b>aNMCNR distal</b>															
N	10	32	41	40	38	44	14	35	41	39	40	31	16	9	8
Mean (SD)	11 (9)	16 (8)	10 (9)	19 (10)	12 (4)	21 (11)	14 (6)	15 (12)	13 (8)	14 (7)	17 (11)	16 (10)	14 (14)	13 (11)	16 (7)
Median (IQR)	9 (7, 11)	16 (11, 19)	10 (3, 15)	20 (11, 25)	12 (9, 15)	20 (14, 29)	14 (10, 18)	16 (6, 22)	12 (7, 17)	14 (11, 18)	15 (9, 23)	15 (10, 23)	13 (4, 21)	12 (8, 12)	12 (12, 17)
Range	0, 34	-4, 36	-4, 42	1, 41	3, 18	1, 50	4, 25	-11, 48	1, 38	-6, 32	3, 49	-3, 39	-7, 43	2, 41	9, 29
SI: signal intensity; aSNR: apparent signal-to-noise ratio; aNMCNR: apparent nerve-muscle contrast-to-noise ratio; SD: standard deviation; IQR: interquartile range															

## CHAPTER 9

# 3D CRANI validation in PTN patients: a case-control study

*This chapter is based on the following manuscript:*

Bangia M, Ahmadzai I, Casselman J, Politis C, Jacobs R, **Van der Cruyssen F.** Accuracy of MR neurography as a diagnostic tool in detecting injuries to the lingual- and inferior alveolar nerve in patients with iatrogenic post-traumatic trigeminal neuropathy.

*Submitted to European Radiology.*

## **Abstract**

### **Background and Purpose**

MR neurography has the ability to detect and depict peripheral nerve injuries. This study evaluated the potential of MR neurography in the diagnosis of post-traumatic trigeminal neuropathy.

### **Materials and Methods**

Forty-one participants prospectively underwent MR neurography of the lingual and inferior alveolar nerves using a 3D TSE STIR black-blood sequence. Two blinded and independent observers recorded the following information for each nerve of interest: presence of injury, nerve thickness, nerve signal intensity, MR neurography Sunderland class, and signal gap. Afterwards, the apparent nerve-muscle contrast-to-noise ratio and apparent signal-to-noise ratio were calculated. Clinical data (neurosensory testing score and clinical Sunderland class) was extracted retrospectively from the medical records of patients diagnosed with post-traumatic trigeminal neuropathy.

### **Results**

Compared to neurosensory testing, MR neurography had a sensitivity of 38.2% and specificity of 93.5% detecting nerve injuries. When differentiated according to clinical Sunderland class, sensitivity was 19.1% in the presence of a low class (I to III) and improved to 83.3% in the presence of a high class (IV to V). Specificity remained unchanged. The area under the curve using the apparent nerve-muscle contrast-to-noise ratio, apparent signal-to-noise ratio, and nerve thickness to predict the presence of an injury was 0.78 ( $P<.05$ ). Different imaging parameters were greater in injured nerves ( $P<.05$ ). Clinical and MR neurography Sunderland scores positively correlated (correlation coefficient = 0.53;  $P=.005$ ).

### **Conclusion**

This study shows that MR neurography can accurately differentiate between injured and healthy nerves, especially in the presence of a high clinical Sunderland class.

## Introduction

The trigeminal nerve (TN) provides sensation to the face via its three major branches: the ophthalmic, maxillary, and mandibular nerves. The latter has an additional function in supplying innervation to the muscles responsible for biting and chewing. Maxillofacial surgery and dental procedures (e.g., implant placement, molar tooth extraction, local anesthesia) have a risk of damage to one of these branches, which can result in the development of neurosensory deficiencies, a condition called iatrogenic post-traumatic trigeminal neuropathy (PTN).<sup>1–3</sup> When accompanied with pain, the term post-traumatic trigeminal neuropathic pain is used. The lingual nerve (LN) and inferior alveolar nerve (IAN) are most frequently affected.<sup>1,3</sup> Post-traumatic trigeminal neuropathic pain is described by the International Classification of Orofacial Pain (ICOP) as “unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction, and persisting or recurring for more than three months.”<sup>4</sup> It suggests the following criteria for diagnosis: pain in an area innervated by the TN, association of this pain with signs of nerve dysfunction in that same area, history of an injury to the TN, onset of the pain within six months after the injury, not better accounted for by another ICOP or ICHD-3 diagnosis, and the presence of a lesion in the TN, which should be able to explain the pain, confirmed by a diagnostic test.<sup>4</sup> The same criteria can be used for PTN. In current clinical practice, the diagnosis of PTN is primarily based on the patient’s history, description of symptoms, and physical and neurological examinations. The diagnostic test is clinical neurosensory testing (NST).<sup>5</sup> NST findings can be translated into a degree of injury similar to the Sunderland classification, which correlates with surgical findings.<sup>6</sup> The different Sunderland classes were designed to provide information regarding prognosis (e.g., the possibility of functional recovery) and whether surgical treatment is needed to functionally recover.<sup>7</sup> Despite having the advantage of being easily accessible and non-invasive, this diagnostic approach has the disadvantage of being subjective and difficult to standardize. Furthermore, this approach is not able to provide information about the location and other anatomical specifications of the injury, which can be important in surgical planning. An accurate diagnostic tool that, ideally, is able to provide additional information about location, anatomical specifications, and degree of injury is necessary to make the right diagnostic and therapeutic decisions. An imaging modality called MR neurography (MRN) was designed to adequately visualize peripheral nerves, such as the LN and IAN. It has shown potential in depicting and diagnosing, as well as stratifying, peripheral nerve injuries.<sup>8–10</sup> However, most of these studies have some shortcomings in their

methodology.<sup>11,12</sup> We conducted a prospective, blinded, and standardized study about the potential of MRN in detecting injuries to the LN and IAN in patients with PTN. The secondary objectives were to demonstrate that MRN is able to stratify nerve injuries, elucidate how to differentiate injured and healthy nerves using MRN, and illustrate the potential of individual MRN parameters in predicting nerve injury.

## Methods

This study was performed at the Department of Oral and Maxillofacial Surgery at University Hospitals Leuven, Belgium. Ethical approval was received from the Ethics Committee of the University Hospital Leuven (S61077). Informed consent was obtained from all participants.

## Participants

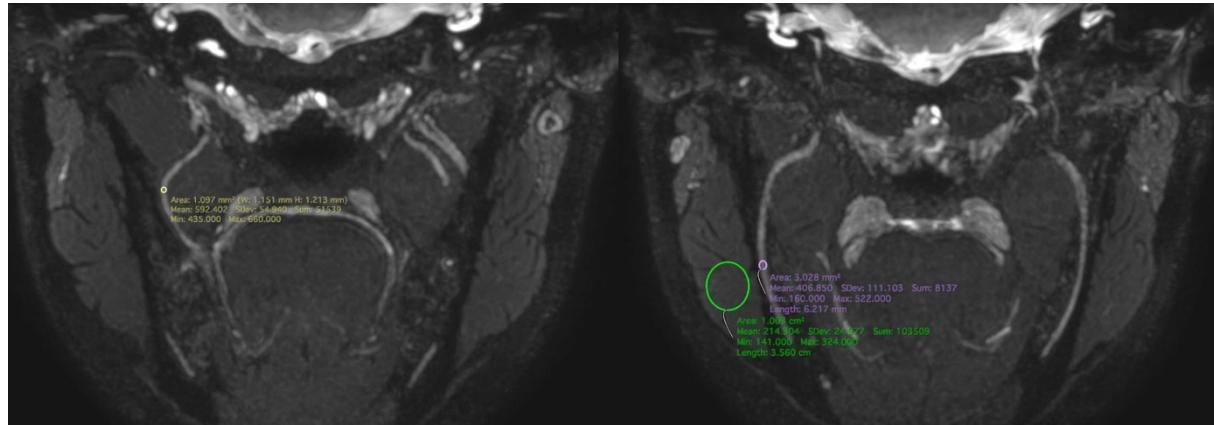
A total of 30 patients diagnosed with orofacial neuropathy upon their visit to the Department of Oral and Maxillofacial Surgery at University Hospitals Leuven between June 2020 and June 2021 were recruited for the present study. The case series consisted of patients who fulfilled the following criteria: diagnosis of PTN (with or without pain) based on the ICOP criteria, clinical evidence of involvement of the LN or IAN, and an iatrogenic traumatic cause of injury. Patients who did not meet the inclusion criteria served as the control group together with 11 healthy volunteers. Age and gender were recorded for all participants.

## Image acquisition and analysis

MRN examinations were prospectively acquired at the Radiology Department at University Hospitals Leuven on an Ingenia 3-Tesla MR scanner (Philips Medical Systems, Best, the Netherlands) using a 32-channel standard head coil. We used the 3D cranial nerve imaging sequence (3D CRANI), a newly developed 3D TSE STIR black-blood sequence.<sup>13,14</sup> It uses a pseudo steady-state (PSS) sweep in combination with a motion-sensitized driven equilibrium (MSDE) pulse and is able to suppress signals from fat, muscle, and blood to generate a nerve-selective image. Gadolinium contrast was administered. The same examination protocol was used in all participants.

We recruited two independent observers to rate the images and extract information using a standardized questionnaire. They were blinded to the patient's clinical history and diagnosis. Presence of injury (yes/no), nerve thickness (mm), and signal intensity of the nerve were to be determined for each nerve of interest (left LN, right LN, left IAN, and right IAN). Signal

intensities were measured by placing circular regions of interest (ROIs) within the identified nerves (iROI) (**Figure 1**). The same was done for the masseter muscle (mROI) and air (aROI) measured inside the maxillary sinus using circular ROIs of 1 cm<sup>2</sup>.



*Figure 1. Coronal plane 3D CRANI image shows signal intensity measurements made by placing circular regions of interest (ROIs).*

Measurements were made on axial/coronal reformatted images at predetermined standardized locations. If the site was injured, the measurement was made just proximal to the injury. If normal, the mid-mandibular canal (for the IAN) and maximum curvature of the LN were used as reference standards. Furthermore, if an injury was thought to be present, the observers were asked to give that injury a score based on the Sunderland classification criteria (**Table 1**).<sup>8</sup> If it was not possible to assign a classification with confidence (e.g., an injury classified as III/IV), it was classified as indeterminate.

*Table 1. MRN Sunderland classification criteria.*

Class	MRN
I	Qualitative: Homogeneously increased T2 signal for nerve with no change in caliber Quantitative: No changes
II	Qualitative: Homogeneously increased T2 signal for nerve and mild nerve thickening, perineural fibrosis Quantitative: <50% larger than contralateral/normal nerve

- III      Qualitative: Homogeneously increased T2 signal for nerve and moderate to marked nerve thickening, perineural fibrosis  
 Quantitative: >50% larger than contralateral/normal nerve
  - IV      Qualitative: Heterogeneously increased T2 signal for nerve and focal enlargement in otherwise continuous nerve (neuroma in continuity), perineural and intraneuronal fibrosis  
 Quantitative: Focal swelling with heterogeneous T2 signal or fascicular disruption
  - V      Qualitative: Discontinuous nerve with end-bulb neuroma  
 Quantitative: Complete disruption with gap and end-bulb neuroma
- 

If an injury was classified as class V, they were asked to measure the signal gap (mm). All measurements were recorded in a spreadsheet for data analysis. Afterwards, the apparent nerve-muscle contrast-to-noise ratio (aNMCNR) and apparent signal-to-noise ratio (aSNR) were calculated for each nerve using the following formulations:  $i\text{ROI} \div SD_{air}$  and  $i\text{ROI} - m\text{ROI} \div SD_{air}$ .<sup>14,15</sup> Nerves that could not be evaluated due to low quality or large artifacts were left out of the analysis. Missing data were also left out of the analysis.

### **Acquisition of clinical parameters**

Clinical data obtained by experienced oral and maxillofacial surgeons from the University Hospital Leuven was retrospectively extracted from the patients' medical files. Cause of injury, nerve involved, side of nerve involved, presence of pain, NST score, and clinical Sunderland class were extracted and recorded in a spreadsheet for further analysis.

### **Statistical analysis**

Statistical analyses were performed using RStudio Team (2020) (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA). The required sample size was calculated based on pilot experiments suggesting a minimum of 20 participants when assuming 95% power and an  $\alpha$  of 0.05. To compare demographic data (sex, age) between cases and controls, the chi-squared test for sex and independent samples t-test for age were used.

The reliability of measurements was calculated for the following imaging parameters: presence of injury on MRN, nerve signal intensity (SI), nerve thickness, and MRN Sunderland classification score. Kappa coefficient and intraclass correlation coefficient were used. The

interpretation of the Kappa coefficient value was as follows: <0.00 poor agreement, 0.00 to 0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.00 almost perfect agreement.<sup>15</sup> For the intraclass correlation coefficient, the following interpretation was used: <0.5 poor agreement, 0.5 to <0.75 moderate agreement, 0.75 to <0.9 good agreement, 0.9 to 1.0 excellent agreement. Contingency tables comparing the presence of an injury clinically and via MRN were created and sensibility, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio calculated for different subgroups of data to investigate whether MRN would be of greater value in the presence of certain features (i.e., nerve involved and clinical Sunderland class).

The different subgroups of data were:

- All data;
- Patients diagnosed with
  - PTN of the LN,
  - PTN of the IAN,
  - PTN and a low clinical Sunderland class,
  - PTN and a high clinical Sunderland class,
  - PTN of the LN and a low clinical Sunderland class,
  - PTN of the LN and a high clinical Sunderland class,
  - PTN of the IAN and a low clinical Sunderland class,
  - PTN of the IAN and a high clinical Sunderland class.

