Magnetic resonance imaging assessment of pain related changes in the brain

Tara Renton

Definitions / parameters

- **Magnetic resonance imaging (MRI)**
  - A magnetic resonance imaging (MRI) scan uses magnets and radio waves to make detailed cross-sectional images of the inside of your body.
- **Models assessed include;**
  - Control patients with and without induced pain
  - Chronic or acute pain patients (of different diagnoses) compared with controls
- **Type of scan** ASL arterial spin labelling; bilateral; BOLD, blood-oxygen-level-dependent; CBF, cerebral blood flow; DWI, diffusion-weighted imaging, FA, fractional anisotropy; FC, functional connectivity; fMRI, functional magnetic resonance imaging; GMV, gray matter volume, MRS, magnetic resonance spectrum; SC, structural connectivity (probabilistic tractography); sMRI, structural magnetic resonance imaging; WMV, white matter volume.
- **Brain areas assessed**
  - Whole brain analysis
  - Region of interest (ROI)-specific analyses
- **Types of assessments**
  - Voxel-based morphometry (VBM) is a computational approach to neuroanatomy that measures differences in local concentrations of brain tissue, through a voxel-wise comparison of multiple brain images
- **Alterations assessed in selected or all regions usually include**;
  - Structural changes including brain volume and grey and white matter changes
  - Functional changes
  - Activational changes
  - Connectivity between brain regions
  - And some studies include pharmako kinetic assessments looking at glutamate and glutamine, GABA and other neuro-transmitter levels

Gray vs White matter

What is gray matter?

Gray matter consists primarily of neuronal cell bodies, or *soma*. This a spherical structure that houses the neuron's nucleus.

What is white matter?

White matter areas of the brain mainly consist of myelinated axons, which are long relays that extend out from the soma, and which are whiteish in color due to the relatively high lipid fat content of the myelin protein that sheathes them, These form connections between brain cells, and white matter is typically distributed into bundles called tracts.

Is it really that simple?

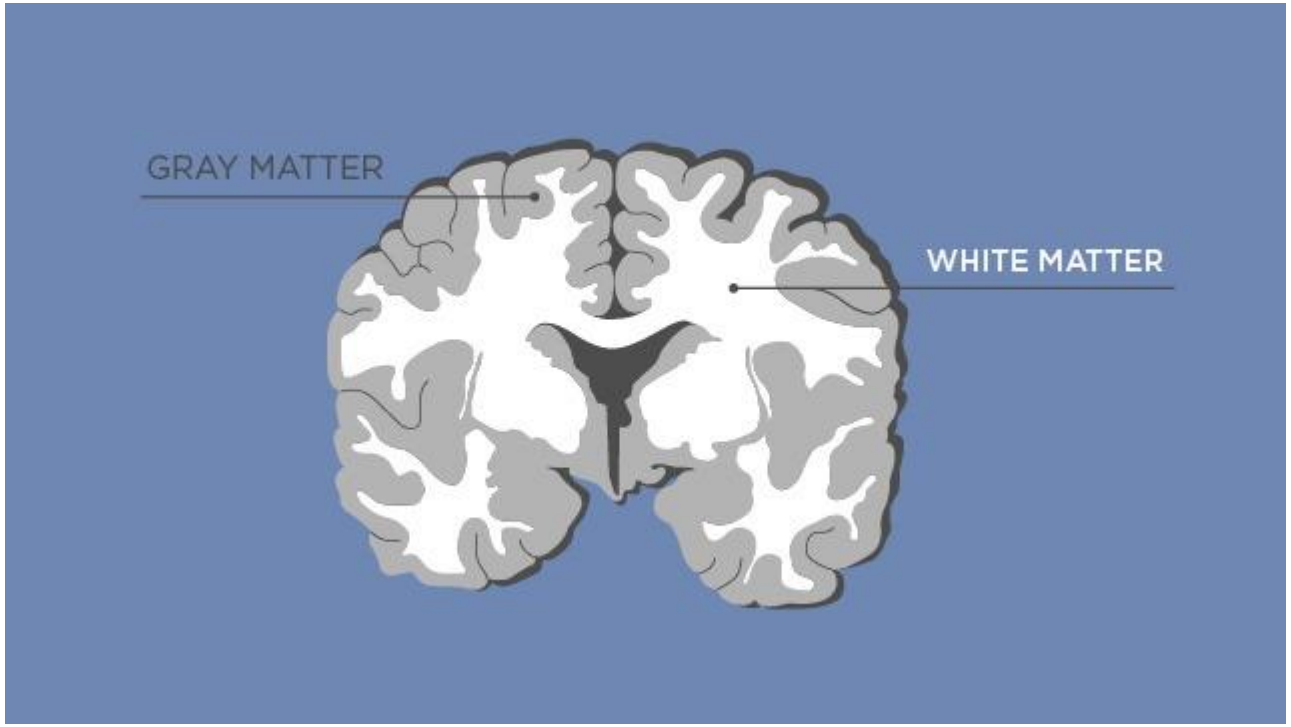
Not quite. Whilst the above division is physiologically accurate on a system level, there are a mix of cell types present in both gray and white matter.

Gray matter also contains:

- Axon tracts
- Glial cells
- Capillary blood vessels
- Neuropil – a mix of dendrites, unmyelinated axons, and glia

White matter also contains:

- Oligodendrocytes – glial cells which produce myelin
- Astrocytes



Where is it?

Gray Matter Neuronal cell bodies are abundant in the cerebrum, brain stem and cerebellum. This latter structure, which makes up just 10% of brain volume, contains more neurons than the rest of the brain put together. In the spinal cord, gray matter forms a "butterfly" structure. We can think of the cerebrum and cerebellum as the brain regions which have an external layer of gray matter

White matter

As previously mentioned, white matter is organized into tracts of axons. In the cerebrum and cerebellum, white matter is predominantly found in deeper areas – with gray matter coating the white matter - see figure 1. Other gray matter structures, like the basal ganglia, are embedded within this white matter core. The brain's fluid-filled ventricles are also found within the white matter.
In the spinal cord, things are largely reversed – the white matter is distributed around the central gray matter "butterfly".

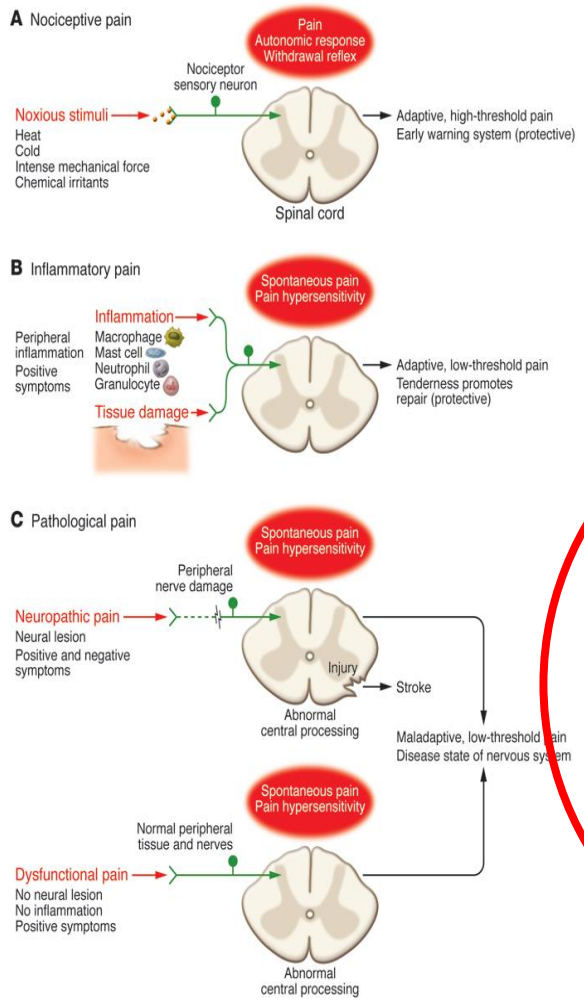
Why do brain imaging in orofacial pain? Review

- The available studies implied that the
- **anterior cingulate cortex plays a role in the emotional-affective component of pain**, as well as in **pain-related attention and anxiety**.
- The **somatosensory cortices may be involved in encoding spatial, temporal, and intensity aspects of noxious input.**
- The insula may **mediate both affective and sensory-discriminative aspects of the pain experience**.
- The thalamus **appears to be a multifunctional relay system**.
- The prefrontal cortex has been **implied in the pain-related attention processing; it does not have intensity encoding properties.**
- Chronic pain conditions were associated with increased activity in the somatosensory cortices, anterior cingulate cortex, and the prefrontal cortex, and with decreased activity in the thalamus.
- Few neuroimaging studies used experimental stimuli to the trigeminal system or included orofacial pain patients.
- Overall, the available data suggest that chronic (orofacial) pain states may be related to a dysfunctional brain network and may involve a compromised descending inhibitory control system. The somatosensory cortices, anterior cingulate cortex, thalamus, and prefrontal cortex may play a vital role in the pathophysiology of chronic pain and should be the main focus of future neuroimaging studies in chronic pain patients.

de Leeuw R, Albuquerque R, Okeson J, Carlson C. **The contribution of neuroimaging techniques to the understanding of supraspinal pain circuits: implications for orofacial pain**. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100(3):308-314. doi:10.1016/j.tripleo.2004.11.014

Definitions of pain

Chronic pain involves a complex interplay between peripheral and central sensitization, endogenous modulatory pathways, cortical processing and integration and numerous psychological, behavioural and social factors.



Healthy acute pain

Nociceptive
healthy feeling pain 'pain'

Nociceptive pain

Inflammatory pain
healthy short lived after insult

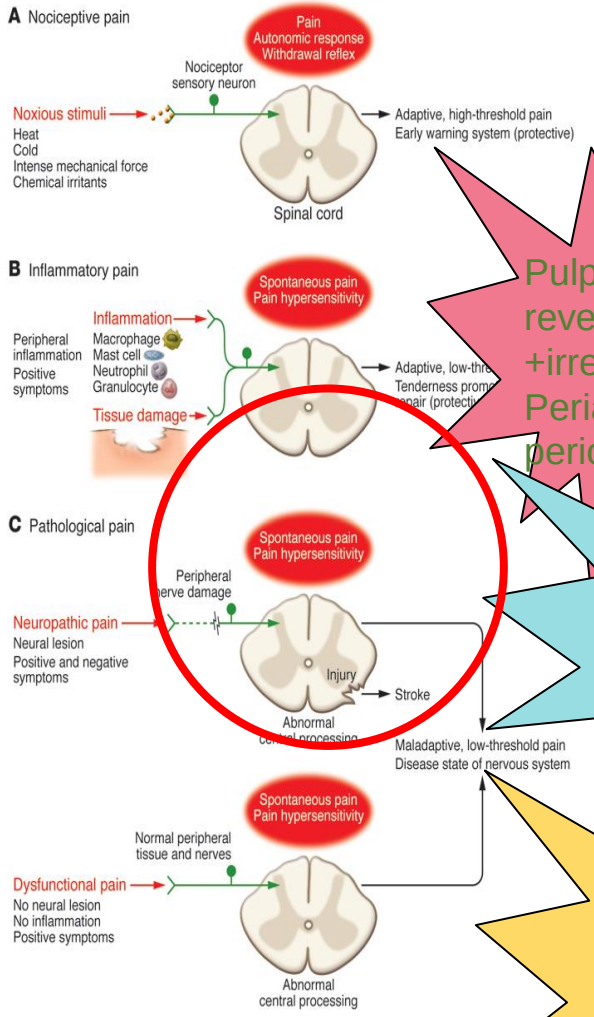
Chronic pain = disease of neuromatrix

Neuropathic pain
Associated with nerve lesion

Neuropathic pain

Dysfunctional or centralised pain
Unknown cause

Nociplastic pain



Dentine sensitivity

Pulpitis reversible +irreversible Periapical periodontitis

Trigeminal neuropathic pain
PTN, CPSP, 2y TN, BMS, PDAP/ PHN

Fibromyalgia
PIFP
Myofacial TMD

J Clin Invest. 2010 Nov 1; 120(11): 3742–3744. ***What is this thing called pain?*** *Clifford J. Woolf*