Classes I, II, and III were considered low. Classes IV and V were considered high. To measure differences in the mean values of imaging parameters between healthy and injured nerves, independent sample t-tests were used. Correlation was determined using the spearman correlation coefficient and predictive statistics used logistic regression with receiver operating characteristic analysis.

## Results

### Patient population

All 41 participants were included in the final analysis. Sixteen patients were included in the case series. The other 14 patients were excluded due to neither the IAN nor LN being clinically suspected of being involved or no iatrogenic traumatic cause. These patients were included in the control group, together with the 11 healthy volunteers (total n = 25).

The cases had a total of 18 injuries: 9 to the LN and 9 to the IAN. One patient had injuries to both lingual nerves and another to both inferior alveolar nerves. All other patients in the case series had an injury to a single nerve.

The case series consisted of 10 females and 6 males, and the control group of 16 females and 9 males. There was no significant difference in sex between cases and controls ( $P=.92$ ).

Age in the case series varied between 16 and 62 years, with a mean age of 40.31 years. In the control group, age varied between 13 and 83 years, with a mean age of 51.12 years. The difference in mean age between both groups was not significant ( $P=.66$ ). Clinical data could be extracted from the medical files of all 16 patients in the case series. Neuropathic pain was present in nine patients. The others experienced neurosensory disturbances without them being described as painful. Clinical Sunderland classifications based on NST included eight class I, two class II, two class III, two class IV, three class V, and one undetermined injury.

Iatrogenic causes of trauma were implant placement ( $n=2$ ), tooth extraction ( $n=8$ ), xanthoma curettage ( $n=1$ ), bilateral sagittal split osteotomy (BSSO;  $n=1$ ), BSSO+genioplasty ( $n=1$ ), open reduction internal fixation (ORIF;  $n=1$ ), and iatrogenic undefined ( $n=2$ ).

### **Reliability of measurement**

Interrater agreement for injury detected on MRN, nerve thickness, nerve signal intensity (SI nerve) and MRN Sunderland classification score was substantial, moderate, good, and moderate, respectively.

Intrarater agreement for observer 1 for injury detected on MRN, nerve thickness, SI nerve, and MRN Sunderland classification score was moderate, moderate, excellent, and moderate, respectively. For observer 2, they were almost perfect, good, good, and substantial, respectively.

### **Diagnostic accuracy**

Globally, compared to NST, MRN had a sensitivity (true-positive rate) of 38.2% and specificity (true-negative rate) of 93.5%. Positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value were 5.9, 0.66, 46, and 91.3, respectively.

When differentiated by clinical Sunderland class, both groups had a specificity of 93.5%. Sensitivity differed between both, with the low clinical Sunderland class group having a sensitivity of 19.1% and the high clinical Sunderland class having a sensitivity of 83.3%. Positive likelihood ratios in the low and high clinical Sunderland class groups were 2.96 and 12.89, respectively. The same tendency was seen when differentiated for both nerves. For the

LN, the global sensitivity, specificity, and positive likelihood ratio were 48.6%, 96.5%, and 13.95. Differentiated according to clinical Sunderland class, specificity remained the same in both groups but sensitivity differed. Sensitivity and the positive likelihood ratio in the low clinical Sunderland class group were zero because of the absence of any true-positive results. In the high clinical Sunderland class group, sensitivity was 81.8%, with a positive likelihood ratio of 23.45.

The sensitivity, specificity, and positive likelihood ratio for the IAN group was 28.2%, 90.7%, and 3.02. Specificity remained the same when differentiated by clinical Sunderland class. In the presence of a low Sunderland class, the sensitivity and positive likelihood ratios were 25.7% and 2.76. For the higher classes, these values were 100% and 10.72, respectively.

### **Correlation and prediction**

For the overall dataset, clinical and MRN Sunderland classification scores significantly and positively correlated, with a correlation coefficient of 0.53 (P=.005; **Table 2**).

*Table 2. Correlation of clinical and MRN Sunderland classification scores.*

Clinical	I	II	III	IV	V	VI	MRN
I	0	0	0	0	0	0	
II	0	1	1	0	0	0	
III	2	1	1	1	0	0	
IV	0	0	0	0	6	0	
V	0	3	0	0	9	1	
VI	0	0	0	0	3	0	

MRN = MR neurography. VI represents the answer ‘indeterminate’

The prediction model using aSNR, aNMCNR, and nerve thickness to predict the presence of injury had an area under the receiver operating characteristic curve of 0.78 ( $P=<.05$ ), with an F-score of 0.19 and an accuracy rate of 0.89. The permutation feature importance test showed the following levels of importance for the different variables: 408.03 for aNMCNR ( $P=<.05$ ), 293.33 for aSNR ( $P=<.05$ ), and 28.50 for nerve thickness ( $P=<.05$ ). Additional receiver operating characteristic analyses of aSNR in combination with nerve thickness and aNMCNR in combination with nerve thickness were performed due to the multicollinearity between aSNR and aNMCNR. The area under the receiver operating characteristic curve, F-score, and accuracy rate were 0.73, 0.10, and 0.89, respectively ( $P=<.05$ ), for the model using aSNR and 0.75, 0.12, and 0.89 ( $P=<.05$ ) for the model using aNMCNR.

### **Descriptive statistics**

Differences in aSNR, aNMCNR, and nerve thickness between healthy and injured nerves are shown in **Table 3**. A significant difference in mean nerve thickness was found for the overall dataset but not for both nerves separately. For aSNR and aNMCNR, a significant difference was found for the overall dataset and both nerves separately.

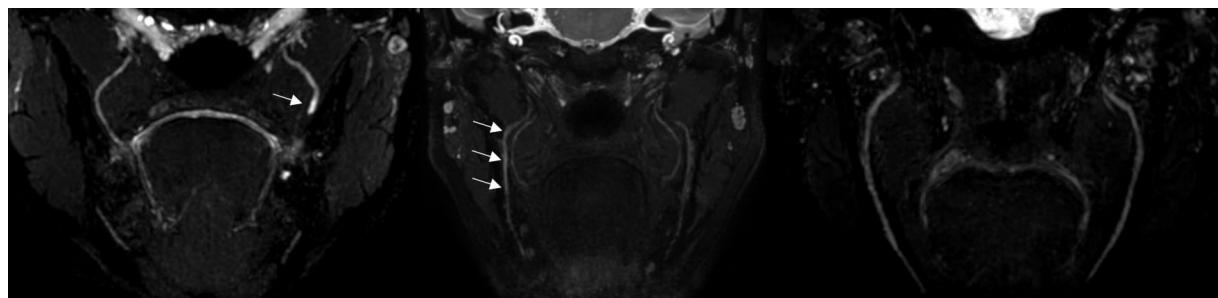
Table 3. Comparison of thickness, aSNR, and aNMCNR between healthy and injured nerves.

	Overall			Lingual nerve			Inferior alveolar nerve		
	Injured	Healthy	P-value	Injured	Healthy	P-value	Injured	Healthy	P-value
<b>Nerve thickness (mm)</b>									
<b>Mean (SD)</b>	1.77 (0.94)	1.62 (1.07)	.033	1.29 (0.84)	1.38 (0.55)	.8	1.29 (0.84)	1.38 (0.55)	.8
<b>Median (IQR)</b>	1.70 (1.37, 2.21)	1.59 (1.25, 1.95)		1.48 (0.81, 1.73)	1.42 (1.17, 1.74)		1.48 (0.81, 1.73)	1.42 (1.17, 1.74)	
<b>Range</b>	0.00, 4.09	0.00, 21.49		0.00, 2.68	0.00, 3.20		0.00, 2.68	0.00, 3.20	
<b>aSNR</b>									
<b>Mean (SD)</b>	180 (138)	119 (84)	<.001	207 (176)	109 (75)	.002	207 (176)	109 (75)	.002
<b>Median (IQR)</b>	149 (97, 251)	103 (59, 164)		185 (87, 363)	97 (49, 157)		185 (87, 363)	97 (49, 157)	
<b>Range</b>	0, 561	0, 450		0, 561	0, 370		0, 561	0, 370	
<b>aNMCNR</b>									
<b>Mean (SD)</b>	114 (114)	68 (62)	<.001	136 (151)	59 (55)	.001	136 (151)	59 (55)	.001
<b>Median (IQR)</b>	86 (53, 147)	60 (31, 97)		101 (52, 252)	52 (27, 87)		101 (52, 252)	52 (27, 87)	
<b>Range</b>	-66, 455	-129, 310		-66, 455	-129, 236		-66, 455	-129, 236	

aNMCNR = apparent nerve-muscle contrast-to-noise ratio; aSNR = apparent signal-to-noise ratio; IQR = interquartile range; SD = standard deviation

## Discussion

In current practice, the diagnosis and stratification of injuries to the LN and IAN in patients with PTN is based on NST, but this approach has limitations. MRN, a nerve-selective MRI technique, has shown potential as a more standardized and reliable tool in detecting and stratifying these lesions and providing additional information about location and other anatomical specifications (**Figure 2**).



*Figure 2. Coronal plane 3D CRANI images. Left, an end-bulb neuroma (white arrow) of the left lingual nerve compatible with a class V injury. Middle, increased signal intensity (white arrows) of the right inferior alveolar nerve compared to the left inferior alveolar nerve. Right, healthy inferior alveolar nerves.*

The latter would be very useful in surgical planning. Therefore, our goal was to determine whether MRN is an accurate tool in diagnosing these injuries.

Overall, MRN had a good specificity of 93.5% but a rather low sensitivity of 38.2%, which accounts for a high rate of false-negative results. Differentiating by the degree of injury using the clinical Sunderland classification system, we found higher sensitivity in the presence of a higher classification score. Lingual nerve injuries with a clinically high degree of injury had a sensitivity of 81.8% with a positive likelihood ratio of 23.45. For inferior alveolar injuries, the values were 100% and 10.72, respectively.

Compared to MRI, for which a previous study had calculated a sensitivity of 0.18, MRN performs much better in detecting nerve injuries.<sup>16</sup>

A high sensitivity (i.e., low false-negative rate) is vital for detecting a certain condition or disease, such as the presence of a peripheral nerve injury. The sensitivity of MRN in the presence of a lower clinical Sunderland class was not great, but this would be of lesser importance when considering the specific use of MRN in practice. In practice, MRN would not be offered to every patient presenting with PTN. Logically, because of its additional benefits in providing information about the location and anatomical specifications of the injury, MRN

would be of greater use to patients with a higher degree of damage who are eligible for surgery as a possible treatment option.

For a clinician, understanding the context in which MRN can contribute to medical decision-making is important. If a low degree of damage clinically is suspected, the chance in accurately visualizing damage via MRN is rather low due to its high false-negative rate in this context. Therefore, a good clinical diagnosis is necessary before making the decision to use MRN for further investigation and visualization of damage.

Stratifying the degree of injury using MRN positively correlated with clinical stratification using NST. These results are in accordance with a previous study in which a positive correlation was found between Sunderland classes based on MRN and NST.<sup>8</sup> That study also compared the degree of injury on MRN with surgical findings, finding a positive correlation.

This study also showed the possible application of aSNR, aNMCNR, and nerve thickness as quantitative imaging markers for peripheral nerve injuries. Injured nerves had a significantly higher mean value for all of these parameters. In addition, our prediction model showed the ability of these variables to accurately predict whether an injury is present. Because of the multicollinearity between aSNR and aNMCNR, one of these in combination with nerve thickness should be sufficient. Accuracy did not differ in separate models (aSNR in combination with nerve thickness and aNMCNR in combination with nerve thickness), but feature importance and regression coefficient analysis showed a preference for aNMCNR over aSNR. This was confirmed by comparing the areas under both models' receiver operating characteristic curves.

This study has some limitations. Excluded patients who did not fit the ICOP criteria were included as controls. Theoretically, it cannot be ruled out that these patients did have neurological abnormalities not picked up by NST and as such led to false-positive results on MRN.

Secondly, we used NST as our reference test knowing that NST itself is not perfect in detecting peripheral nerve injuries. This decision was made because we could not use surgical findings for ethical reasons.

Finally, our two observers got a course in interpreting MRN but were not experienced radiologists. This could enhance the number of false results and could be a reason why MRN was not successful in detecting injuries in the presence of a low clinical Sunderland class.

In future research, we suggest using surgical findings as the reference test if it is ethically possible (e.g., using retrospective surgical data) and assigning experienced radiologists as observers.

## **Conclusion**

Our study showed that MRN is an accurate tool for detecting injuries to the IAN and LN in patients with PTN and that the presence of a high clinical Sunderland class increases its accuracy. Not only would MRN be of benefit in detecting the injuries, but would also provide information about the anatomical specifications of the injury, which is not possible when using NST. This makes MRN beneficial in the management of PTN.

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# SECTION 4



consensus, conclusion and future perspectives



## **CHAPTER 10**

# **Consensus guidelines on training, diagnosis, treatment and follow-up care of trigeminal nerve injuries.**

*This chapter is based on the following manuscript:*

**Van der Cruyssen F, Palla B, Van der Tas J, Jacobs R, Politis C, Zuniga J, Renton T.**  
Consensus guidelines on training, diagnosis, treatment and follow-up care of trigeminal nerve injuries.

*Submitted to the International Journal of Oral and Maxillofacial Surgery.*

## **Abstract**

We aimed to present an expert-based guideline on the management of trigeminal nerve injuries (TNIs). A two-round multidisciplinary Delphi study was conducted amongst international TNI experts with a set of statements and three summary flowcharts using a nine-point Likert scale (one = totally disagree and nine = totally agree). An item was deemed appropriate if the median panel score ranged from seven to nine, undecided (four to six) and inappropriate if it ranged from one to three. Consensus was achieved if at least 75% of panellists scored within one range. Eighteen specialists from dental, medical and surgical specialties participated in both rounds. Consensus was reached on most (78%) training/services related statements and diagnostic statements (80%). Treatment related statements were mainly undecided due to lack of sufficient evidence for some of the proposed treatments. Nevertheless, the summary treatment flowchart reached consensus with a median score of eight. Recommendations on follow-up and opportunities for future research were discussed. None of the statements were deemed inappropriate. A set of recommendations and accepted flowcharts are presented that will aid professionals involved in managing patients with TNIs.