Reported MRI findings in chronic pain - Syst Rev Chronic low back pain (CLBP)

- **Results:** The search query returned 27 articles meeting the inclusion criteria. Methodological quality varied from poor to good. **A total of 10 studies evaluated structural gray matter changes.** There is conflicting evidence in global gray matter changes, with both increases and decreases shown in different studies.
- **Gray matter changes were demonstrated in specific brain regions with regional differences**.
- **Structural white matter changes were reported in five studies**. There is conflicting evidence in total white matter volume due to both increases and unchanged white matter.
- Functional organization during rest was evaluated in 10 studies. **CLBP patients showed increased activation in specific regions, together with a disrupted default mode network**.
- A total of six studies evaluated brain activity in response to a nociceptive stimulus -suggest that patients demonstrated increased activity in pain-related regions, and decreased activity in analgesic regions.
- **Conclusions:** Overall, there is moderate evidence for regional changes in gray and white matter, together with an altered functional connectivity during rest and increased activity in pain-related areas following painful stimulation, evidencing an upregulated pain matrix. More longitudinal research is needed to clarify the temporal relationship regarding pain and neuroplastic changes, and integration of different brain imaging techniques is warranted.

Kregel J, Meeus M, Malfliet A, et al. Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Semin Arthritis Rheum*. 2015;45(2):229-237. doi:10.1016/j.semarthrit.2015.05.002

Reported MRI findings in chronic pain

- **Patients and methods:** We recruited 56 chronic pain patients and 60 healthy controls to compare brain metabolic characteristics. The concentrations of glutamic acid (Glu), myo-inositol (Ins), *N*-acetylaspartate (NAA), Glu + glutamine (Glx), and creatine + phosphocreatine (total creatine [tCr]) in the anterior cingulate cortex of participants were measured using ^{1}H-MRS. We used age- and gender-adjusted general linear models and receiver-operating characteristic analyses for this investigation. Patients were also assessed using the Hospital Anxiety and Depression Scale (HADS) to reveal the existence of any mental health issues.
- **Results:** Our analysis indicates that pain patients have statistically significantly higher levels of Glu/tCr (p=0.039) and Glx/tCr (p<0.001) and lower levels of NAA/tCr than controls, although this did not reach statistical significance (p=0.052). Receiver-operating characteristic analysis performed on the combination of Glx/tCr, Ins/tCr, and NAA/tCr effectively discriminated chronic pain patients from healthy controls. Patients with higher HADS-Depression scores had increased Glx/rCr levels (p=0.015), and those with higher HADS-Anxiety scores had increased NAA/tCr levels (p=0.018).
- **Conclusion: Chronic pain patients have a different metabolite status in the anterior cingulate cortex to controls. Within the pain patient group, HADS scores had a positive relationship with NAA/tCr and Glx/tCr levels**. ^{1}H-MRS successfully detected metabolic changes in patients' brains in a noninvasive manner, revealing its potential as a superior diagnostic tool for pain patients.

Ito T, Tanaka-Mizuno S, Iwashita N, et al. Proton magnetic resonance spectroscopy assessment of metabolite status of the anterior cingulate cortex in chronic pain patients and healthy controls. *J Pain Res*. 2017;10:287-293. Published 2017 Jan 31. doi:10.2147/JPR.S123403

MRI experimental trigeminal pain

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International Classification of Orofacial Pain, 1st edition (ICOP)

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The Orofacial Pain Classification Committee

The committee is a collaborative group consisting of members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for Orofacial Pain and Related Disorders Methodology (INfORM), the American Academy of Orofacial Pain (AAOP) and the International Headache Society (IHS).

Co-chairmen

Rafael Benoliel, USA; Arne May, Germany; Peter Svensson, Denmark

1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures
2. Myofascial orofacial pain
3. Temporomandibular joint (TMJ) pain
4. Orofacial pain attributed to lesion or disease of the cranial nerves
5. Orofacial pains resembling presentations of primary headaches
6. Idiopathic orofacial pain

ICOP 2020

Experimental pain
Healthy cohort

- Nine healthy pain-free women (mean age 26.2 +/- 6.9 yrs) with a natural, regular menstrual cycle participated in the study. Whole-brain functional magnetic resonance imaging (fMRI) data were acquired for each participant on day 2 or 3 after the onset of menses using echo-planar imaging at 1.5T with near-isotropic spatial resolution and a temporal resolution of 4 s.
- Whole-brain fMRI with a Peltier thermode inside the head coil yielded a feasible imaging protocol with little disturbance from the thermode. **Painful thermal stimulation of the left trigeminal system** activated discrete brain regions within the **insula, cingulate gyrus, thalamus, inferior parietal lobe/postcentral gyrus, right middle and inferior frontal gyri, cuneus, precuneus, and precentral gyrus**.
- **Conclusion:** Painful stimulation of the trigeminal nerve resulted in activation of similar brain areas generally known for pain processing of painful peripheral stimulation.

Reny de Leeuw [1], C Ervin Davis, Romulo Albuquerque, Charles R Carlson, Anders H Andersen. **Brain Activity During Stimulation of the Trigeminal Nerve With Noxious Heat.** Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006 Dec;102(6):750-7. doi: 10.1016/j.tripleo.2005.12.018. Epub 2006 Jul 14.

TMD: Stim review

- A total of 622 papers, 25 studies met inclusion criteria for this review.
- Brain changes were found in pathways responsible for abnormal pain perception, including the classic trigemino-thalamo-cortical system and the lateral and medial pain systems.
- Dysfunction and maladaptive changes were also identified in the default mode network, the top-down antinociceptive periaqueductal gray-raphe magnus pathway, as well as the motor system.
- TMD patients displayed **altered brain activations in response to both innocuous and painful stimuli compared with healthy controls**.
- Additionally, evidence indicates that splint therapy can a
- lleviate TMD-related symptoms by inducing functional brain changes. In summary, MRI research provides important novel insights into the altered neural manifestations underlying chronic pain in TMD.

Yin Y, He S, Xu J, et al. The neuro-pathophysiology of temporomandibular disorders-related pain: a systematic review of structural and functional MRI studies. *J Headache Pain*. 2020;21(1):78. Published 2020 Jun 19. doi:10.1186/s10194-020-01131-4

ICOP Definitions
MRI and OFP Reviews

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ICOP 2020

COFP Syst Rev Structural Changes in the Brain TNP and TMD pain pts

- Qualitative meta-analysis was performed by examining the brain regions which showed significant changes in either brain functions (including the blood-oxygen-level dependent signal, cerebral blood flow and the magnetic resonance spectroscopy signal) or brain structure (including gray matter and white matter anatomy).
- We hypothesized that the neuroimaging findings would display a common pattern as well as distinct patterns of brain signature in the disorders.
- This major hypothesis was supported by the following findings:
  - (1) TNP and TMD patients showed consistent functional/structural changes in the thalamus and the primary somatosensory cortex, indicating the thalamocortical pathway as the major site of plasticity.
  - (2) The TNP patients showed more alterations at the thalamocortical pathway, and the two disorders showed distinct patterns of thalamic and insular connectivity.
  - Additionally, **functional and structural changes were frequently reported in the prefrontal cortex and the basal ganglia**, suggesting the role of cognitive modulation and reward processing in chronic orofacial pain.

Lin CS. Brain signature of chronic orofacial pain: a systematic review and meta-analysis on neuroimaging research of trigeminal neuropathic pain and temporomandibular joint disorders. *PLoS One*. 2014;9(4):e94300. Published 2014 Apr 23. doi:10.1371/journal.pone.0094300

Table 2. Demographic and clinical profiles of the included studies.

Source	Diagnosis	Patient					Control		
		F	M	Age	Severity (0–10)	Duration (Year)	F	M	Age
Trigeminal neuropathic pain									
Becerra 2006	TNP	5	1	48.8[1]	>4[3]	N/A	-		
Blatow 2009	TN	14	4	48–73	N/A	N/A	8	5	25–70
		6	4	44–76	N/A	N/A			
Scrivani 2010	TNP	4	2	48.3	>3–4[3]	N/A	-		
Gustin 2011	TNP[6]	17	4	54.7	3.5/3.4[4]	8.5	24	6	53.6
Moisset 2011	TNP-i	6	9	67.2	4–6	8.3			
Gustin 2012	TNP	12	3	50	3.8/3.6[4]	4.7	27	26	41
Henderson 2013	TNP	19	4	49.8	3.9	5.8	31	12	49.8
Obermann 2013	TN[7]	36	24	62	7.7	8.3	28	21	61.8
DeSouza 2013	TN-i	15	9	48.5	N/A	6.3	15	9	47.6
DeSouza 2014	TN	11	7	54.1	N/A	N/A	11	7	49.6
Temporomandibular joint disorder pain									
Jiang 2006	TMD-s	6	1	26.9	N/A	1–6(mo)	5	5	31
Younger 2010	TMD-m	15	0	38	4.3[1]	4.4	15	0	N/A[5]
Abrahamsen 2010	TMD-m	18	1	40.7	4.8	12.4	-		
Nebel 2010	TMD	13	0	28.7	2.4	N/A	12	0	28.8
Zhao 2011	TMD-s	12	4	33.7	≥5	N/A	7	7	23.7
Gerstner 2011	TMD-m	9	0	25.4[1]	2.2	2.5	9	0	24.8[2]
Gustin 2011	TMD	16	4	45.7	4.7/3.2[4]	11.5	25	6	46.8
Moayedi 2011	TMD-i	17	0	33.1	4.3/5.4[2]	9.8	17	0	32.2
Weissman-Fogel 2011	TMD	17	0	35.2[1]	4.2	9.3	17	0	N/A[5]
Gerstner 2012	TMD	10	1	25.8	3.8	0.5–7	10	1	24.8
Ichesco 2012	TMD	8	0	25.4	2.2	2.5	8	0	24.9
Moayedi 2012	TMD-i	17	0	33.1	4.3/5.4[2]	9.8	17	0	32.8
Salomons 2012	TMD	17	0	33.1	4.3/5.4[2]	9.8	17	0	32.2
Gustin 2012	TMD	13	4	44	4.2/4.5[4]	10.7	27	26	41

i, idiopathic; m, myofascial; s, synovitis; F, number of female participants; M, number of male participants; N/A, not available from the full text; TNP, trigeminal neuropathic pain; TMD, temporomandibular joint disorder.

[1]Mean age is calculated based on the data revealed in the original table; [2]average pain intensity/unpleasantness over the last month; [3]brushing-evoked/spontaneous pain; [4]pain a week before/pain before scanning; [5]age matched with the patient group; [6]including TN patients; [7]including TN patients with concomitant chronic facial pain.

Table 3. Experimental design and neuroimaging findings of the included studies: Trigeminal neuropathic pain.