## Introduction

The trigeminal nerve is a cranial nerve responsible for transmitting sensory information from the face to the brain, as well as controlling the muscles of mastication.<sup>1</sup> An injury to the trigeminal nerve can disrupt these functions and cause various symptoms, including facial pain, numbness, and muscle weakness. Trigeminal nerve injuries (TNIs) can be caused by multiple factors, including trauma, surgery, infections, and underlying medical conditions.<sup>2</sup> Diagnosing and treating TNIs can be challenging due to the complexity of the nerve and the wide range of symptoms that can be associated with an injury.<sup>3</sup> Despite an ever-increasing literature base, there is a limited amount of high-quality evidence available to guide the diagnosis and management of these injuries, with no overall consensus guideline on its management available to date. Guidelines and consensus statements can provide healthcare professionals with recommendations and evidence when caring for patients. One method to attain reliable expert opinion is through a Delphi study design.<sup>4,5</sup> This research method utilizes a series of anonymous feedback and discussion rounds to elicit independent opinions of experts on a specific topic or issue. This study aims to present an expert consensus guideline on the management of trigeminal nerve injuries by means of a Delphi study design.

## Materials and Methods

A two-round Delphi study was conducted among experts in the field of TNIs, as described below (**Figure 1**). All experts were contacted by e-mail, provided with a study information sheet and consented to participate.

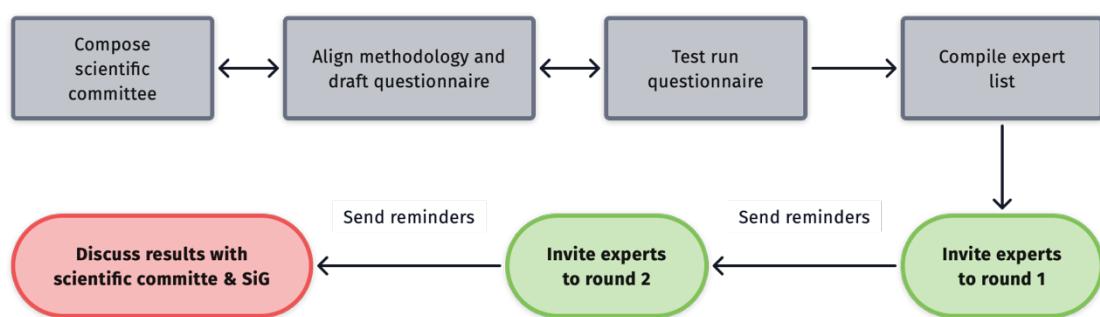


Figure 1. Delphi study flowchart.

## **Expert panel and questionnaire design**

A scientific committee comprised five international members: one orofacial pain expert, three maxillofacial surgeons with extensive experience in trigeminal injury and one methodological expert. International experts across several specialties were identified by the scientific committee and invited based on their scientific and clinical contributions in the field of orofacial pain and nerve injuries. They were invited by e-mail and did not receive any incentive for their participation besides acknowledgements at the end of this article.

A scoping literature review on TNIs was conducted by the first author (FVDC) in Medline and Cochrane databases for articles published in English. Based on this, a questionnaire was constructed with items in four domains: training/services, diagnosis, treatment and follow-up of TNI. The questionnaires were presented to the scientific committee several times until agreement on the final form was reached. Two co-authors timed the final questionnaire and ensured comprehension. The questionnaire included a general section on expert age, gender, background, location, setting (public, private, mixed), years of experience and current specialization. All experts were asked if they diagnose and treat patients with TNI, and how many cases of TNI they treat per month.

## **The Delphi consensus process**

Following the Delphi method, two rounds were organized in which the experts could give anonymous feedback on each statement. To improve the response rate, experts had two weeks to complete each round. At two days and one week experts received a reminder email if they had not already responded. In the first round, each expert responded to all statements using a Likert scale from one to nine (one: totally disagree, nine: agree). In addition, there was a comment box provided for further feedback below each item. Three flowcharts summarizing the available evidence for diagnostic, sensory testing and treatment were provided to experts to review and provide feedback. The first round also included several checkbox questions to assess the expert's preference for the use of diagnostic tools, treatment choice and deterministic factors for surgical success.

The second round questionnaire was also distributed by e-mail. This modified version still utilized the Likert scale, but included no checkbox questions. In addition, experts were provided their answer from the first round, as well as the group median for each question. The final results were shared and discussed with the Global Network on Nerve Injuries scientific board to improve validity further. A core value of the Global Nerve Foundation is to assemble experts

in the field for the dissemination of known research and consultation of future research. As such, the GNF approves the methodology used in this study.

### **Statistical analysis**

All statistical analyses were done by a certified statistician (FVDC) with RStudio Team (2020) (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA) and Microsoft Excel (Microsoft Corporation, Washington). Descriptive statistics were carried out by calculating mean and median values if data was normally or non-normally distributed respectively. Absolute and relative frequencies were calculated for each answer. A statement was considered appropriate if the median score was higher than seven, inappropriate if the median score was lower than three, and undecided if the median score was four to six. The consensus was based on the RAND-UCLA appropriateness method<sup>6</sup>, and the measure of dispersion was the mean absolute deviation from the median. This meant that consensus was achieved when at least 75% of the panel scored within any range of one-three, four-six, or seven-nine.

## **Results**

The initial invitation to participate was sent by e-mail to 38 eligible specialists. Twenty-one specialists participated in the first round (response rate: 55%), of which 18 also completed the second round (response rate: 47%), resulting in an 86% retention rate over both rounds. The experts consisted of 12 maxillofacial surgeons (58%), two oral surgeons (9%), one dentist (5%), two orofacial pain experts (9%), one neurosurgeon (5%), two pain experts (9%), and one endodontist (5%). Fifteen of them worked in a university hospital (71%), four worked in public hospitals (19%), and two worked in a mixed setting (9%). They had a mean ( $\pm SD$ ) of 18 ( $\pm 10$ ) years of experience treating trigeminal nerve injuries. On average, they treated 6 ( $\pm 4$ ) patients per month suffering from TNI. Nineteen (90%) experts participated in research on TNI, and twenty (95%) experts trained others in managing TNI patients. Of the 38 statements, there was consensus on 21 (55%) of them in round one and 25 (66%) in round two (**Table 1, Figure 2**).

Table 1. Results from both rounds of the Delphi study. MAD: mean absolute deviation from the median.

Items	Median	Round 1				Round 2			
		MAD	Appropriateness	Conensus	Median	MAD	Appropriateness	Conensus	
<b>Training and services</b>									
All oral and maxillofacial surgeons should be trained in diagnosing trigeminal nerve injuries.	9	0,9	Appropriate	Y	9	0,8	Appropriate	Y	
All oral and maxillofacial surgeons should be trained in treating trigeminal nerve injuries.	6,5	2,5	Undecided	N	6	1,6	Undecided	N	
All patients with trigeminal nerve injuries should be referred to a specialist unit experienced in trigeminal nerve injuries.	8	1,6	Appropriate	Y	8	1,4	Appropriate	Y	
Referral protocols are necessary between primary care and specialist centers so that patients can be referred to the right person at the right time.	8	1,3	Appropriate	Y	8	0,7	Appropriate	Y	
There should be a central register of nerve injury experts with contact details so that primary care givers and patients have better access to specialist care.	8	1,4	Appropriate	Y	8	0,5	Appropriate	Y	
All experts dealing with trigeminal nerve injury patients should have thorough training in orofacial pain conditions and their medical treatment	8	1,5	Appropriate	Y	8	0,4	Appropriate	Y	
All experts dealing with trigeminal nerve injury patients should have thorough training in microsurgical nerve repair techniques.	7,5	2,8	Appropriate	N	6	2,2	Undecided	N	
Trigeminal nerve injury services should include a (neuropathic) pain expert.	8,5	1,0	Appropriate	Y	8	0,5	Appropriate	Y	
Trigeminal nerve injury services should include a psychologist or psychiatrist with an expertise in acute and chronic pain conditions.	8	1,6	Appropriate	Y	7,5	0,9	Appropriate	Y	
<b>Diagnosis</b>									
All patients with trigeminal nerve injuries should undergo qualitative (bedside) sensory testing using level A-B-C testing after delineating the neuropathic area in accordance with the ICOP criteria.	8	0,9	Appropriate	Y	8	0,5	Appropriate	Y	
In my opinion, grading of injury should be performed in all patients according to the underneath tables (MRCS and Sunderland classification).	8	1,9	Appropriate	Y	8	1,5	Appropriate	Y	
All patients with trigeminal nerve injuries should undergo quantitative sensory testing.	5,5	1,9	Undecided	N	6	1,6	Undecided	N	
In patients where level A-B-C testing is unclear, quantitative sensory testing should be performed.	8	1,2	Appropriate	Y	7	0,9	Appropriate	Y	
(CB)CT should be considered in patients suffering a trigeminal nerve injury after trauma, wisdom tooth removal, orthognathic surgery, endodontic treatment or implant placement.	8	1,4	Appropriate	Y	8	1,1	Appropriate	Y	
Routine magnetic resonance imaging is useful in diagnosing trigeminal neuropathy.	5,5	2,4	Undecided	N	5	1,6	Undecided	N	
Magnetic resonance neurography is useful in diagnosing trigeminal neuropathy.	8	1,4	Appropriate	Y	8	1,4	Appropriate	Y	
More accurate diagnostic tools are necessary to assess patients with trigeminal nerve injuries.	7	1,7	Appropriate	N	8	0,9	Appropriate	Y	
A simplified diagnostic protocol and assessment tool should be searched for.	8	0,9	Appropriate	Y	8	0,4	Appropriate	Y	
The recent International Classification for Orofacial Pain criteria on post-traumatic trigeminal neuropathic pain should be implemented for all patients.	7,5	1,5	Appropriate	N	7	1,0	Appropriate	Y	
<b>Treatment</b>									
A personalised approach should be adopted when treating trigeminal neuropathic pain.	8	0,8	Appropriate	Y	8	0,4	Appropriate	Y	
Medical (pharmaceutical) treatment of trigeminal neuropathy with neuropathic pain should follow the international NeuPSIG guideline.	8	1,0	Appropriate	Y	8	0,8	Appropriate	Y	

Items		Round 1				Round 2			
		Median	MAD	Appropriateness	Conensus	Median	MAD	Appropriateness	Conensus
Implant and endodontic related injuries should be treated as soon as possible, preferably within 48 hours after injury.	9	0,9	Appropriate	Y	8	0,8	Appropriate	Y	
Patients suffering grade I-II hypoesthesia without neuropathic pain should only be offered counseling and regular follow-up.	6,5	1,8	Undecided	N	7	0,8	Appropriate	N	
All patients suffering a trigeminal nerve injury should be treated by high dose step down corticosteroids when they present within 6 weeks after injury.	5	1,9	Undecided	N	5	1,1	Undecided	N	
All patients suffering a trigeminal nerve injury should be treated by high dose vitamin B complex when they present within 6 weeks after injury.	5,5	2,5	Undecided	N	6	1,7	Undecided	N	
Corticosteroids and vitamin B complex are only useful in acute nerve injuries (presenting within 6 weeks after injury) and are only useful for patients with trigeminal neuropathy without neuropathic pain.	5	1,7	Undecided	N	5	1,3	Undecided	N	
Central sensitisation and chronic neuropathic pain can be prevented by early intervention.	7,5	1,2	Appropriate	Y	8	1,0	Appropriate	Y	
Neuromodulation (e.g. peripheral or central neurostimulation) should be considered in patients with chronic trigeminal neuropathic pain not responding to pharmacological treatment and after excluding a surgical indication.	8	1,2	Appropriate	Y	7	0,9	Appropriate	Y	
Ablative surgery has no role in post-traumatic trigeminal neuropathic pain (e.g. thermocoagulation of gasserian ganglion, rhizotomy, pulsed radiofrequent ablation (PRF))	8	2,2	Appropriate	N	7	1,4	Appropriate	N	
Cyberknife (gamma) radiation therapy should be considered	5	1,6	Undecided	N	5	1,3	Undecided	N	
Opioids should be considered in treating trigeminal neuropathic pain.	3,5	2,0	Inappropriate	N	3,5	1,4	Undecided	N	
<b>Follow-up</b>									
Baseline measurements and longitudinal assessments every 3 months are necessary in all patients.	7,5	1,7	Appropriate	N	7	1,2	Appropriate	Y	
Magnetic resonance neurography should be used to follow up on nerve regeneration.	5	1,4	Undecided	N	5	1,4	Undecided	N	
More accurate tools are needed to register outcomes.	8	0,9	Appropriate	Y	8	0,5	Appropriate	Y	
All patients should be registered in an international registry.	7,5	2,0	Appropriate	N	7	1,4	Appropriate	N	
<b>Flowcharts</b>									
Please indicate your level of agreement with the diagnostic protocol above.	7	1,1	Appropriate	Y	7	0,7	Appropriate	Y	
Please indicate your level of agreement with the sensory testing protocol above.	8	0,8	Appropriate	Y	8	0,8	Appropriate	Y	
Please indicate your level of agreement with the treatment protocol above.	8	1,1	Appropriate	N	8	0,7	Appropriate	Y	



Figure 2. Frequency of expert scores on statements that reached consensus in the second round. On a scale from one to nine, with one being total disagreement and nine being total agreement, experts were asked to rate their level of agreement with a given statement. The statement was considered appropriate if the median score fell within the range of seven to nine, undecided if the score was between four and six, and inappropriate if the score fell within the range of one to three. R1: first round; R2: second round; ICOP: International Classification of Orofacial Pain.

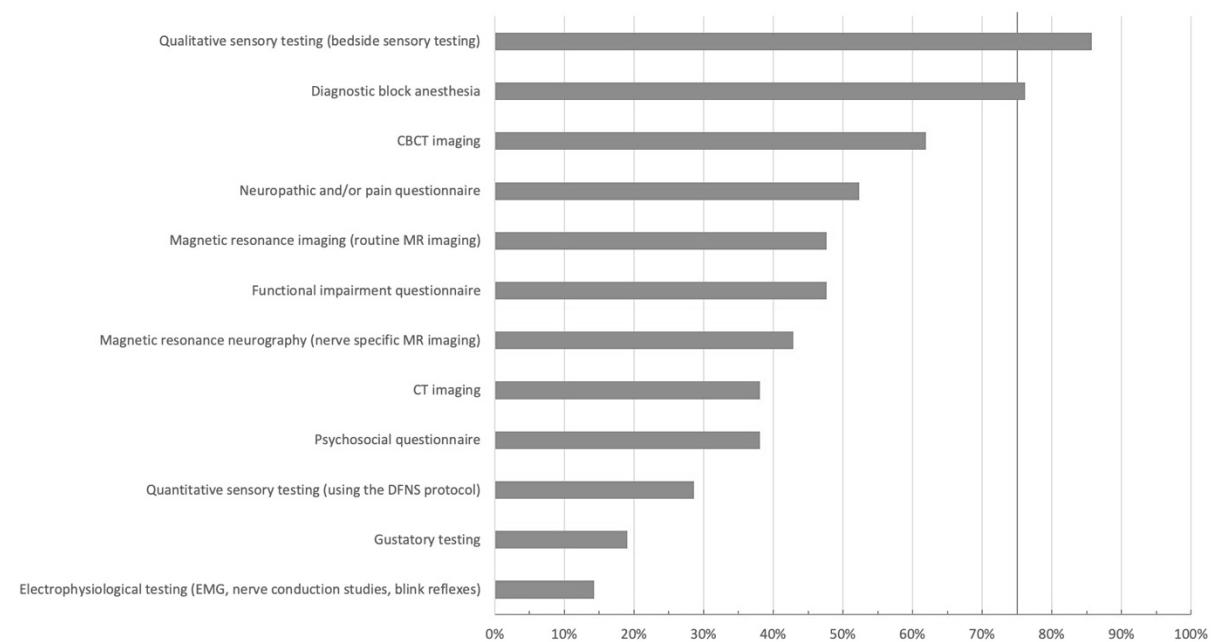
## TNI Services and Training

Most statements (78%) on services and training reached a consensus among experts. They strongly agreed that all maxillofacial surgeons should be able to diagnose patients with TNI, as well as knowing when, how and where patients can be referred. One expert stressed that an early accurate diagnosis is necessary in order not to miss the window of opportunity when surgery is indicated. According to the experts, not all maxillofacial surgeons should be competent in treating and microsurgically repairing nerve damage. In addition, several experts commented that treatment and microsurgical repair belongs to a fellowship after maxillofacial surgery training. Experts agreed that the team responsible for treating patients with TNI should include a neuropathic pain expert and have access to a psychologist or psychiatrist with experience in acute and chronic pain conditions.

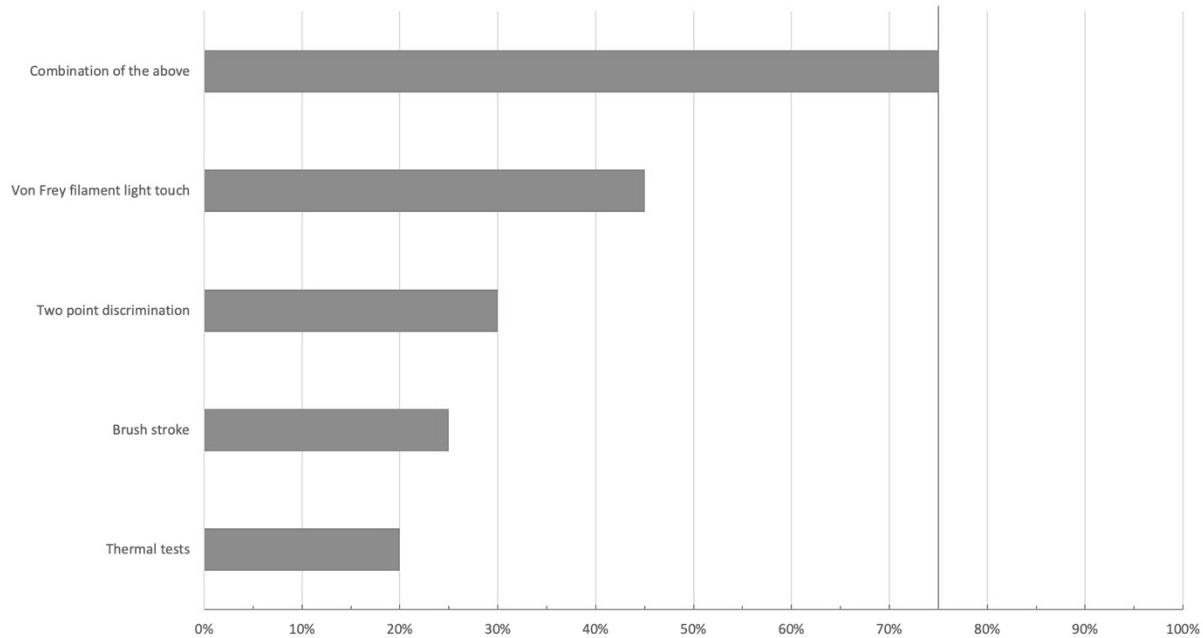
## TNI Diagnosis

Most statements (80%) on diagnosis reached consensus among experts. According to most experts, bedside qualitative neurosensory testing (qualST)<sup>7</sup> is required to diagnose TNI with grading of the injury according to the medical research council scale (MRCS)<sup>8</sup> and modified Sunderland classification.<sup>9</sup> Quantitative sensory testing (QST) was recommended to investigate patients where qualST does not bring sufficient diagnostic clarity or for research purposes. Experts used a variety of assessment methods including a combination of qualST methods both in hypoesthetic and hyperesthetic TNIs (**Figure 3**).

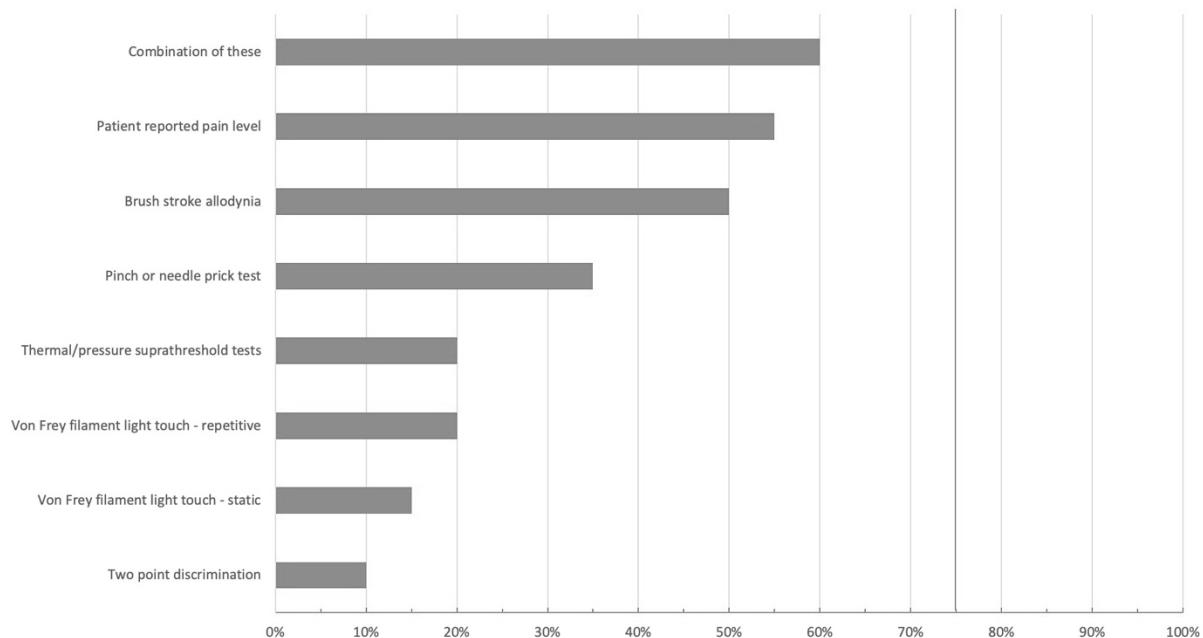
Which assessment tools do you use in patients with a trigeminal nerve injury?



In your opinion what is the best clinical outcome parameter to assess resolution of HYPOesthetic complaints?



In your opinion what is the best clinical outcome parameter to assess resolution of HYPEResthetic neuropathy?



*Figure 3. Frequencies of the preferred assessment tools as reported by the experts in patients with a TNI and stratified for patients with hypoesthetic and hyperesthetic complaints. (CBCT: cone beam CT; DFNS protocol<sup>10</sup>; EMG: electromyography; MRCS: medical research council scale; VAS: visual analogue scale).*

Many experts considered the use of a diagnostic block with local anesthesia, but the indication and the method of administration differed between experts and lacked consensus. In select cases, further imaging was deemed beneficial. Some authors recommended using cone beam

CT (CBCT) in select cases but commented that the patients' etiology is most important and the diagnostic yield of CBCT is low. The use of routine MRI imaging was undecided in both rounds of questions, but magnetic resonance neurography (MRN) was indicated as useful in further diagnostics. Several experts did indicate that MRN is not yet widely available. Experts also indicated that the know-how to diagnose and manage TNIs is yet to be widespread among oral and maxillofacial surgeons. Applying diagnostic criteria according to the International Classification of Orofacial Pain (ICOP)<sup>11</sup> or NeuPSIG<sup>12</sup> and developing guidelines could contribute to this by providing clear and up to date evidence.

### TNI Treatment

Only five items (42%) for treatment reached consensus among experts. All experts agreed that a personalized approach is required for the treatment of TNI. For the pharmacological approach, adopting the NeuPSIG guideline was accepted. Most experts also agreed that implant- and endodontically-related TNIs require prompt treatment. Moreover, experts agreed that early treatment can prevent central sensitization and chronification. Although most experts did not recommend ablative surgery or gamma knife in neuropathic pain patients, no consensus could be obtained on this. In both rounds, experts agreed that neuromodulation for patients not responding to pharmacological treatment and without a surgical indication should be considered. The use of opioids was assessed as inappropriate by most, others considered it as a last pharmacological treatment option and no consensus could be reached on their use. The use of vitamin B and corticosteroids was undecided in both rounds, several authors indicated a lack of evidence as the reason to reject its use. More than 75% of experts indicated that the most important factors determining treatment choice were time since onset, sensory profile, impairment level, imaging findings and psychological impact. Others also indicated patient expectations and severity of the injury as important factors. For surgical treatment, multiple factors were considered important to improve outcomes (**Figure 4**). The most important factor was early intervention within six months from the time of nerve injury onset.

In your opinion, the following factors are crucial for surgical treatment success