Source	Experimental design					Major neuroimaging findings on the pain-related brain regions
	Modality	Stimuli	Site	Covariate	Signal	
Becerra 2006	fMRI	Mechanical	R V2 area	-	BOLD	AF>UF: THA/SI/R aINS/R ACC
		Thermal	(with allodynia)			
Blatow 2009	fMRI	Mechanical	R/L fingers and lips	-	BOLD	Pre-OP<HC (finger and lip): [B S1/B S2]
Scrivani 2010	fMRI	Mechanical Thermal	R/L V2 or V3 area	-	BOLD	Medication<Placebo (Thermal): R THA/R MCC/R S1
						Medication>Placebo (Mechanical): R INS/R S1
Gustin 2011	sMRI	-	-	age/sex/TBV	GMV	TNP>HC: CL pINS
						TNP<HC: B THA/IL S1/IL aINS
	fMRI	Mechanical	R bottom lips	-	BOLD	(for localizing ventroposterior THA)
	MRS	-	-	-	NAA/Cr	TNP<HC: [THA]
Moisset 2011	fMRI	Mechanical	AF/UF V2/V3 area, R hand	-	BOLD	AF>UF (evoked pain): L S1/R THA/L aINS/R ACC/L MCC
Gustin 2012	fMRI	Mechanical	IL lower lip/fingers	-	BOLD	Functional reorganization: [CL S1]
	DWI	-	-	age/sex	FA	TNP<HC: [CL S1]
	ASL	-	-	age/sex	CBF	TNP<HC: [CL S1]
Henderson 2013	sMRI	-	-	age/sex/TBV	GMV	TNP<HC: IL aINS/IL S1/B THA
	fMRI	Mechanical	lower lip	-	BOLD	(for localizing ventroposterior THA)
		Resting-state		-	FC	Negative correlation with thalamic GABA level
	ASL	-	-	age/sex	CBF	TNP<HC: [CL THA/CL S1]
	MRS	-	-		GABA	TNP<HC: [THA]
Obermann 2013	sMRI	-	-	age	GMV	TN<HC: L S1/B INS/B ACC/L THA/L S2
DeSouza 2013	sMRI	-	-	age	GMV	TN>HC: [IL THA]
				age	CT	TN>HC: [CL S1]
						TN<HC: [B ACC/IL pINS/IL aINS]
DeSouza 2014	DWI	-	-	-	FA	TN<HC: CC/cingulum/CL SLF/B pCOR

ACC, anterior cingulate cortex;
AF, affected side;
aINS, anterior insula;
CC, corpus callosum;
CL, contralateral;
COR, corona radiate;
CT, cortical thickness;
IL, ipsilateral; L, left side;
MCC, mid-cingulate cortex;
pINS, posterior insula;
R, right side;
S1, primary somatosensory cor
S2, secondary somatosensory c
SLF, superior longitudinal fascic
TBV, total brain volume;
THA, thalamus;
TNP, trigeminal neuropathic pai
UF, unaffected side;
V2, the maxillary nerve;
V3, the mandibular nerve

Table 4. Experimental design and neuroimaging findings of the included studies: Temporomandibular joint disorder pain.

Source	Experimental design					Major neuroimaging findings on the pain-related brain regions
	Modality	Stimuli	Site	Covariate	Signal	
Jiang 2006	fMRI	Clenching	N/A	-	BOLD	TMD (clenching > resting): R S1/L ACC
Younger 2010	sMRI	-	-	-	GMV	TMD>HC: R aINS/B THA
						TMD<HC: R S1
Abrahamsen	fMRI	Mechanical	L V3 area	-	BOLD	Stim > No stim: R pINS/R S1
2010		Hypnosis				Hyperalgesia>Hypoalgesia: L IPL
Nebel 2010	fMRI	Mechanical	R index finger	-	BOLD	TMD>HC: B THA/CL S1/B S2/CL INS/B ACC
						TMD<HC: CL INS/CL S1/CL S2
Zhao 2011	fMRI	Clenching	R molars	-	BOLD	TMD (CL clenching>resting): B ACC
Gerstner 2011	sMRI	-	-	age	GMV	TMD<HC: L ACC/R aINS
					WMV	TMD>HC: B STG
						TMD<HC: B ACC
Gustin 2011	sMRI	-	-	age/sex/TBV	GMV	TMD v. HC: n.s.
	fMRI	Mechanical	R bottom lips	-	BOLD	(for localizing ventroposterior THA)
	MRS	-	-	-	NAA/Cr	[THA]: TMD v. HC n.s.
Moayedi 2011	sMRI	-	-	age/TIV	GMV	[THA]: TMD v. HC n.s.
				age	CT	TMD>HC: [R S1]
Weissman- Fogel 2011	fMRI	Stroop task		-	BOLD	TMD>HC (cognitive interference): ACC/L S1
						TMD>HC (emotional interference): L ACC
Gerstner 2012	MRS	Pressure	R anterior temporalis	-	Glu/Gln/	TMD>HC (NAA/Cho): [L pINS]
			R thumb		NAA/Cho level	
Ichesco 2012	fMRI	Pressure	L anterior temporalis	age	FC	TMD>HC: L aINS-R ACC/R aINS-R ACC
		Resting-state				TMD>HC: L aINS-R ACC/L pINS-L PHG/R aINS-R THA
Moayedi 2012	DWI	-	-	age	FA	TMD<HC: [R THA/R S1](nearby)
					SC	TMD>HC: CC-L FP
Salomons 2012	sMRI	-	-	-	CT	Correlated with helplessness- positive: [L SMA], negative: [L MCC/ L PCC]
	DWI				FA	Correlated with helplessness-positive: [cingulum], negative: [CC/ CST]
Gustin 2012	fMRI	Mechanical	IL lower lip/fingers	age/sex	BOLD	No functional reorganization at CL S1
	DWI	-	-	-	FA	[CL SI]: TMD v. HC n.s.
	ASL	-	-	age/sex	CBF	[CL SI]: TMD v. HC n.s.

Table 7. The findings of meta-analysis on functional changes by pain-related regions: BOLD/CBF.

Source	Positive changes									Negative changes								
	THA	S1	S2	CC	INS	PFC	BG	MT	PAG	THA	S1	S2	CC	INS	PFC	BG	MT	PAG
Trigeminal neuropathic pain																		
Becerra 2006[1]	PM	2		a	a	mi	↑			↓					↓	↓	↓	
Blatow 2009											*	*						
Scrivani 2010[2]	PF	1		m		smio	↑				↓			a	i			
Moisset 2011[1]	PM	3b		am	a	i	↑	↑		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gustin 2012[3]											*							
Henderson 2013[3]										*	*							
Temporomandibular joint disorder pain																		
Jiang 2006		2		a		o	↑			N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Abrahamsen 2010		2			p	m				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nebel 2010	PF	1/3b		m	p			↑			2/1	↓		p				
Zhao 2011				a		mi				N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weissman-Fogel 2011[4]		1		a		sm	↑	↑		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ichesco 2012[5]	PF			a		s		↑		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

See Table 3 for the abbreviations of the brain regions. N/A: The study did not report the findings of negative changes. The asterisk denotes that the finding was derived from a ROI-specific analysis. Upward and downward arrows denote positive and negative changes, respectively (without showing the sub-region of the change). a, anterior; m, mid; p, posterior; i, inferior; s, superior; o, oribitofrontal; PM, connection with the premotor cortex; PF, connection with the prefrontal cortex.
[1]Affected side > Unaffected side; [2]the findings shown in 'Decreased activation' represents 'placebo>drug'; [3]baseline cerebral blood flow; [4]effect of cognitive and emotional interference; [5]increased resting-stated/pain-evoking functional connectivity between the insula and these regions.
doi:10.1371/journal.pone.0094300.t007

ACC, anterior cingulate cortex;
AF, affected side;
aINS, anterior insula;
BG basal ganglia
CC, corpus callosum;
CL, contralateral;
COR, corona radiate;
CT, cortical thickness;
IL, ipsilateral; L, left side;
MCC, mid-cingulate cortex;
MT
PAG paraaqueductal grey
PFC Prefrontal cortex
pINS, posterior insula;
R, right side;
S1, primary somatosensory corte
S2, secondary somatosensory co
SLF, superior longitudinal fasciculu
TBV, total brain volume;
THA, thalamus;
TNP, trigeminal neuropathic pain;
UF, unaffected side;
V2, the maxillary nerve;
V3, the mandibular nerve

Table 9. The findings of meta-analysis on structural changes by pain-related regions: Gray matter.

Source	Positive changes									Negative changes								
	THA	S1	S2	CC	INS	PFC	BG	MT	PAG	THA	S1	S2	CC	INS	PFC	BG	MT	PAG
Trigeminal neuropathic pain																		
Gustin 2011					p					PF	3b			a		↓		
Obermann 2013										TP	1	↓	a	a	dlo	↓		
DeSouza 2013[1]	PF[2]	2/1				pl	↑	↑	↑				a	p	o			
Temporomandibular joint disorder pain																		
Younger 2010	PF				a	i	↑				3b							
Gerstner 2011													m	a	i		↓	
Moayedi 2011[1]		3b*				vl*												

See Table 3 for the abbreviations of the brain regions. The asterisk denotes that the finding was derived from a ROI-specific analysis. Upward and downward arrows denote positive and negative changes, respectively (without showing the sub-region of the change). a, anterior; m, mid; p, posterior; i, inferior; oribitofrontal; vl, ventrolateral; dl, dorsolateral; PF, connection with the prefrontal cortex; TP, connection with the temporal cortex.

[1]cortical thickness; [2]gray matter volume.

doi:10.1371/journal.pone.0094300.t009

Chronic OFP and brain changes: Metanalysis

- Identifying convergent abnormalities across COFPs provides a basis for future hypothesis-driven research aimed at elucidating common CNS mechanisms.
- We perform three coordinate-based meta-analyses according to PRISMA guidelines to elucidate the central mechanisms of orofacial pain disorders. We computed our coordinate-based meta-analyses using GingerALE.
- Specifically, we investigated consistent patterns of:
  - (1) brain function to experimental orofacial pain in healthy subjects
    - **Results increased brain activity in bilateral thalami, posterior mid-cingulate cortices, and secondary somatosensory cortices, the right posterior parietal cortex extending to the orofacial region of the right primary somatosensory cortex and the right insula,**
    - **and decreased activity in the right somatomotor regions**.
  - (2) structural
    - **identified consistent higher grey matter volume/concentration in the right ventral thalamus and posterior putamen of COFP patients compared to healthy controls**.
  - (3) functional brain abnormalities in COFP
    - **increase in brain activity in the left medial and posterior thalamus and lesser activity in the left posterior insula in COFP, compared to healthy controls**.

  The convergence of thalamic abnormalities in both structure and function suggest a key role for this region in COFP pathophysiology

Ayoub LJ, Seminowicz DA, Moayedi M. A meta-analytic study of experimental and chronic orofacial pain excluding headache disorders. *Neuroimage Clin*. 2018;20:901-912. doi:10.1016/j.nicl.2018.09.018

Table 1
Summary of experimental orofacial pain studies.