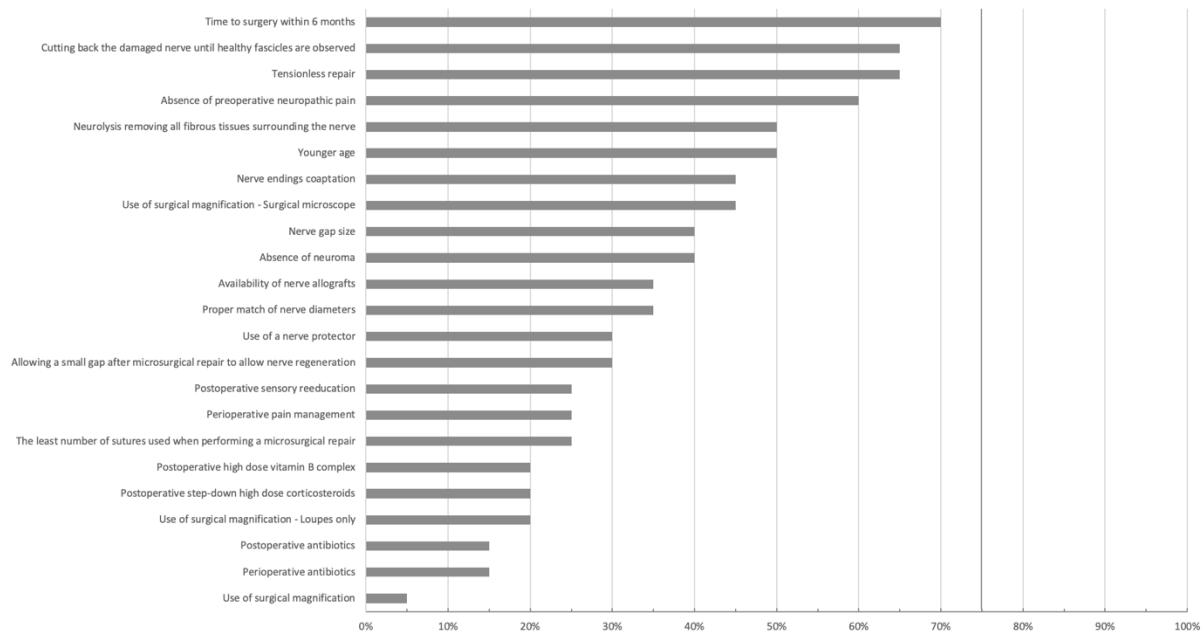
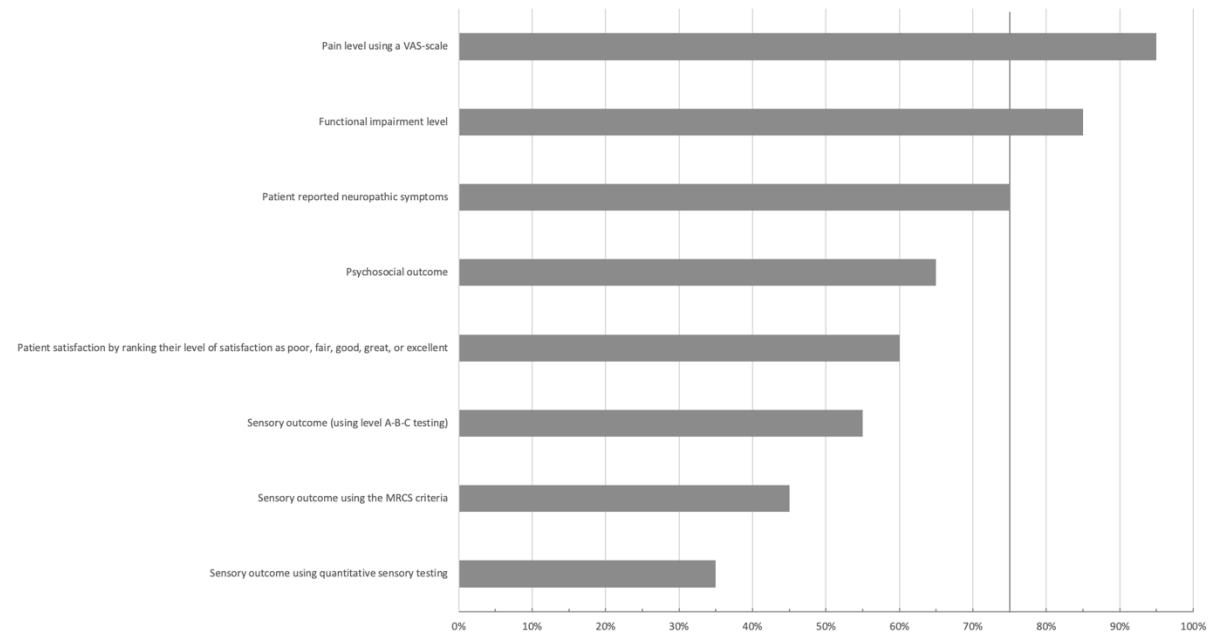


Figure 4. Expert-rated frequencies of crucial factors for surgical success in treating TNIs.

### TNI Follow-up

Two of the four statements for follow-up reached consensus among experts. Experts agreed that baseline clinical examination with subsequent longitudinal follow-up every three months is recommended. No consensus could be reached on the total duration of follow-up, but some experts recommended a follow-up of two years, while others use an adaptive follow-up time depending on the outcome. Experts welcomed the idea of more accurate and validated tools in registering outcomes. Crucial outcomes to assess were: pain visual analogue scale (VAS) score, functional impairment level and reported neuropathic symptoms (**Figure 5**).

In your opinion the following outcomes are crucial to register in the follow-up of trigeminal nerve injury patients:



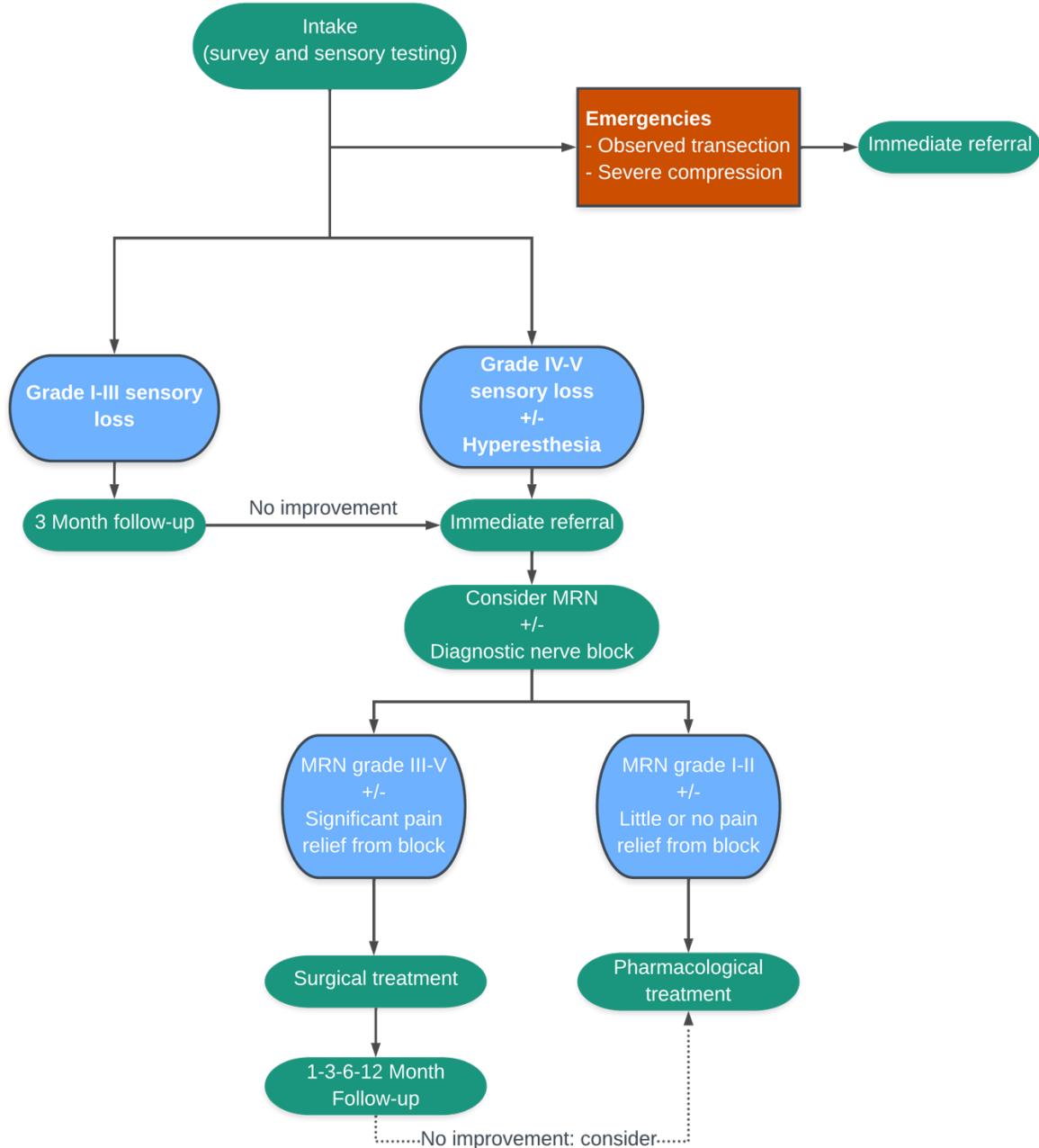
*Figure 5. Expert-rated frequencies of crucial outcome measures in the follow-up of TNI patients.*

## TNI flowcharts

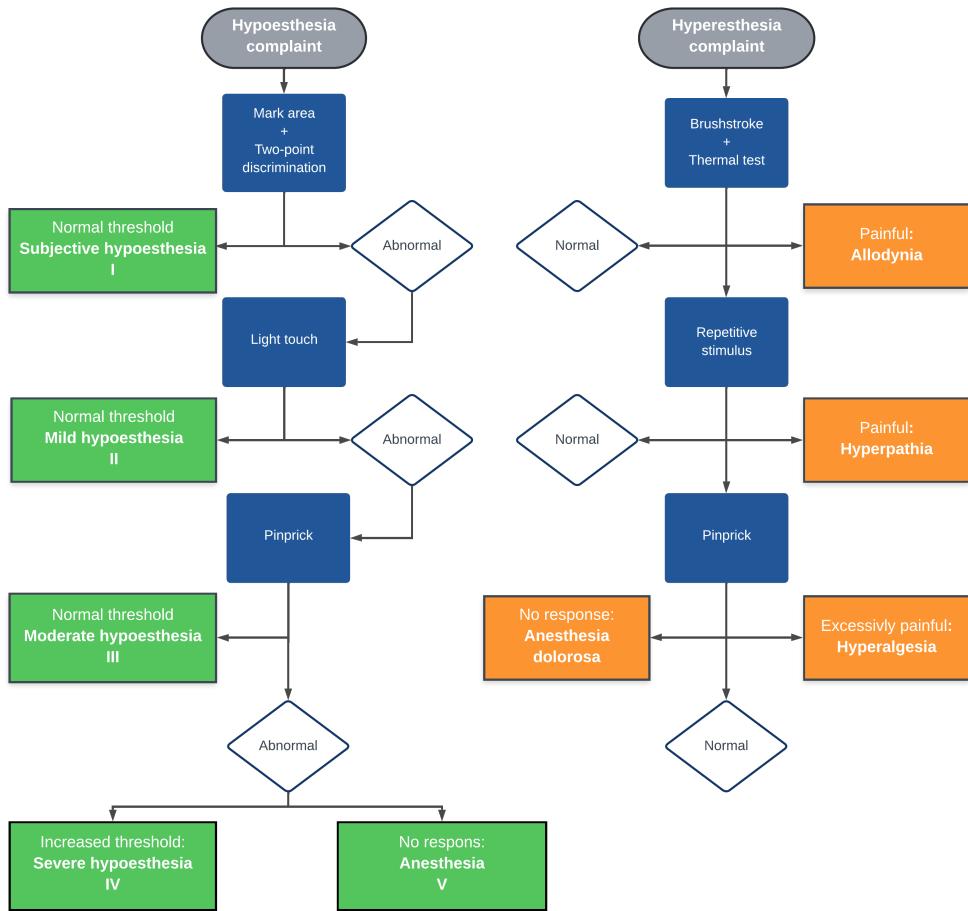
Most experts accepted the proposed diagnostic and sensory testing flowchart (**Figure 6 and 7**).

The treatment flowchart was slightly amended based on the experts' comments in the first round after which the final version was accepted in the second round.

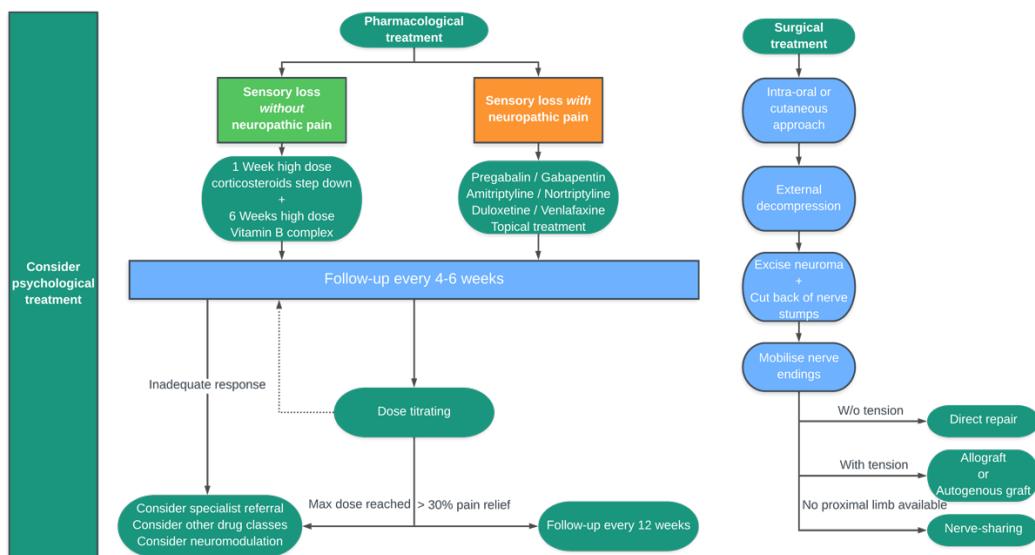
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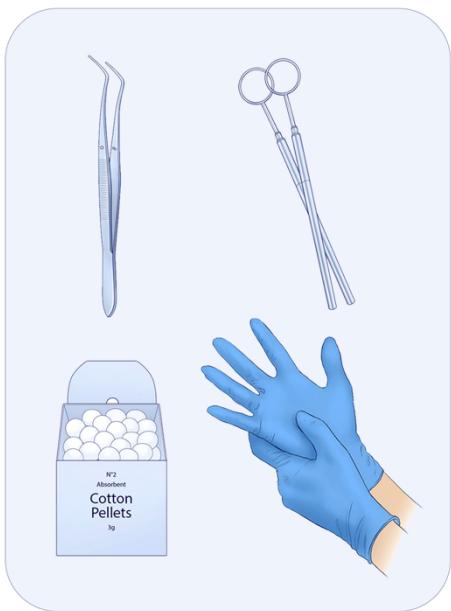
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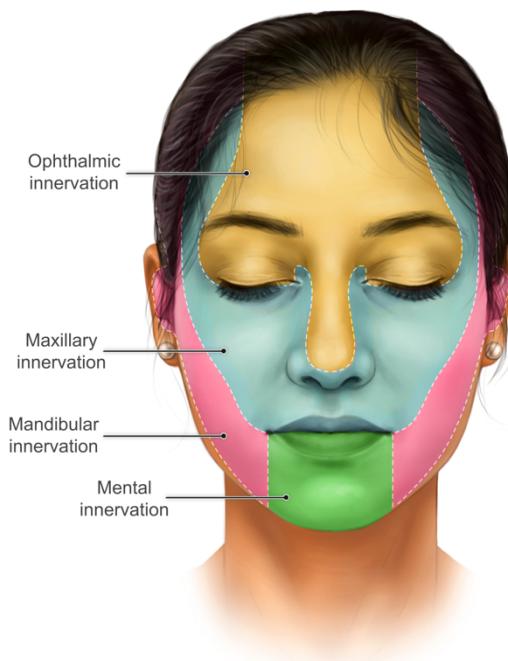
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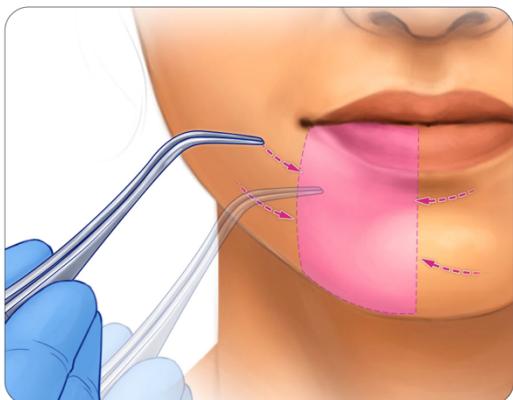
*Figure 6. Final diagnostic (A), sensory testing (B) and treatment (C) flowcharts presented to the expert panel and after reaching consensus.*