Reference	N	W/M	Age (mean ± SD or range in years)	Imaging Modality	Stimulation		QS (/20)
					Modality	Body Part	
Lin et al., 2013a	16	9/7	27.37 ± 11.2	BOLD	Electrical	R Upper central incisor	16
Lin et al., 2013b	15	9/6	26.3 ± 11.2	BOLD	Electrical	R Upper incisor	16
Moulton et al., 2012	12	8/8	28.8 ± 7.7	BOLD	Thermal	R Maxilla	18
Brugger et al., 2011	21	8/13	20–44	BOLD	Electrical	bilat Maxillary canines/central incisors	18
Nash et al., 2010a	17/15/20	8/20	19–52	BOLD	Chemical/Mechanical	R Masseter/cutaneous/lip	16
Nash et al., 2010b	17/15	8/22	19–52	BOLD	Chemical	R Masseter/cutaneous	15
Obermann et al., 2009	11	3/8	23.3 ± 2.0	BOLD	Electrical	R Forehead (trigeminal nerve)	16
Iannilli et al., 2007	23	13/10	44/61[a]	BOLD	Chemical	R Nostril (trigeminal nerve)	15
Moulton et al., 2007	12/9	0/12	30 ± 7	BOLD	Chemical/Thermal	L Maxillary division (trigeminal nerve)	16
Brooks et al., 2005	14	11/3	28.9 ± 4.1	BOLD	Thermal	R Below lower lip	16
de Leeuw et al., 2006	9	9/0	26.2 ± 6.9	BOLD	Thermal	L Masseter	16
Kupers et al., 2004	10	4/6	21–25	rCBF	Chemical/Mechanical	R Masseter	16

Abbreviations: *bilat* bilateral, *BOLD* functional magnetic resonance blood-oxygen-level dependent imaging, *L* left, *M* men, *QS* quality score, *R* right, *rCBF* positron-emission tomography resting cerebral blood flow, *W* women.

[a] Only mean age for women and men (without standard deviation) is reported.

Table 2
Summary of VBM studies of COFP.

Reference	Patients				Healthy controls			Grey matter findings	QS (/20)
	COFP	N	W/M	Age (mean ± SD in years)	N	W/M	Age (mean ± SD in years)		
Tsai et al., 2018	CTN (right)	36	20/16	58.0 ± 7.7	19	15/4	55.6 ± 6 8.2	GMV	16
	CTN (left)	26	18/8	59.0 ± 6.6				GMV	
Wang et al., 2017a	CTN	38	22/16	55.87 ± 8.38	38	22/16	55.89 ± 8.06	GMV	17
Li et al., 2017	TN	28	13/15	45.86 ± 11.17	28	13/15	44.89 ± 7.67	GMV	19
Sinding et al., 2016	BMS	12	7/5	59.4 ± 12.1	13	10/3	59.0 ± 3.4	GMC	17
Khan et al., 2014	BMS	9	9/0	54.0 ± 7.7	9	9/0	56.0 ± 8.2	GMV	19
Obermann et al., 2013	TN	60	36/24	62.0 ± 13.2	49	18/21	61.8 ± 9	GMV	19
Gerstner et al., 2011	TMD	9	9/0	25.4 ± 2.5	9	9/0	24.8 ± 1.4	GMV	17
Gustin et al., 2011	PTN	21	17/4	54.7 ± 2.1	30	24/6	53.6 ± 3.2	GMV	19
Schmidt-Wilcke et al., 2010	PIFP	11	9/2	52.2 ± 8.9	11	9/2	51.3 ± 8.6	GMV	16
Younger et al., 2010	TMD	14	14/0	38.0 ± 13.7	15	15/0	age-matched	GMV	17

Abbreviations: *BMS* burning mouth syndrome, *COFP* chronic orofacial pain, *CTN* classic trigeminal neuralgia, *GMC* grey matter concentration, *GMV* grey matter volume, *M* men, *PIFP* persistent idiopathic facial pain, *PTN* painful trigeminal neuropathy, *QS* quality score, *TMD* temporomandibular disorder, *TN* trigeminal neuralgia, *VBM* voxel-based morphometry, *W* women.

Response to experimental stimuli

- The first key set of findings in this study are related to experimental orofacial pain in healthy participants were;
- Consistent activations along the ascending trigeminal pathway,including:thalamus,S1, S2, PPC, pMCC, insula, i.e. regions typically reported ir pain neuroimaging (DuerdenandAlbanese,2013).
- We also found **less activation in the hand region of S1 and M1.** The sensory-discriminative dimension (location,duration,andintensity) of pain is thought to be processed in somatosensory regions, including S1, S2 and the PPC (Oshiro et al. 2009). S1and S2 receive orofacial nociceptive input from VPM, among other regions (Davis and Moayedi, 2013; Willis and Westlund, 1997).
- Our findings are consistent with a previous quantitative meta-analysis of experimental dental pain, **which reported S1 activation of the orofacial region (Lin et al., 2014).**

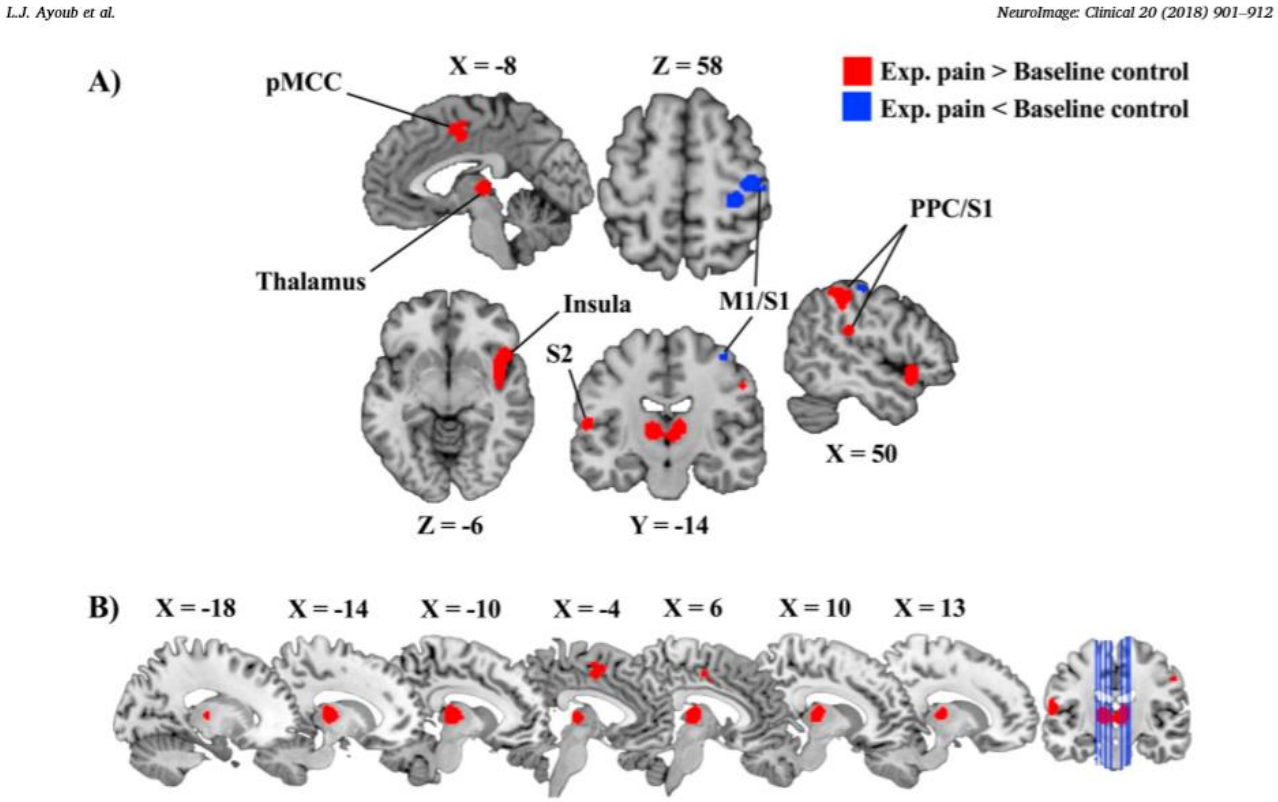


Fig. 3. (A) Significant ALE effects of functional MRI studies of healthy subjects during experimental orofacial pain. The functional MRI meta-analysis in healthy subjects identified significant ALE effects in bilateral thalami, bilateral posterior mid-cingulate cortex (pMCC) and bilateral secondary somatosensory cortices (S2), the right PPC extending to the primary somatosensory cortex (S1), the right insula and the primary motor cortex (M1) in healthy subjects during experimental pain (Exp.) (cluster-corrected $p < .05$ and cluster-forming threshold of $p < .005$). (B) Axial slices of thalamic activity in healthy subjects during experimental orofacial pain. Thalamic activation cluster from the meta-analysis of experimental studies (cluster-corrected $p < .05$, cluster-forming threshold $p < .005$).

Functional changes

- Consistent activation salience processing regions: pMC Candinsula(Seeleyetal.,2007).
- The pMCC finding is in line with an electrophysiological study in humans, which identified nociceptive responsive cells in this region (Hutchison et al., 1999). Additionally, evidence from tracing studies in non-human primates show that the spinothalamic tract projects to the MCC via the MD (Dumetal.,2016).
- **observed activation in a large region of the thalamus, including MD, in response to experimental orofacial nociceptive stimulation**. There are several roles ascribed to **the MCC in the context of pain**. For example, some suggest it is implicated in **encoding emotional value of pain**(Price,2000), others in **nocifensive behaviours** (Moayedi et al., 2015). Therefore, **this region could act as an interface between the cognitive and affective dimensions of pain** and the motor response (Perinietal.,2013;Shackmanetal.,2011).
- This **meta-analysis also identified activation in the insula, a region referred to as a multidimensional integrator for pain (Brooks and Tracey, 2007).** Several studies have suggested that the **posterior aspect of the insula encodes nociceptive stimulus properties (i.e. pain intensity)** (Craig, 2003; Moayedi, 2014; Montavont et al., 2015), **while the anterior insula is thought to be implicated in the cognitive-motivational dimension of pain** (Augustine,1996).These findings are helpful in understanding the regions activated by nociceptive stimulation of the orofacial region in healthy subjects.

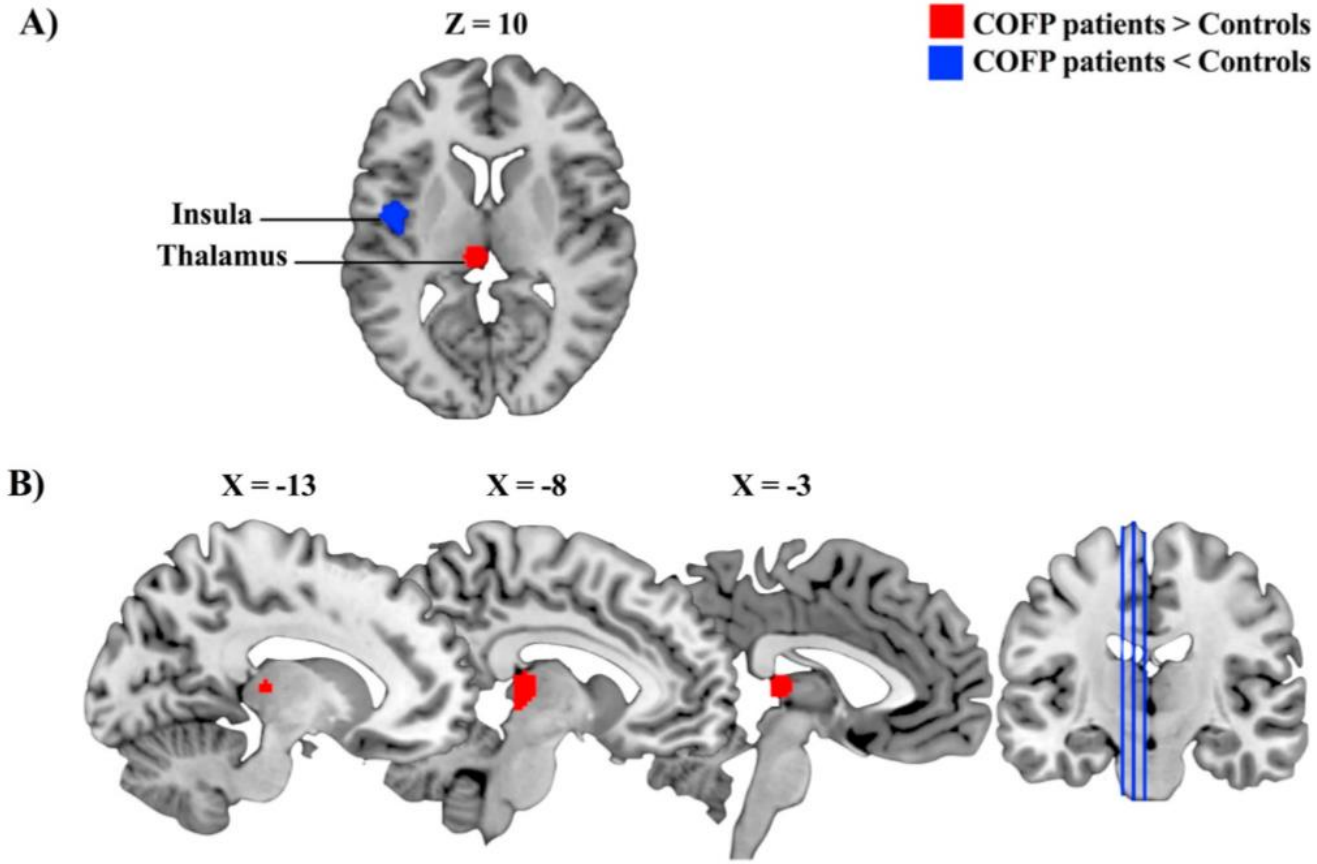


Fig. 5. (A) Significant ALE effects of functional COFP studies. The functional MRI COFP meta-analysis identified significant ALE effects in the left posterior thalamus and left posterior insula of COFP patients compared to healthy controls, significant at $p < .05$ (cluster-corrected, cluster-forming threshold of $p < .005$). (B) Axial slices of functional thalamic abnormalities in chronic orofacial pain patients. Thalamic cluster from the meta-analysis of functional MRI COFP studies (cluster-corrected $p < .05$, cluster-forming threshold $p < .005$).

Table 4
Summary of functional COFP studies.

Reference	Patients					Healthy controls			fMRI analysis method	Stimulation			QS (/20)
	COFP	N	W/M	Age (mean ± SD or S.E.M. in years)	Pain intensity (/10)	N	W/M	Age (mean ± SD or S.E.M. in years)		Rest/task	Pain intensity (/10)	Body Part	
Wang et al., 2017a	CTN	17	10/7	62.53 ± 7.41	6.12 ± 1.50	19	11/8	61.75 ± 6.02	fALFF	Rest			16
Yuan et al., 2018	ITN	23	9/14	59.6 ± 12.5	8.1 ± 1.6	23	11/12	63.1 ± 9.8	ReHo and fALFF	Rest			16
Alshelh et al., 2016	NP	17	14/3	50.6 ± 2.8	4.12 ± 2.61	44	33/11	45.9 ± 2.0	Task	Chemical	Healthy: 5	R Masseter	18
Wang et al., 2015	ITN	17	10/7	63.41 ± 7.25	6.12 ± 1.50	19	10/9	62.53 ± 7.41	ReHo	Rest			19
He et al., 2014	TMD	23	14/9	22.4 ± 3.6	47.3 ± 21.4[a]	20	11/9	23.1 ± 2.4	fALFF	Rest			17
Weissman-Fogel et al., 2011	TMD	17	17/0	35.2 ± 11.6	4.41 ± 1.77	17	17/0	34.0 ± 9.9	Task	Stroop task			19
Nebel et al., 2010	TMD	13	13/0	28.7 ± 7.6	2.4	12	12/0	28.8 ± 7.9	Task	Electrical	TMD[b]: 32.0 ± 15.4 Healthy[b]: 19.2 ± 12.5	R Index	18
Albuquerque et al., 2006	BMS	8	8/0	49.1 ± 10.1	5.6 ± 1.9	8	8/0	50.3 ± 12.3	Task	Thermal	BMS: 7.1 ± 1.4 Healthy: 5.8 ± 1.8	R Masseter	18

Abbreviations: *BMS* burning mouth syndrome, *COFP* chronic orofacial pain, *CTN* classical trigeminal neuralgia, *fi* idiopathic trigeminal neuralgia, *M* men, *NP* neuropathic pain, *QS* quality score, *R* right, *ReHo* regional homogen

[a] Graded Chronic Pain Scale of 52% of patients.

[b] Stimulus intensity: Labeled magnitude scale (0–100; 0 being "felt nothing" and 100 being "most intense vib

Table 5
Functional findings in COFP studies.

COFP	S1	Thal	Insula	Cingulate	PFC	Others	Reference
COFP > controls							
BMS				R aMCC		bilat PCu	Albuquerque et al., 2006
CTN			L pINS		L dlPFC/latFP	R Fus/TPJ, L TP/SPL/MTG, bilat Cereb	Wang et al., 2017a,b
ITN				R ACC	L dlPFC	R Cereb/PCu, L MTG/SFG	Yuan et al., 2018 (Reho)
						bilat Pu	Yuan et al., 2018 (fALFF)
		R Thal				R IPL/Fus, L SPL	Wang et al., 2015
PTN	L S1	L VP/MD/VL	L dpINS, R mid INS	L MCC	bilat dlPFC	R STn, L dlPons, bilat Cereb	Alshelh et al., 2016
TMD	L S1		R aINS/pINS	R aMCC, L PCC/RSC /sACC, bilat pACC	R dlPFC, bilat PMCv/mFP	R CN/STN, L Fus/IPL/ParaHc, bilat Amyg/SPL/MTG	Weissman-Fogel et al., 2011
	bilat S1	bilat Thal	L pINS	bilat aMCC		L Amyg/PT, bilat A1/S2	Nebel et al., 2010
Controls > COFP							
BMS	R S1	bilat MD			R dlPFC	bilat Cereb	Albuquerque et al., 2006
CTN					L dlPFC	R Fus/Cu/ITG, L Cereb/MOG, bilat PCu	Wang et al., 2017a,b
ITN			L pINS			R Cereb	Yuan et al., 2018 (Reho)
						R Cereb, L V2	Yuan et al., 2018 (fALFF)
						R ParaHc, L Amyg/Cereb	Wang et al., 2015
PTN					R dlPFC		Alshelh et al., 2016
TMD					R OFC, L latFP/SMA	L M1	He et al., 2014
					bilat dlPFC	R MTG	Weissman-Fogel et al., 2011
	bilat S1		L mid INS			L S2	Nebel et al., 2010

Abbreviations: *A1* primary auditory cortex, *aINS* anterior insular cortex, *aMCC* anterior mid-cingulate cortex, *Amyg* amygdala, *bilat* bilateral, *BMS* burning mouth syndrome, *Cereb* cerebellum, *CN* caudate nucleus, *CTN* classic trigeminal neuralgia, *COFP* chronic orofacial pain, *Cu* cuneus, *dlPFC* dorsolateral prefrontal cortex, *dlPons* dorsolateral pons, *dpINS* dorsal posterior insular cortex, *fALFF* fractional aptitude of low-frequency fluctuation, *Fus* fusiform gyrus, *GP* globus pallidus, *IPL* inferior parietal lobule, *ITG* inferior temporal gyrus, *ITN* idiopathic trigeminal neuralgia, *L* left, *latFP* lateral frontal polar, *M1* primary motor cortex, *MCC* mid-cingulate cortex, *MD* mediodorsal thalamus, *mFP* medial frontal pole, *mid lNS* mid insular cortex, *MOG* middle occipital gyrus, *MTG* middle temporal gyrus, *OFC* orbitofrontal cortex, *pACC* pregenual anterior cingulate cortex, *ParaHc* parahippocampal gyrus, *PCC* posterior cingulate cortex, *PCu* precuneus, *PFC* prefrontal cortex, *pINS* posterior insular cortex, *PMCv* ventral premotor cortex, *PT* planum temporale, *PTN* painful trigeminal neuropathy, *Pu* putamen, *R* right, *ReHo* regional homogeneity, *RSC* rostral splenial cortex, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *sACC* subgenual anterior cingulate cortex, *SFG* superior frontal gyrus, *SMA* supplementary motor area, *SPL* superior parietal lobule, *STn* spinal trigeminal nucleus, *STN* subthalamic nucleus, *SPL* superior parietal lobule, *TPJ* temporoparietal joint, *Thal* Thalamus, *TMD* temporomandibular disorder, *TP* temporal pole, *V2* secondary visual cortex, *VP* ventral posterior thalamus, *VL* ventral lateral thalamus.

Structural

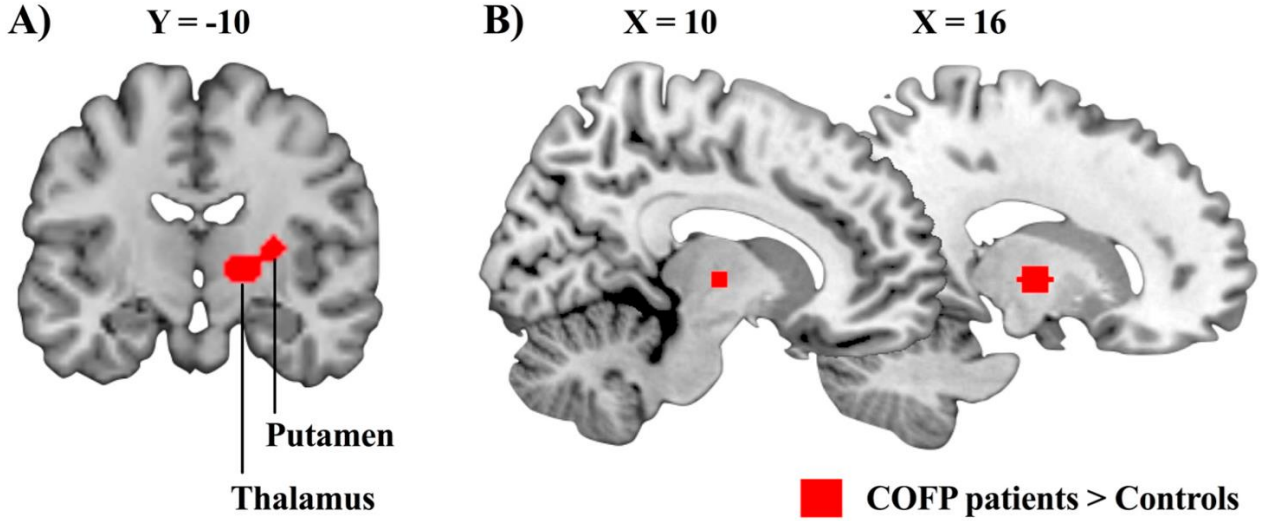


Fig. 4. (A) Significant ALE effects of structural COFP studies. The structural MRI (grey matter) COFP meta-analysis identifies structural GMV/GMC increase in the right thalamus and putamen in COFP patients compared to healthy subjects, significant at $p < .05$ (cluster-corrected, cluster-forming threshold of $p < .005$). (B) Axial slices of structural thalamic abnormalities in COFP patients. Representation of the thalamic activation cluster from the meta-analysis of structural chronic pain studies (cluster-corrected $p < .05$, cluster-forming threshold $p < .005$).