**Equipment**



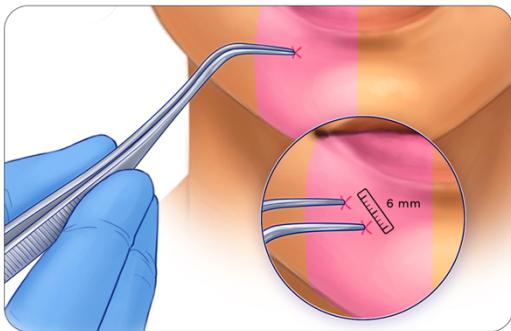
**Extra-oral trigeminal dermatomes**



#### **Step 1: Determining affected area**

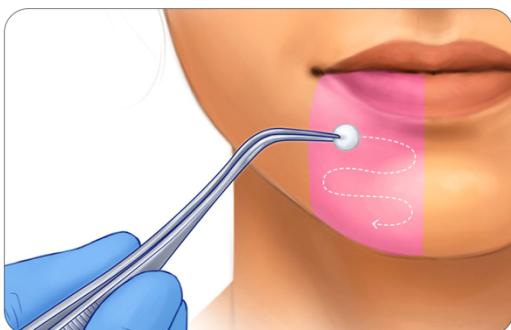
*Start: Explain that you will be testing nerve function. For this, the patient should close their eyes so that the examination is not visually influenced.*

Using forceps run over normal to neuropathic area warning the patient that there may be hypersensitivity as well as hyposensitivity. Ask the patient to raise their hand as soon as it feels abnormal and repeat until the area is mapped. Map out the area by using pen marks and record pictorially or by photograph. Estimate what percentage of the dermatome is affected and write this down.



### Step 2: Two-point discrimination (TPD)

Using forceps with beaks open and closed, TPD function can be estimated. Some authors prefer specially designed calipers which can be set to a specific distance. The patient is asked with their eyes closed if they can detect two points touching the skin or only one. The distance between the beaks is increased or decreased accordingly until the patient only detects one point, next the sequence is reversed until a threshold value is obtained. Normal TPD in the V3 dermatome extraorally ranges from 2-4 mm on the lip vermillion to 6-8 mm on the skin of the chin.



### Step 3: Light touch

To evaluate light touch thresholds von Frey filaments are recommended. If these are not available, a cotton pellet can be used instead. Place the pellet softly on the unaffected skin first then repeat on affected side; ask the patient to report differences. If the patient is experiencing numbness on stimulation, they will have reduced light touch detection thresholds. However, if the patient is suffering from hyperesthesia and possible allodynia (pain on touch) this test can be very uncomfortable and mechanical allodynia is diagnosed. This can be further confirmed by a gentle brush stroke.



### Step 4: Light touch with cold object

Using a cold forceps or frozen cotton pellet touching the unaffected area and next the affected area, presence of cold allodynia is assessed. The patient is asked to compare the unaffected side to the affected side. They should report if they experience a similar feeling, hypersensitive/painful or less sensitive feeling.



### Step 5: Painful stimulus

Finally, a painful stimulus is presented after warning and instructing the patient. First the unaffected side is tested. Next, the same stimulus is presented in the middle of the affected dermatome. The patient is asked to report if the stimulus is similar, less painful (hypoalgesia) or more painful (hyperalgesia) compared to the other side.

*Figure 7. Diagnostic testing algorithm using qualitative or bedside sensory testing.*

## **Discussion**

The current study used a Delphi study design to acquire an expert consensus on training/services, diagnosis, treatment and follow-up care of trigeminal nerve injuries. Experts from various dental, medical and surgical specialties were consulted. They participated in a two-round Delphi study and provided recommendations on a wide range of TNI topics related to training/services, diagnosis, treatment and follow-up.

Experts agreed that knowledge and information regarding TNIs should be disseminated. They agreed that every oral and maxillofacial surgeon should be able to make an accurate diagnosis of TNIs, and be knowledgeable about the further management of TNIs in order to make a timely referral. Specialist teams at higher levels of care can then institute treatment and intervene surgically where necessary. Diagnostic and treatment delays should be kept to a minimum as treatment delays dictate the outcome according to the experts of this study and others<sup>13</sup>. Etiology of the injury might play another role in treatment success. Some consider endodontic and implant-related injuries an emergency that should be treated within 48 hours but more outcome data is necessary to confirm this statement<sup>14</sup>. In the meantime, an observed transection or severe compression, as in endodontic and implant-related lesions, is included as an emergency in the diagnostic flow chart and thus requires immediate action.

A high degree of consensus was reached on statements concerning the diagnosis of TNIs. The use of bedside sensory testing is widely utilized in this field<sup>15–18</sup> and supported by the respondents of this study. The proposed diagnostic and neurosensory testing flow chart was supported by the experts and follows the recommendations by others in the past.<sup>19,20</sup> Imaging techniques such as CBCT and MRN were also considered useful in the diagnostic process but these techniques are indicated on a case-by-case basis. There is still much scope for researching and validating diagnostic methods. These should be easy to use, accurate, reproducible, inexpensive, and easily accessible.

Consensus was reached in less than half of the statements about the treatment of TNIs. This was likely related to the inclusion of several statements examining the role of vitamin B and corticosteroids, whose use was undecided. To date, most studies investigating the role of these drugs are animal studies or lack convincing clinical evidence.<sup>21,22</sup> However, others do recommend its use in acute neuropathies given the few side effects and growing level of evidence for their beneficial effect.<sup>23,24</sup> The role of ablative therapy and gamma knife surgery in patients with neuropathic pain was undecided in the current study and recent reviews confirm that its use remains investigational for now until more randomized studies are performed<sup>25,26</sup>.

The use of neuromodulation was considered in cases without surgical indication and where previous pharmacological treatments failed. However, the evidence around invasive and non-invasive neuromodulation remains limited and, for now, is mainly based on case series or other trigeminal pain conditions such as migraine and trigeminal neuralgia.<sup>26,27</sup> There was consensus about applying the NeuPSIG treatment guideline<sup>28</sup> in the case of neuropathic pain and it was therefore adopted in the accepted treatment flowchart. The role of opioids remains ambiguous both in the current study and in the broader research field of neuropathic pain.<sup>29,30</sup>

Regular follow-up was supported by most experts, especially as long as no consolidation of injury was obtained. Outcome registration should consist of a combination of methods according to most respondents and a suggestion as to which methods were indicated. Future research will need to determine which set of validated outcome measures is the most accurate, reproducible, cost-effective and easily interpretable.

Clearly, there is still a long way to go in dealing with TNI. At the same time, this offers many opportunities for the future. The authors made a comprehensive list of future research opportunities based on the responses by the panelists (**Table 2**).

*Table 2. List of future research opportunities based on item scores and comments provided by the panelists. (TNI: trigeminal nerve injury; ICOP: International Classification of Orofacial Pain; CBCT: cone beam CT; MRN: magnetic resonance neurography).*

Training and services
Validation of referral guidelines
Development of TNI expert centers registry or webpage
Postgraduate TNI fellowship
Diagnosis
Validation of neurosensory testing algorithm and grading scales
Diagnostic accuracy and cost-effectiveness of imaging modalities (e.g. CBCT, MRN)
Guidelines on the use of imaging for TNI
Validation of ICOP criteria in TNI
Treatment
Real world data on the effectiveness of the NeuPSIG treatment guideline in TNI patients
Predicting treatment efficacy in patients and subpopulations with TNI
Outcome data on implant and endodontic related injuries and assessing the effect of treatment delay
Role of an early intervention on the prevention of sensitization and chronicification
Randomized controlled trial on systemic or local corticosteroids in acute and chronic TNI
Randomized controlled trial on systemic vitamin B in acute and chronic TNI
Role of non-invasive and invasive neuromodulation in chronic TNI
Role of neuroablative techniques in chronic TNI
Role of opioids in acute and chronic TNI
Follow-up
Development and validation of outcome measures in TNI

Strengths of this study are the good retention rate of experts over the two rounds and the international nature of the panel. Also, we hope by presenting the results in a clear and easy-to-interpret way by means of flowcharts, the results find their way to the clinic and improve the outcomes of our patients. Limitations are the initially low response rate, which is more often seen in electronic Delphi studies. As a result, subgroup analyses were not possible. Also, we noticed a low number of statements that were deemed inappropriate, this might indicate a bias of respondents not daring to disagree with statements. More likely, this is due to the fact that most statements were based on the best quality evidence and were not constructed to disagree on. The change in consensus from round one to round two might have resulted from respondents dropping out of the study, however, additional analyses revealed their scores did not affect the final range.

In conclusion, the current study provides consensus guidelines on the management of TNIs by means of a Delphi study amongst TNI experts and further aimed to disseminate its results through the presented summary flowcharts.

## Acknowledgements

We would like to thank all the participating experts: Baad-Hansen L, De Laat A, Meyer R, Miloro M, Morlion B, Nixdorf D, Nout E, Pigg M, Politis P, Renton T, Selvi F, Steed M, Susarla S, Tay A, Theys T, Van Buyten JP, van Es R, Willaert R, Yates J, Ziccardi V, Zuniga J. We recognize and appreciate the review and comments of the Global Nerve Foundation board of directors and research committee (<https://globalnervefoundation.org>).

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# CHAPTER 11

## Discussion

Trigeminal nerve injury (TNI) can result in post-traumatic trigeminal neuropathy (PTN) after trauma and numerous dental, oral and maxillofacial procedures, causing significant comorbidity that impact patients' quality of life (QoL) and incur substantial healthcare costs. These patients suffer from a range of neurosensory abnormalities, such as anesthesia, hypoesthesia, allodynia, hyperpathia and hyperalgesia which can significantly interfere with their daily activities and psychosocial functioning. Unfortunately, the medical field has largely overlooked the negative implications of TNIs on patients, resulting in a lack of guidelines and scientific evidence on the effective diagnosis and management of these injuries.

Symptoms vary widely and can range from a small numb area in the chin region to pronounced disabling burning pain in a large part of the face.<sup>1</sup> To date, the diagnosis is primarily made clinically but, according to recent guidelines, also requires confirmatory diagnostic tests such as biopsy, neurosensory testing (NST), electrophysiological studies or imaging.<sup>2</sup> Guidelines on appropriate tests are not available to date, so diagnostic and treatment delays occur all too often.<sup>1</sup> Unfortunately, this also means for a subset of these patients that the chances of a successful neurosensory recovery by, for example, microsurgical intervention decrease.<sup>3</sup> The main objectives of this thesis were to identify the socioeconomic impact of PTN as well as the impact on patient quality of life (QoL). Next, we were interested in predicting outcomes in these patients using patient-reported and clinical factors collected before or shortly after injury occurred. We also questioned which clinical factors are the most predictive of quality of life. Next, we aimed to develop and validate a new imaging technique with the hope to improve diagnostic accuracy in these patients. We hypothesized that magnetic resonance neurography (MRN), could highlight the peripheral trigeminal nerve branches and subsequent nerve damage. Finally, we performed a Delphi study amongst PTN experts to summarize current evidence, identify scientific knowledge gaps and provide guidelines on services, diagnosis, management and follow-up of trigeminal nerve injuries.