Table 3
Grey matter findings in COFP studies.

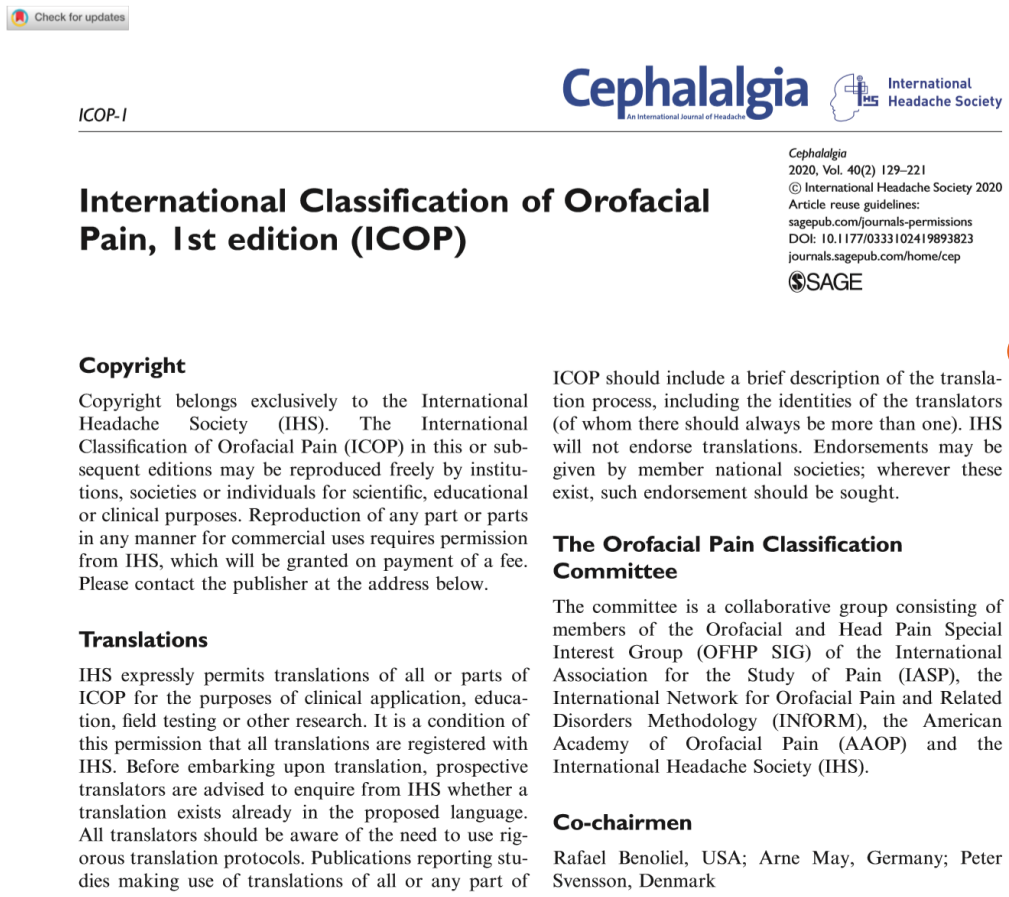
COFP	S1	Thal	Insula	Cingulate	PFC	Other	Reference
COFP > Controls							
BMS					R dlPFC	R PCL/Ti	Sinding et al., 2016
						R Hc	Khan et al., 2014
DYS	R S1					bilat MTG	Sinding et al., 2016
TMD		L VP, R VL	R aINS		R vlPFC	R GP/ML/Pu, bilat MCP/VMN/VMSN	Younger et al., 2010
CTN						R SPL	Wang et al., 2017a,b
PTN			R pINS				Gustin et al., 2011
Controls > COFP							
BMS				L PCC/sACC		L Cereb	Sinding et al., 2016
					L mPFC		Khan et al., 2014
DYS				R sACC/MCC	R pre-SMA, L mOFC		Sinding et al., 2016
PIFP	L S1		L pINS	bilat aMCC	L dlPFC/FP, R PMC	L STG, bilat M1	Schmidt-Wilcke et al., 2010
			R aINS	R PCC, L pACC	L vlPFC/dlPFC	R MTG/ParaHc/PCu, bilat STG	Gerstner et al., 2011
	R S1						Younger et al., 2010
CTN		R VP, L MD			bilat SMA	bilat Cereb, R NAc, L Hypo/IFG	Tsai et al., 2018 (right CTN)
		bilat pulvinar			L SMA	bilat Cereb, L VS/Pu/IFG	Tsai et al., 2018 (left CTN)
			R pINS	L ACC/MCC		R S2, bilat ITG, L STG/ M1/PMC	Wang et al., 2017a,b
TN				L sACC		R Cereb/Fus, L CN, bilat MTG/ParaHc/STG	Li et al., 2017
	L S1				R OFC		Obermann et al., 2013
PTN	L S1	bilat Thal	L aINS			R NAc, L Pu	Gustin et al., 2011

Abbreviations: *ACC* anterior cingulate cortex, *aINS* anterior insular cortex, *aMCC* anterior mid-cingulate cortex, *bilat* bilateral, *BMS* burning mouth syndrome, *Cereb* cerebellum, *CN* caudate nucleus, *COFP* chronic orofacial pain, *CTN* classic trigeminal neuralgia, *dlPFC* dorsolateral prefrontal cortex, *DYS* dysgeusia, *Fus* fusiform gyrus, *FP* frontal polar, *GP* globus pallidus, *Hc* hippocampus, *Hypo* hypothalamus, *IFG* inferior frontal gyrus, *ITG* inferior temporal gyrus, *L* left, *M1* primary motor cortex, *MCC* middle cingulate cortex, *MCP* middle cerebellar peduncle, *MD* mediodorsal thalamus, *ML* medial lemniscus, *mOFC* medial orbitofrontal cortex, *mPFC*

Activity

- COFP studies found consistently greater function – defined as greater activation in contrast BOLD studies, and **abnormal BOLD variability in resting-state fMRI – in the medial and posterior thalamus (MD, pulvinar)** and **lesser function in the posterior insula of patients compared to healthy controls** across COFP studies. This MD thalamus region also overlaps with the thalamic cluster we reported in our meta-analysis of orofacial stimulation in healthy subjects. Together, these findings highlight that COFP patients either have **increased nociceptive drive from the periphery or central sensitization**.
- Our results are inline with a qualitative meta-analysis of trigeminal disorders which reported **greater activation in the thalamus and S1 in trigeminal neuropathic pain(Lin, 2014), painful trigeminal neuralgia (PTN) (Becerra et al., 2006) and trigeminal neuralgia (Moisset et al., 2011).**
- Previous studies show consistent **thalamic hyperactivity** may result from persistent pain (Alshelh et al., 2016), increased thalamocortical oscillatory activity within the ascending pain pathway(Alshelhetal.,2016;Jietal.,2013) or metabolite changes (Wang et al., 2015).
- However, there has been growing evidence of **altered thalamic activity in PTN associated with significant reduction in gamma-aminobutyricacid (GABA) content**, an inhibitory neurotransmitter, and reduced cerebral blood flow in response to persistent pain (Gustin et al., 2011; Gustin et al., 2014; Henderson et al., 2013). Interestingly, a previous study evaluated altered thalamic neuronal activity in patients with neuropathic pain and reported blood flow increase in the early stages of the disease and decrease as the condition became chronic(Ushidaetal.,2010).
- We also report that COFP patients have **less function in the posterior insula**, a region typically observed in experimental pain studies, and inline with previous evidence of insular abnormality in TN (Yuanetal.,2018)and TMD (Nebeletal.,2010).
- We also **did not identify consistent differences across other brain regions that are observed in chronic pain, including S1, S2 and the mid- and anterior cingulate cortex** (Apkarian et al., 2011), although some of the studies did report activation in these regions. Indeed, mechanistic differences among neuropathic pain compared to non-neuropathic pain conditions have yet to be elucidated and more COFP studies would be required for that direct comparison.

MRI according to ICOP Definitions and Diagnostic Groups



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The Orofacial Pain Classification Committee

The committee is a collaborative group consisting of members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for Orofacial Pain and Related Disorders Methodology (INfORM), the American Academy of Orofacial Pain (AAOP) and the International Headache Society (IHS).

Co-chairmen

Rafael Benoliel, USA; Arne May, Germany; Peter Svensson, Denmark

1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures
2. Myofascial orofacial pain
3. Temporomandibular joint (TMJ) pain
4. Orofacial pain attributed to lesion or disease of the cranial nerves
5. Orofacial pains resembling presentations of primary headaches
6. Idiopathic orofacial pain

ICOP 2020

Chronic TMD generalised versus TMD localised: spectroscopic patterns

- The aim of this study was to compare **spectroscopic** metabolite concentration **patterns of N-Acetyl-aspartate (NAA), total creatine (tCr), choline (Cho), myo-inositol (MI), glutamate (Glu), and the combination of Glu and glutamine** in the posterior insula in patients with chronic generalized or regional chronic TMD pain (gTMD and rTMD, respectively) compared to healthy individuals (HI) in relation to clinical findings of TMD pain.
- Thirty-six female patients with chronic rTMD or gTMD with at least 3 months duration were included in the study. Ten healthy women were included as controls. All participants completed a questionnaire that comprised assessment of degrees of depression, anxiety, stress, catastrophizing, pain intensity, disability and locations.
- Pressure-pain threshold (PPT) over the masseter muscle and temporal summation to pressure stimuli were assessed with an algometer. underwent non-contrast enhanced MRI on a 3T MR scanner assessing T1-w and T2-w fluid attenuation inversion recovery. A single-voxel 1H-MRS examination using point-resolved spectroscopy was performed.
- Results
  - **significantly higher total creatine levels within the posterior insula in patients with rTMD or gTMD pain than in HI** (p=0.029).
  - **choline** was negatively correlated to maximum mouth opening capacity with or without pain (rs=-0.42, n=28, p=0.031 and rs=-0.48, n=28, p=0.034, respectively) as well as pressure-pain threshold on the hand (rs=-0.41, n=28, p=0.031).
  - **Glutamate was positively correlated to temporal summation to painful mechanical stimuli** (rs=0.42, n=26, p=0.034).

The present study found that increased concentrations of Cho and Glu in the posterior insular cortex is related to clinical characteristics of chronic TMD pain, including generalized pain

Harfeldt K, Alexander L, Lam J, et al. Spectroscopic differences in posterior insula in patients with chronic temporomandibular pain. *Scand J Pain*. 2018;18(3):351-361. doi:10.1515/sjpain-2017-0159

MR Spectroscopy: TMD vs controls

- Single-voxel proton magnetic resonance spectroscopy ((1)H-MRS) was used before and after pressure-pain testing to assess glutamate (Glu), glutamine (Gln), N-acetylaspartate (NAA), and choline (Cho) levels in the right and left posterior insulae of 11 individuals with myofascial TMD and 11 matched control individuals.
- Glu levels were significantly lower in all individuals after pain testing.
- Patients with TMD, **left-insular Glutamine** levels were related to reported pain, left posterior insular **N-acetylaspartate (NAA) and Choline levels were significantly higher at baseline than in control** and significantly correlated with pain-symptom duration, suggesting adaptive changes.