**In our first chapter**, we introduced PTN by means of a case report and a review article and further illustrated the main causes such as third molar surgery, implant placement, endodontic treatment and oromaxillofacial trauma in a demographic study, which was the start to embark

on this doctoral thesis.<sup>4</sup> This study also revealed a large time delay between the onset of the injury and tertiary referral for this difficult to diagnose and treat condition. A retrospective analysis on diagnostic features, psychosocial and QoL outcomes illustrated that pain and numbness were reported in more than half of our patients.<sup>1</sup> There was a high interference with patients' lifestyle and quality of life was lowest in painful trigeminal neuropathies. Also, we identified sensory profiles based on basic neurosensory testing. These profiles were sensory loss (when a numb or absent feeling is present), thermal hyperesthesia (when patients show a hyperresponse toward thermal stimuli for example a cold breeze during winter could evoke severe neuropathic pain in some patients) or mechanical hyperesthesia (when patients show a hyperresponse towards mechanical stimuli for example touch). These sensory profiles are important as they might correlate with QoL, psychosocial impact, therapeutic response, and clinical outcome.<sup>5-7</sup> We also introduced some definitions and terminology based on the International Association for the Study of Pain (IASP) and the recently published International Classification of Orofacial Pain (ICOP).<sup>8</sup> The use of correct semantics is crucial in this field since all too often confusion still occurs with trigeminal neuralgia, neuralgia, causalgia, phantom tooth pain, idiopathic facial pain etc, which can lead to unwarranted interventions.<sup>9</sup>

**In the second chapter**, we assessed the direct healthcare costs of patients with PTN in the five years after the occurrence of nerve damage as well as the use of services and medication and to compare this between patients with temporary damage versus those with persistent damage.<sup>10</sup> Quality of life was also assessed using the EuroQoL-5 questionnaire and the index value was determined. We collaborated with the largest Belgian health insurer to examine these parameters in 158 patients within a cohort of UZ Leuven patients. The total average cost per patient in the first year was €2353. There was a high frequency of primary and secondary care visits (annual average of five general practitioner visits and nine specialist visits). For each cost category, expenditure was significantly higher in patients with persistent PTN than in those with temporary PTN. The average direct healthcare costs were almost three times as high for patients with persistent nerve injuries. If a patient suffered from persistent nerve damage, an increasing direct cost was shown in the years after the nerve damage occurred, while the cost decreased if the damage was temporary. This is of course of paramount importance for secondary prevention and value-based healthcare. A small group of patients accounted for 28% of the total costs of the entire cohort. These patients all suffered from persistent nerve injury and had a mean QoL index of 0.4, which can be considered very low. PTN patients received repeated and frequent head and neck imaging. Medication consumption was high, with

unwarranted higher use of opioids and antibiotics in persistent PTN cases. This study was the first of its kind making it difficult to compare with literature. It adds to the literature that a subset of these patients incurs a high socioeconomic impact comparable to other chronic neuropathic conditions.<sup>11</sup> The study's findings on the high number of imaging studies for PTN patients highlight the challenges in accurately diagnosing this condition. The study also reveals a concerning trend of high medication use, with opioids and antibiotics being prescribed frequently for patients with persistent PTN. This is a worrying finding, as misdiagnosis and improper treatment could lead to patients seeking medical shopping or taking legal action. Unfortunately, this is a common occurrence in clinical settings.<sup>12</sup> These results further emphasize the urgent need for the development of diagnostic and treatment guidelines, as well as increased awareness and education for PTN among both patients and medical professionals.

In the following **chapters 3 and 4** we evaluated the importance of diagnostic features on prognosis. In a prospective observational study including all new iatrogenic nerve injuries at the department we identified some of the key factors for persistency.<sup>13</sup> Furthermore, using principal component analysis we determined which clinical tests are most relevant in assessing these injuries and how they correlate with patient-reported outcome measures, as there is little or no literature on what really affects the wellbeing of our patients and the prognosis and how we can measure this in the clinic. When assessing correlations between objective measurements, we noticed that most tests and scales have a significant correlation with each other. Strong correlation was seen between stimulus localization and directional discrimination. Between sensory loss and two-point discrimination and between two-point discrimination and Sunderland score. Surprisingly these clinical factors did not correlate with the patient-reported QoL but the presence of allodynia and the percentage of affected dermatome did. Thus, we should focus on these gain-of-function complaints and try to alleviate these in the first instance. In another retrospective study we identified prognostic factors in PTN patients by running a multivariable analysis based on longitudinal data of a large patient cohort from our center and built a prognostic prediction model using these data.<sup>14</sup> We determined if and when neurosensory disturbances persist, what the key factors are for persistency, and poor QoL and how symptoms evolve over time. The model showed that gender, the triggering cause, and presence of thermal hyperesthesia were most predictive for persistent complaints. Accuracy of the model was considered very good, as such we were able to develop a prognostic prediction model for patients suffering a trigeminal neuropathy. The model was converted into a clinical calculator to allow for future external validation by researchers and clinicians. This study further

confirmed that the presence of gain-of-function phenomena is important in the prognosis of these patients. In fact, these patients might suffer from a completely different pathophysiological phenomenon compared to patients suffering from a hypoesthetic or anesthetic neuropathy.<sup>15,16</sup> Already in the postbellum era, Sedon and colleagues identified a group of nerve injury patients suffering from *causalgia* necessitating a different diagnostic and treatment approach.<sup>17</sup> Unfortunately, there still seems to be a gap in knowledge on how to manage these patients effectively and new evidence shows that current treatment strategies are of little benefit for these patients.<sup>18-20</sup>

In **chapters 5 through 9**, we investigated magnetic resonance neurography, a new non-invasive diagnostic method in peripheral nerve imaging. We commenced by investigating the current evidence by means of a systematic review.<sup>21</sup> We noticed a high risk of bias in almost all studies. There was no standardized approach in timing, techniques, acquisition parameters, nor reference testing. Thus, our primary goal of determining diagnostic test accuracy of MRN in PTN cases was not achieved. We did find that most studies rely on 3-Tesla heavily T2 weighted sequences and show moderate to excellent inter- and intrarater agreement. Based on limited data there was a correlation between MRN, clinical and surgical findings. One study showed an association between signal intensity and persistency of the neurosensory complaints, suggesting a prognostic value of magnetic resonance neurography. Another study that evaluated a new MRN sequence, reported a change in policy in about one third of all cases.

Next, in a retrospective analysis we commissioned all MRIs by the department of Oral and Maxillofacial Surgery UZ Leuven to assess diagnostic accuracy of *routine* MRI in post-traumatic trigeminal neuropathy and its ability to change the management of the PTN patients.<sup>22</sup> Forty-one cases matched inclusion criteria. Analysis revealed that the diagnostic value of *routine* MRI sequences in diagnosing PTN is low, with high artifact susceptibility and a low impact on our clinical decision making.

Finally, we believed it was necessary to develop our own *nerve-specific* sequence to visualize the peripheral cranial nerve branches. In a series of feasibility experiments in collaboration with prof. dr. Jan Casselman, we were able to develop and optimize a 3D STIR Black Blood cranial nerve imaging (3D CRANI) sequence which allowed us to visualize the small peripheral cranial nerve bundles. A feasibility study showed near-perfect agreement in nerve visualization with excellent to good visualization of the extraforaminal trigeminal, greater occipital, and facial nerves.<sup>23</sup> Suppression of surrounding tissues was deemed excellent to good. Thus, 3D CRANI

could produce nerve selective imaging of extraforaminal cranial and spinal nerve branches. In a narrative review we then summarized the current state of the art, MRN anatomy, pathology and future perspectives.<sup>24</sup>

Next, in **chapter 8**, we validated 3D CRANI with and without the use of gadolinium contrast administration in eleven healthy subjects.<sup>25</sup> The use of gadolinium contrast improved the detection of most extraforaminal cranial nerve branches on the 3D CRANI sequence. The ophthalmic trigeminal branch and the occipital nerve branches were the most difficult to distinguish. The nerve identification scores were good to excellent, except for smaller nerve branches. The arterial and fat suppression quality was moderate to excellent both before and after contrast administration. Venous and lymph node suppression quality was scored non-suppressed to excellently suppressed, with an improvement in suppression quality after contrast administration. Nerve benchmarking values were calculated before and after contrast administration, and nerve branches as small as 0.5 millimeters could be identified. There was a significant decrease in nerve diameter measurements and apparent signal-to-noise ratio after contrast administration. The intraclass correlation coefficients showed high concordance for all measurements, with decreasing values from proximal to distal.

To further assess the role of 3D CRANI in PTN patients, we conducted a case-control study. This study was presented in **chapter 9** and aimed to evaluate the diagnostic value of magnetic resonance neurography (MRN) for detecting nerve injuries and to determine its correlation with clinical nerve injury classification. The study included 41 participants, consisting of 16 patients with clinically diagnosed nerve injuries and 25 control participants. The cases had a total of 18 injuries, with nine to the lingual nerve and nine to the inferior alveolar nerve. We found that MRN had an overall sensitivity of 38.2% and a specificity of 93.5% for detecting nerve injuries. The positive likelihood ratio was 5.9, and the negative likelihood ratio was 0.66. The positive predictive value was 46%, and the negative predictive value was 91.3%. We further stratified the injuries into low-grade injuries and high-grade injuries, after which the sensitivity to detect a high-grade injury improved to 83.3%, specificity remained unchanged.

The clinical Sunderland classification based on neurological sensory testing (NST) was used to categorize the severity or grade of nerve injury. We found that both clinical and MRN Sunderland classification scores significantly and positively correlated, with a correlation coefficient of 0.53. A prediction model was also developed using a signal-to-noise ratio (aSNR), apparent nerve magnetic coherence ratio (aNMCNR), and nerve thickness to predict the

presence of nerve injury. The model had an area under the receiver operating characteristic curve of 0.78, with an F-score of 0.19 and an accuracy rate of 0.89. The study also compared aSNR, aNMCNR, and nerve thickness between healthy and injured nerves. The results showed a significant difference in mean nerve thickness for the overall dataset, but not for each nerve separately. For aSNR and aNMCNR, significant differences were found for the overall dataset and both nerves separately. The prediction model using aSNR, aNMCNR, and nerve thickness also showed promising results for predicting the presence of nerve injury. Thus, MRN could be a useful adjunctive tool for assessing nerve injuries, especially in the presence of high-grade injuries. Moreover, it is precisely this group of high-grade injuries where surgical intervention may be best indicated and where nerve integrity can be restored. Further multicenter research will need to test this hypothesis.

In chapter 10, we conducted a Delphi study aimed to obtain expert consensus on the training/services, diagnosis, treatment, and follow-up care of trigeminal nerve injuries (TNIs). The study involved experts from various dental, medical, and surgical specialties who provided recommendations on a wide range of TNI topics. The study found that knowledge and information regarding TNIs should be disseminated, and every oral and maxillofacial surgeon should be able to make an accurate diagnosis of TNIs. Diagnostic and treatment delays should be minimized to improve outcomes. Consensus was reached on the use of bedside sensory testing for diagnosis and the use of the NeuPSIG treatment guideline for neuropathic pain treatment. The role of vitamin B, corticosteroids, ablative therapy, gamma knife surgery, neuromodulation, and opioids in TNI treatment remains unclear. Regular follow-up was recommended, and future research needed to determine the most accurate and cost-effective outcome measures. The study provided consensus guidelines on the management of TNIs, which could improve patient outcomes.

## Methodological limitations

This thesis is limited by several methodological constraints that may impact the reliability of its findings and conclusions. Trigeminal nerve injuries are relatively rare and their presentation can vary significantly, making it challenging to obtain sufficiently large sample sizes. Additionally, the tertiary nature of this condition means that many patients in the presented studies were seen in university settings, potentially leading to selection bias. Furthermore, there is currently no straightforward method for identifying patients with TNI as there is no national

registry or ICD coding system available. Therefore, for the studies in Chapters 1, 2, and 4, among others, the researchers had to manually review records from the past few years to find TNI cases, which may have also led to selection bias.

The development of a nerve-specific MR sequence was an iterative process, with continuous modifications and improvements. It is likely that the presented results may become outdated in the future, as nerve-specific imaging techniques continue to evolve. Additionally, manual measurements performed by both radiologists and non-radiologists may have introduced measurement bias. In Chapter 8, there was also measurement bias due to some cranial nerves not being equally well-highlighted by the field-of-view.

The response rate for the Delphi study in Chapter 10 was low, although the retention rate was reasonable, likely due to the limited number of experts focused on TNIs who agreed to participate.

## **Conclusion**

Trigeminal nerve injuries are often overlooked until they progress into persistent post-traumatic trigeminal neuropathy and become chronic. PTN is a highly debilitating condition that has a significant personal and socioeconomic impact. Extraction of third molars, local anesthesia injuries, implant-related injuries, teeth extractions, endodontic treatment, dental implant placements, and maxillofacial trauma are among the major causes of PTN.

Given the limitations of this thesis, it is important to inform patients of the risks of nerve damage associated with dental and oral and maxillofacial procedures. Prior to any treatment, a risk-benefit assessment should be conducted to avoid unnecessary nerve damage. The final outcome depends on many factors, including gender, the cause of injury, time since onset, the sensory profile, the level of impairment, and psychosocial measures. Early diagnosis by means of neurosensory testing and in selected cases by MRN could potentially improve the chances of patients recovering. The presented consensus guidelines are the first step towards a uniform approach, should create more awareness and improve the lives of our patients. Further research is needed to improve the accuracy of diagnostic and treatment methods, reduce healthcare costs, and enhance the QoL of patients suffering from TNIs.

## **Future perspectives**

This thesis aimed to map patients with PTN, focusing on their presentation, symptoms, prognosis, and socioeconomic impact, as well as different diagnostic methods and their correlation with clinically relevant outcomes. The subjective nature of sensory neuropathies makes diagnosis difficult for clinicians, leading to significant diagnostic, referral and treatment delays. This thesis highlights the importance of providing clinicians with guidelines, continuing research, improving registration, and creating awareness of TNI to improve patient outcomes. Also, predicting outcomes is possible and combining multifactorial data will likely result in even better prediction models in the near future aiding in early diagnosis of PTN. As a consequence of our work, it is quickly becoming apparent that some patient groups are more at risk for chronic PTN. Identifying these patients preoperatively could further contribute to improved patient care and primary prevention for TNI. Establishing a risk profile for TNI and subsequent PTN could become increasingly important in counselling the patient and in an increasingly medico-legal landscape.<sup>26</sup>

The treatment of TNI was not a primary focus of this thesis partly due to the lack of national or international treatment guidelines. This provides a significant opportunity for future studies. Currently, expert opinions and experiences from other research fields and the broader pain sciences are relied upon for treating PTN, resulting in a wide variation in treatment strategies that often produce disappointing results in our patients. To design effective studies, a broad-based consensus on patient selection, diagnostic methods, and outcome measures is necessary, for which I hope this thesis can be a first step. Multicentric studies comparing treatment strategies with sufficiently long and close follow-up and attention to cost-effectiveness are now urgently needed.

The development of high-field MRI devices has improved the spatial resolution of MR neurography but has also increased susceptibility artifacts, requiring dedicated MRI sequences with high resolution and low artifact susceptibility to visualize post-traumatic injuries of the peripheral trigeminal branches in the maxillofacial area. The 3D CRANI sequence for MR neurography is a novel technique that offers improved nerve visualization and reproducible quantitative measurements. It has the potential to serve as a benchmark for future case-control studies on cranial nerve disorders.

There is also a growing interest in using diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) to obtain functional information about nerve injuries and pathology.<sup>27,28</sup> These techniques offer a standardized and multiparametric approach to nerve injuries and pathology, which is currently lacking, especially in extraforaminal cranial nerve imaging.

Future research should focus on developing effective prevention and treatment strategies for TNI, establishing consensus on patient selection, diagnostic methods, and outcome measures, and using advanced imaging techniques such as the 3D CRANI sequence, DTI, and DTT to improve diagnosis and treatment.

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## SUMMARY

Trigeminal nerve injuries (TNIs) are injuries to the trigeminal nerve, a crucial cranial nerve responsible for the sense of touch, temperature, vibration, proprioception, pain perception, taste sensation, and motor innervation of the chewing muscles. These injuries can result from extraction of third molars, local anesthesia administration, dental implant placement, teeth extractions, endodontic treatment, and maxillofacial trauma. TNIs can progress into a painful or non-painful post-traumatic trigeminal neuropathy (PTN) with a wide variety of symptoms.

PTN has a negative impact on patients. Patients experience a significant decrease in their quality of life (QoL) due to interfered psychosocial functioning caused by the neuropathic complaints. Patients with persistent complaints beyond three months after injury experience increasing healthcare costs and decreased psychosocial and QoL measures. We revealed which clinical neurosensory tests are most predictive of QoL and chronicity. By combining clinical and patient-reported data, we could accurately predict clinically relevant outcomes early on.

Magnetic resonance (MR) imaging is often applied in PTN patients trying to depict the injury, but we showed that routine MR sequences are of little clinical benefit in diagnosing PTN. Therefore, we developed a nerve-specific MR sequence called 3D CRANI. This sequence was reliable and accurate in depicting healthy and pathological cranial nerves and could be beneficial in generating further diagnostic clarity in a subset of patients, ensuring less susceptibility to artifact interference.

In a Delphi study, experts agreed that spreading knowledge among oral and maxillofacial surgeons and developing consensus guidelines for the management of TNIs is crucial. Combining various diagnostic and assessment methods, such as bedside neurosensory testing, psychosocial profiling and nerve-specific imaging could improve diagnostic clarity and guide patient-specific treatments. Experts agree that prompt treatment is crucial, and that incorporating various experts in the treatment team and continued training are necessary steps towards effective treatment and management of TNIs and PTN.



## SAMENVATTING

De nervus trigeminus is een cruciale hersenzenuw die verantwoordelijk is voor tastzin, temperatuur, trillingen, proprioceptie, pijnpercepcie, smaakbeleving en motorische innervatie van de kauwspieren. Verschillende oorzaken kunnen zenuwschade van de nervus trigeminus tot gevolg hebben, zoals extractie van wijsheidstanden, letsels door plaatselijke verdoving, tandextracties, endodontische behandeling, plaatsing van tandheelkundige implantaten en trauma's aan de kaak. Ze kunnen overgaan in een pijnlijke of niet-pijnlijke post-traumatische trigeminusneuropathie (PTN) met een grote verscheidenheid aan symptomen.

Patiënten ervaren een aanzienlijke afname van hun kwaliteit van leven (QoL) door verstoord psychosociaal functioneren als gevolg van de neuropathische klachten. Patiënten met persisterende klachten (> drie maanden) ervaren toenemende gezondheidszorgkosten en een verminderde psychosociaal functioneren. Wij lieten zien welke klinische neurosensorische testen het meest voorspellend zijn voor QoL en chroniciteit. Door klinische en patiëntgerapporteerde gegevens te combineren, konden we klinisch relevante parameters in een vroeg stadium nauwkeurig voorspellen.

Magnetische resonantie (MR) beeldvorming wordt vaak toegepast bij PTN patiënten om het letsel in beeld te brengen, maar wij toonden aan dat routine MR sequenties weinig klinisch nut hebben bij het diagnosticeren van PTN. Daarom ontwikkelden wij een zenuwspecifieke MR-sequentie genaamd 3D CRANI. Deze sequentie was betrouwbaar en nauwkeurig in het afbeelden van gezonde en pathologische craniale zenuwen en zou bij een subset van patiënten verdere diagnostische duidelijkheid kunnen verschaffen, waarbij de gevoeligheid voor artefacten minder groot is.

In een Delphi-studie waren de deskundigen het erover eens dat het verspreiden van kennis onder MKA-chirurgen en het ontwikkelen van consensusrichtlijnen voor de behandeling van TNI's van cruciaal belang is. De combinatie van verschillende diagnostische en beoordelingsmethoden, zoals neurosensorische tests, psychosociale fenotyping en zenuwspecifieke beeldvorming, kan de diagnostische accuraatheid verbeteren en richting geven aan patiënten specifieke behandelingen. De deskundigen zijn het erover eens dat spoedige behandeling cruciaal is en dat het opnemen van verschillende deskundigen in het behandelteam

en voortdurende bijscholing noodzakelijke stappen zijn voor een doeltreffende aanpak en behandeling.

## **PERSONAL CONTRIBUTION**

Fréderic Van der Cruyssen conceived, planned and carried out the experiments, interpreted the results and wrote all manuscripts presented in this thesis in consultation with the supervisors and co-authors with the following exceptions: in Chapter 3, Jeroen Meewis analysed the data and wrote the manuscript under supervision of Fréderic Van der Cruyssen. In chapter 9: Mado Bangia and Iraj Ahmadzai collected the data, Mado analysed the data and wrote the manuscript under supervision of Fréderic Van der Cruyssen. The intermezzo on diagnostic accuracy of none-nerve-selective MR imaging was written by Frederik Peeters under the supervision of Fréderic Van der Cruyssen and the co-authors.

## **CONFLICT OF INTEREST**

The authors declare no conflict of interest.



## SCIENTIFIC ACKNOWLEDGEMENT

The author of this thesis received no financial support for the research, authorship, and/or publication of this thesis.

Chapter 1      *Van der Cruyssen F, Verhelst PJ, Stevens O, Casselman J, Renton T, Piagkou M, Bonte B, Politis C. Severe progressive post-traumatic trigeminal neuropathic pain after total temporomandibular joint replacement - A case report. Oral and Maxillofacial Surgery Cases. 2020;6(July):100175.*

Frédéric Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Verhelst PJ, Stevens O, Casselman J, Renton T, Piagkou M, Bonte M, Politis C: critical revision and approval of article.

*Van der Cruyssen F, Politis C. Neurophysiological aspects of the trigeminal sensory system: an update. Reviews in the Neurosciences. 2018;29(2):115-123.*

Frédéric Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Politis C: critical revision and approval of article.

*Klazen Y, Van der Cruyssen F, Vranckx M, Van Vlierberghe M, Politis C, Renton T, Jacobs R. Iatrogenic trigeminal post-traumatic neuropathy: a retrospective two-year cohort study. International Journal of Oral and Maxillofacial Surgery. 2018;47(6):789-793.*

Frédéric Van der Cruyssen: critical revision and approval of article. Klazen Y: data collection, analysis, drafting article, critical revision and approval of article. Vranckx M, Van Vlierberghe M, Politis C, Renton T, Jacobs R: critical revision and approval of article.

*Renton T, Van der Cruyssen F. Diagnosis, pathophysiology, management and future issues of trigeminal surgical nerve injuries. Oral Surgery. 2019;13(4):389-403.*

Frédéric Van der Cruyssen: drafting article, critical revision and approval of article. Renton T: drafting article, critical revision and approval of article.

*Van der Cruyssen F, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, Renton T. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. Journal of Oral Rehabilitation. 2020;47(10):1212-1221.*

Frédéric Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Peeters F, data collection, critical revision and approval of the article. Gill T, De Laat A, Jacobs R, Politis C, Renton T: critical revision and approval of article.

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- T: critical revision and approval of the article. Vandeleene G: data collection and analysis, critical revision and approval of the article. Callens M, Vanhaecht K, Jacobs R, Politis C, Luyten J: critical revision and approval of the article.
- Chapter 3 Fréderic Van der Cruyssen: data analysis, critical revision and approval of article. Meewis J: data collection, analysis, drafting article, critical revision and approval of article. Jacobs R, Politis C: critical revision and approval of article.
- Chapter 4 Fréderic Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Peeters F: data collection, critical revision and approval of article. De Laat A, Jacobs R, Politis C, Renton T: critical revision and approval of article.
- Chapter 5 Fréderic Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Peeters F, Croonenborghs TM: data collection, critical revision and approval of article. Fransen J, Renton T, Politis C, Casselman J, Jacobs R: critical revision and approval of article.
- Chapter 6 Fréderic Van der Cruyssen: sequence development and optimization, data collection, analysis, drafting article, critical revision and approval of article. Croonenborghs TM: data collection, critical revision and approval of article. Casselman J: sequence development and optimization, data collection, analysis, revision and approval of article. Hermans R, Jacobs R: critical revision and approval of article.
- Chapter 7 Fréderic Van der Cruyssen, Croonenborghs TM, Casselman J: drafting article, critical revision and approval of article. Renton T, Hermans R, Politis C, Jacobs R: critical revision and approval of the article.
- Chapter 8 Fréderic Van der Cruyssen: data collection, analysis, drafting article, critical revision and approval of article. Vanhove F: data collection, critical revision of the article. Casselman J: data collection, analysis, critical revision of the article. Peeters R: sequence optimization, critical revision of the article. Hermans R, Politis C, Jacobs R: critical revision of the article
- Chapter 9 Fréderic Van der Cruyssen: data analysis, critical revision and approval of article. Bangia M: data collection, analysis, drafting article, critical revision and approval of article. Ahmadzai: data collection, critical revision and approval of article. Casselman J, Politis C, Jacobs R: critical revision and approval of article.
- Chapter 10 Fréderic Van der Cruyssen: data collection, analysis, drafting of manuscript, critical revision and approval of article. Palla B, Van der Tas J: trial and correction of Delphi questionnaire, critical revision and approval of article. Jacobs R, Politis C, Zuniga J, Renton T: critical revision and approval of article.

- Intermezzo 1 Fréderic Van der Cruyssen: data analysis, critical revision and approval of article. Peeters F: data collection, analysis, drafting article, critical revision and approval of article. Casselman J, Hermans R, Renton T, Jacobs R, Politis C: critical revision and approval of article.
- Intermezzo 2 Fréderic Van der Cruyssen: data collection, analysis, drafting of manuscript, critical revision and approval of article. Van Tieghem L, Croonenborghs TM, Baad-Hansen L, Svensson P, Renton T, Jacobs R, Politis C, De Laat A: critical revision and approval of article.



# CURRICULUM VITAE

Fréderic Van der Cruyssen was born in Waregem, Belgium on January 23th 1992. He received his medical degree magna cum laude from the Catholic University of Leuven in June 2017 with a master's thesis on trigeminal nerve physiology and his dental degree at the same university in 2020. In 2019 he commenced his PhD project at the OMFS-IMPATH research group under promotorship of Prof. dr. Reinhilde Jacobs, Prof. dr. Constantinus Politis, Prof. dr. Jan Casselman and Prof. dr. Tara Renton. In 2020 he started his oral and maxillofacial surgery residency at the University Hospitals Leuven. In 2021 he obtained a master's degree in healthcare policy and management at the Catholic University of Leuven. Currently, he is a third-year oral and maxillofacial resident at the ETZ Elisabeth Hospital, Tilburg, The Netherlands.

## Contributions to (inter)national conferences

19/05/2022	Voorjaarsvergadering NVMKA, Putten (Netherlands) <i>De heilige drievuldigheid in nervus trigeminusschade</i>
19/03/2022	Voorjaarsvergadering KBVSMFH, Brussels (Belgium) <i>Diagnostic &amp; treatment protocols in trigeminal nerve injuries</i>
27/11/2021	Najaarsvergadering KBVSMFH, Leuven (Belgium) <i>Salivary gland obstruction in children and means of treatment</i>
16/11/2021	Symposium Worden we wijzer met wijsheidstanden, Leuven (Belgium) <i>Wijsheidstanden en zenuwen gelinkt</i>
16/09/2021	European association for craniomaxillofacial surgery (EACMFS), Online <i>Management of trigeminal nerve injuries</i>
21/06/2021	World Congress on Pain, Online <i>Trigeminal neuropathy: trouble, trauma, tension and treatment</i>
16/11/2019	Najaarsvergadering KBVSMFH, Brussels (Belgium) <i>Surgical treatment options and outcomes in post-traumatic trigeminal neuropathy</i>
23/10/2019	International Conference on Controversies in Neuropathic Pain, Munich (Germany) <i>Factors affecting evolution of symptoms and QoL in 1331 patients referred for iatrogenic post-traumatic trigeminal neuropathy to two tertiary referral centers in the UK and Belgium</i>
06/12/2018	Association Internationale de Médecine Orale et Maxillo-faciale: dysplasies et malformations, Lille (France) <i>Parry Romberg syndrome, The Leuven Experience</i>

## Awards

06/12/2018	LUTV scientific award on MR neurography
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## List of publications

1. Renton T, **Van der Cruyssen F**. Post-traumatic Trigeminal Neuropathic Pain in Association with Dental Implant Surgery. *Dental Clinics of North America*. 2023;67(1):85-98.
2. Palla B, **Van der Cruyssen F**, Huang Y, Miloro M. Is Surgical Repair With Nerve Allograft More Cost-Effective Than Non-Surgical Management for Persistent Trigeminal Neuropathy? Initial Assessment With Markov Model. *Journal of Oral and Maxillofacial Surgery*. Published online March 2023:S0278239123001763.
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