Gerstner GE, Gracely RH, Deebajah A, et al. Posterior insular molecular changes in myofascial pain. *J Dent Res*. 2012;91(5):485-490. doi:10.1177/0022034512443366

Yin et al. The Journal of Headache and Pain (2020) 21:78
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The Journal of Headache and Pain

REVIEW ARTICLE Open Access

The neuro-pathophysiology of temporomandibular disorders-related pain: a systematic review of structural and functional MRI studies

Yuanyuan Yin[1,2†], Shushu He[2†], Jingchen Xu[2], Wanfang You[1,3], Qian Li[1,3], Jingyi Long[1,3], Lekai Luo[1,3], Graham J. Kemp[4], John A. Sweeney[1,5], Fei Li[1,3*], Song Chen[2*] and Qiyong Gong[1,3]

Abstract

Chronic pain surrounding the temporomandibular joints and masticatory muscles is often the primary chief complaint of patients with temporomandibular disorders (TMD) seeking treatment. Yet, the neuro-pathophysiological basis underlying it remains to be clarified. Neuroimaging techniques have provided a deeper understanding of what happens to brain structure and function in TMD patients with chronic pain. Therefore, we performed a systematic review of magnetic resonance imaging (MRI) studies investigating structural and functional brain alterations in TMD patients to further unravel the neurobiological underpinnings of TMD-related pain. Online databases (PubMed, EMBASE, and Web of Science) were searched up to August 3, 2019, as complemented by a hand search in reference lists. A total of 622 papers were initially identified after duplicates removed and 25 studies met inclusion criteria for this review. Notably, the variations of MRI techniques used and study design among included studies preclude a meta-analysis and we discussed the findings qualitatively according to the specific neural system or network the brain regions were involved in. Brain changes were found in pathways responsible for abnormal pain perception, including the classic trigemino-thalamo-cortical system and the lateral and medial pain systems. Dysfunction and maladaptive changes were also identified in the default mode network, the top-down antinociceptive periaqueductal gray-raphe magnus pathway, as well as the motor system. TMD patients displayed altered brain activations in response to both innocuous and painful stimuli compared with healthy controls. Additionally, evidence indicates that splint therapy can alleviate TMD-related symptoms by inducing functional brain changes. In summary, MRI research provides important novel insights into the altered neural manifestations underlying chronic pain in TMD.

Keywords: Temporomandibular disorders, Chronic pain, Magnetic resonance imaging, Gray matter, White matter, Brain structure and function, Splint therapy Psychoradiology

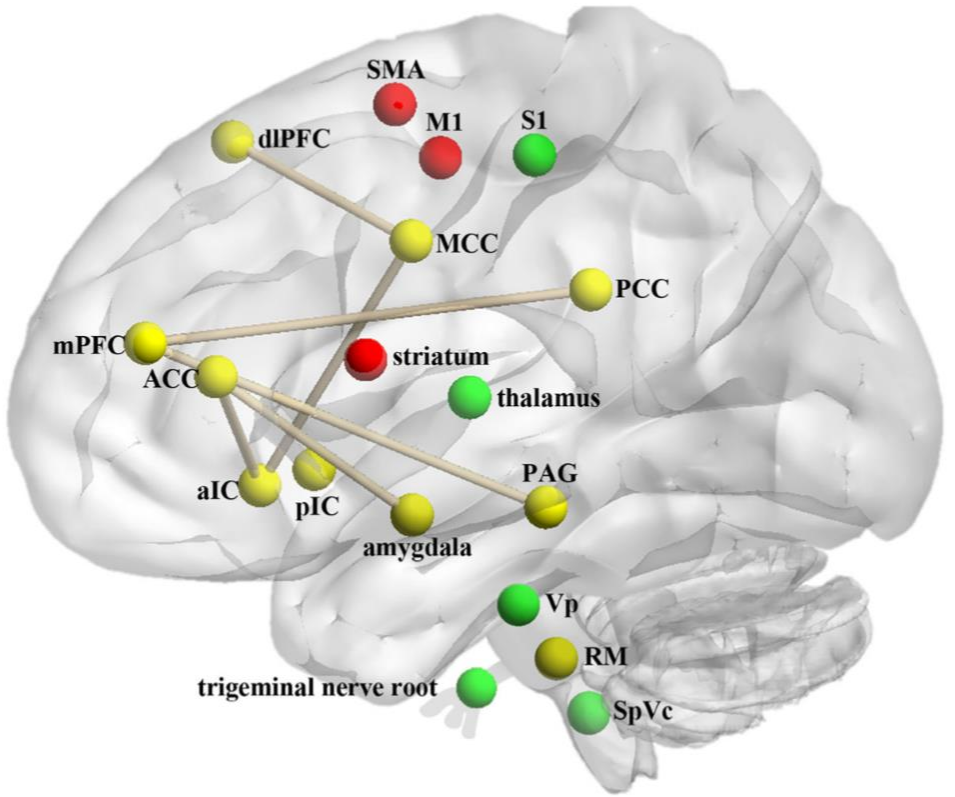

Fig. 2 Schematic representation of main brain regions with altered structure and function involved in TMD related-pain. Green balls represent the areas in the classic trigemino-thalamo-cortical system. Red balls are in the motor system. Yellow balls are the brain cortical regions implicated in pain perception and pain modulation. Brain regions with altered functional connectivity in TMD are connected with lines in khaki. ***Abbreviations:*** SMA, supplementary motor areas; dlPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; S1, primary somatosensory cortex; MCC, mid-cingulate cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; aIC, anterior insular cortex; pIC, posterior insular cortex; PAG, periaqueductal gray; Vp, trigeminal principal sensory nucleus; RM, raphe magnus; SpVc, spinal tract subnucleus caudalis

Conclusions

- There are structural and functional changes in the classic trigemino-thalamo-cortical system, including;
  - peripheral trigeminal nerve roots, brainstem (SpVc and Vp in particular)
  - thalamus, and S1, which provides support for a peripheral origin of TMD.
  - Specifically, the results of increased GMV in the thalamus were consistent, while whether there are alterations in S1 in TMD patients remains to be clarified.
- There are alterations in several cortical regions implicated in pain perception and pain modulation in TMD.
  - Neurochemical alterations are identified in the posterior insula.
  - The altered FCs among anterior insula, pgACC and MCC are correlated with pain intensity.
  - The dysfunctional DMN in TMD patients is characterized by reduced FC in mPFC-PCC/PCu and mPFC-PAG.
  - TMD related pain-attention interaction is mediated by reduced FC in aMCC-dlPFC and pgACC-amygdala.
  - Structural changes in the PAG-raphe magnus pathway may impair the efficiency of the endogenous pain inhibitory system of TMD patients.
- Regional functional brain changes in M1 and SMA, as well as increased GMV and decreased FC in the striatum, indicate the compensatory changes or maladaptive neuroplasticity of the motor system in patients with TMD pain.
- TMD patients displayed different brain activations in the fronto-insulo-thalamo-parietal network under both innocuous and painful stimulus compared with healthy controls, reflecting the involvement of aberrant central pain processing in TMD. Multivariate analysis techniques like SVM may help distinguish the subtypes of TMD patients, i.e. identify whose pain has a more peripheral or a central etiology,

ICOP Definitions and Diagnostic Groups

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The Orofacial Pain Classification Committee

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Co-chairmen

Rafael Benoliel, USA; Arne May, Germany; Peter Svensson, Denmark

1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures
2. Myofascial orofacial pain
3. Temporomandibular joint (TMJ) pain
4. Orofacial pain attributed to lesion or disease of the cranial nerves
5. Orofacial pains resembling presentations of primary headaches
6. Idiopathic orofacial pain

ICOP 2020

TN Gray matter and volume changes

We aimed to identify specific brain regions possibly associated with the development or maintenance of TN using magnetic resonance imaging (MRI) voxel-based morphometry (VBM).

Sixty patients with classical TN were compared to 49 healthy controls (18 with concomitant constant facial pain), a condition previously described as a predictor of worse treatment outcome.

Results

Gray matter (GM) volume reduction in TN patients compared to healthy controls in the **primary somatosensory and orbitofrontal cortices, as well as the in the secondary somatosensory cortex, thalamus, insula, anterior cingulate cortex (ACC), cerebellum, and dorsolateral prefrontal cortex**.

GM volume decrease within the ACC, parahippocampus, and temporal lobe correlated with increasing disease duration in TN.

There were no differences comparing patients with and without concomitant constant facial pain.

The ACC, parahippocampus and temporal lobe volume reduction in parallel with disease duration may point to a pivotal role of these structures in chronic pain.

Obermann M, Rodriguez-Raecke R, Naegel S, et al. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. *Neuroimage*. 2013;74:352-358. doi:10.1016/j.neuroimage.2013.02.029

GM in TN vs controls

- 28 TN patients (thirteen females; mean age, 45.86 years ±11.17)
- 28 healthy controls (HC; thirteen females; mean age, 44.89 years ±7.67) were included.
- Using voxel-based morphometry (VBM)
- TN group showed significantly decreased gray matter volume in the bilateral superior/middle temporal gyrus (STG/MTG), bilateral parahippocampus, left anterior cingulate cortex (ACC), caudate nucleus, right fusiform gyrus, and right cerebellum compared with the HC.
- In addition, we found that the gray matter volume in the bilateral STG/MTG was negatively correlated with the duration of TN. These results provide compelling evidence for gray matter abnormalities in TN and suggest that the duration of TN may be a critical factor associated with brain alterations.

Li M, Yan J, Li S, et al. Reduced volume of gray matter in patients with trigeminal neuralgia. *Brain Imaging Behav*. 2017;11(2):486-492. Brain Imaging Behav

GM and Cortical thickness in Idiopathic TN

- 24 patients with right-sided TN and 24 healthy control participants.
- TN patients had increased GM volume in the sensory thalamus, amygdala, periaqueductal gray, and basal ganglia (putamen, caudate, nucleus accumbens) compared to healthy controls.
- The patients also had greater cortical thickness in the contralateral primary somatosensory cortex and frontal pole compared to controls.
- In contrast, patients had thinner cortex in the pregenual anterior cingulate cortex, the insula and the orbitofrontal cortex. No relationship was observed between GM abnormalities and TN pain duration.

Desouza DD, Moayedi M, Chen DQ, Davis KD, Hodaie M. Sensorimotor and Pain Modulation Brain Abnormalities in Trigeminal Neuralgia: A Paroxysmal, Sensory-Triggered Neuropathic Pain. *PLoS One*. 2013;8(6):e66340. Published 2013 Jun 18. doi:10.1371/journal.pone.0066340

TN metanalysis of consistent and replicable Gray Matter volume abnormalities using effect-size signed differential mapping (ES-SDM).

- And meta-regression to explore the potential effects of clinical characteristics on GM volume alterations in patients with TN.
- 13 studies with 15 datasets, representing 407 TN patients and 376 healthy individuals
- TN patients had GM volume abnormalities mainly in the basal ganglia, including the putamen, nucleus accumbens (NAc), caudate nucleus and amygdala, as well as the cingulate cortex (CC), thalamus, insula and superior temporal gyrus (STG).
- The meta-regression analysis showed that **verbal rating scale (VRS) scores were negatively correlated with decreased GM volume** in the left striatum and that illness duration was negatively correlated with decreased GM volume in the left STG and left insula..

Tang Y, Wang M, Zheng T, et al. Grey matter volume alterations in trigeminal neuralgia: A systematic review and meta-analysis of voxel-based morphometry studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;98:109821. doi:10.1016/j.pnpbp.2019.109821

TN GM and connectivity

- 62 TN patients Voxel-based morphometry was used to analyze the change of gray matter volume using resting-state functional imaging was used to analyze the connectivity between brain regions.
- Findings
  - Gray matter volume reduction in components of the prefrontal cortex, precentral gyrus, cerebellar tonsil, thalamus, hypothalamus, and nucleus accumbens among right TN patient and in the inferior frontal gyrus, precentral gyrus, cerebellum, thalamus, ventral striatum, and putamen among left TN patients.
  - The connections between the right superior frontal gyrus and right middle frontal gyrus were lower in right TN patients.
  - The connection between the left precentral gyrus and the left superior frontal gyrus was lower while the connection between bilateral thalamus was higher in left TN patients.
  - The changes of volume in bilateral thalamus of right TN patients and left ventral striatum of left TN patients,
  - The connectivity between bilateral thalamus of left TN patients were moderately correlated with pain duration.
  - These findings suggest that brain regions such as the thalamus may not only be involved in processing of pain stimuli but also be important for the development of TN.
  - The left hemisphere may be dominant in processing and modulation of TN pain signal. Chronification of TN induces volume changes in brain regions which are associated with emotional or cognitive modulation of pain.

Hum Brain Mapp. 2018 Feb;39(2):609-621. doi: 10.1002/hbm.23696. Epub 2017 Nov 6. **Altered Structure and Functional Connection in Patients With Classical Trigeminal Neuralgia.** Yuan-Hsiung Tsai [1], Rui Yuan [2], Dharni Patel [2], Subhashini Chandrasekaran [2], Hsu-Huei Weng [1], Jen-Tsung Yang [3], Ching-Po Lin [4], Bharat B Biswal [2]

TN vs Controls Assessment of neuronal alterations using voxel-based morphometry (VBM), diffuse tensor imaging (DTI), and resting-state functional connectivity

- 38 patients with CTN and 38 matched healthy controls.
- CTN displayed gray matter volume (GMV) reductions in the anterior-cingulate cortex (ACC) and mid-cingulate cortex, insula, secondary somatosensory cortex (S2), primary motor cortex (M1), premotor area, and several regions in the temporal lobe.
- For DTI analysis, patients compared with controls had increased mean diffusivity (MD) and decreased fractional anisotropy (FA) in the corpus callosum and the bilateral corona radiata, and increased mean diffusivity with no fractional anisotropy changes across the bilateral superior longitudinal fasciculus, the internal and external capsule, the thalamus and brainstem.
- CTN had enhanced functional connectivity between the right insula/S2 and ACC, medial prefrontal cortex, posterior cingulate cortex, and bilateral dorsolateral prefrontal cortex.
- Gray matter volume of left inferior temporal gyrus negatively correlated with current pain intensity and disease duration in patients, and connectivity of the right insula/S2-ACC was negatively correlated with pain intensity, depression, and anxiety ratings.

Yuan Wang [1], Dong-Yuan Cao, Bethany Remeniuk, Samuel Krimmel, David A Seminowicz, Ming Zhang **Altered Brain Structure and Function Associated With Sensory and Affective Components of Classic Trigeminal Neuralgia.** Pain 2017 Aug;158(8):1561-1570. doi: 10.1097/j.pain.0000000000000951.

Meta-analysis of structural and functional changes in TN/TNP

- 322 papers were identified, 11 of which could be included. Eight papers included 279 subjects - structural changes and four papers included 102 subjects, -functional
- ALE analysis showed that in TN/TNP
  - Grey matter decreases are found in the thalamus, (anterior) cingulate gyrus, bilateral striatum, the superior-, middle- and transverse temporal gyrus, subcallosal gyrus, the bilateral insular cortex, the pre- and postcental gyrus, the middle frontal gyrus bilaterally and the anterior cerebellar lobe.
  - Grey matter increases were seen in the periaqueductal grey (PAG). Increased resting state functional organization was found within the bilateral middle- and superior frontal gyri, the (posterior) cingulate cortex and the thalamus/pulvinar.

Henssen D, Dijk J, Knepflé R, Sieffers M, Winter A, Vissers K. Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: A systematic review and meta-analysis. *Neuroimage Clin*. 2019;24:102039. doi:10.1016/j.nicl.2019.102039

NeuroImage: Clinical 24 (2019) 102039

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Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: A systematic review and meta-analysis

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ABSTRACT

Background: Various studies reported changes in grey matter volumes and modifications in functional connectivity of cortical and subcortical structures in patients suffering from trigeminal neuralgia (TN) and trigeminal neuropathic pain (TNP). This study meta-analyzed the concordant structural and functional changes in foci and provide further understanding of the anatomy and biology of TN/TNP.

Methods: Relevant articles on magnetic resonance imaging (MRI) and functional MRI in TN/TNP, published before August 2018, were searched for on PubMed and Embase. Following exclusion of unsuitable studies, a meta-analysis was performed using activation likelihood estimation (ALE).

Results: In total, 322 paper were identified, 11 of which could be included based on the predefined inclusion and exclusion criteria. Eight papers, totaling 279 subjects, discussing structural changes and four papers, totaling 102 subjects, discussing functional changes were included (i.e., one paper investigated both structural and functional alterations). ALE analysis showed that in TN/TNP, grey matter decreases are found in the thalamus, (anterior) cingulate gyrus, bilateral striatum, the superior-, middle- and transverse temporal gyrus, subcallosal gyrus, the bilateral insular cortex, the pre- and postcentral gyrus, the middle frontal gyrus bilaterally and the anterior cerebellar lobe. Grey matter increases were seen in the periaqueductal grey (PAG). Increased resting state functional organization was found within the bilateral middle- and superior frontal gyri, the (posterior) cingulate cortex and the thalamus/pulvinar.

Conclusions: Structural and functional changes meta-analyzed in this paper may contribute to elucidating the central pathophysiological mechanisms involved in TN/TNP. These results may be used as biomarkers to predict the response to medication and, ideally, in the future to offer personalized treatments.

1. Introduction

Painful lesions of the trigeminal nerve or pain attributed to a lesion or disease of the trigeminal nerve forms one group of facial pain disorders in the International Classification of Headache Disorders III-beta (ICHD3-beta) (Olesen, 2018). This group is made up predominantly by 1) trigeminal neuralgia (TN) and 2) trigeminal neuropathic pain (TNP). TN is defined as recurrent, electric, shock-like (neuropathic) pain in one or more divisions of the trigeminal nerve. Generally, a subdivision into primary or classical TN and secondary or symptomatic TN can be made. In classical TN, pain can be paroxysmal or concomitant persistent. Symptomatic TN concerns TN-like pain associated to pathology of the central nervous system (i.e., multiple sclerosis lesions or space-occupying lesions) (Olesen, 2018). TN is frequently misdiagnosed and underdiagnosed, leading to incidence rates ranging from 4.3 to 27 new cases per 100,000 people per year (Katusic et al., 1990; MacDonald et al., 2000; Mueller et al., 2011). In 1934, Dandy already proposed that in at least 30% of the TN patients, a microvascular

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The authors declare that they have had no conflict of interest in the conduction of this research
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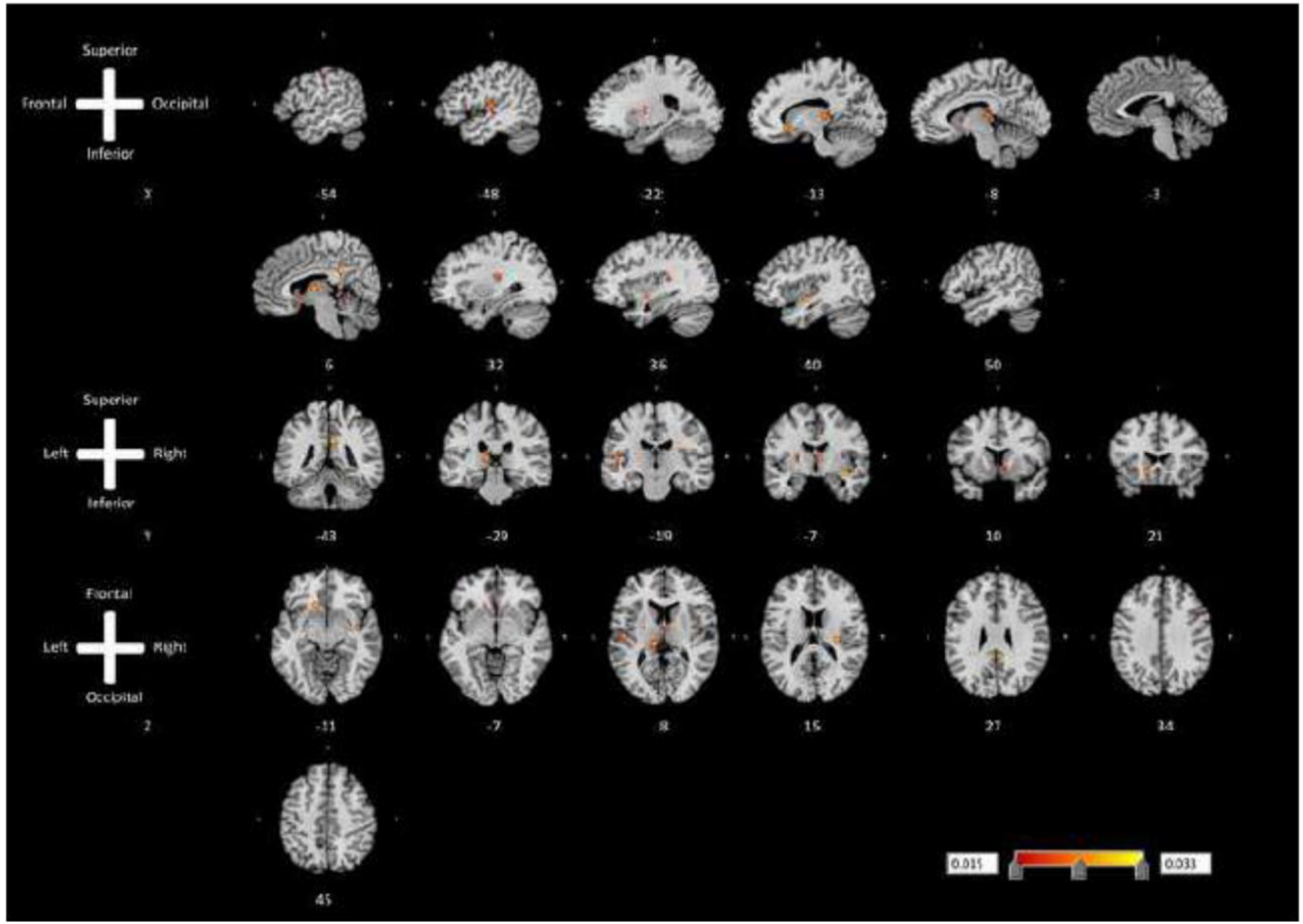

Fig. 2. ALE map investigating differences in grey matter volume between patients suffering from TN/TNP and healthy controls
This image summarizes the results of all the papers involved in this meta-analysis on grey matter volume changes. Red color shows grey matter decreases (ALE maps were computed at a threshold of $p < 0.001$).

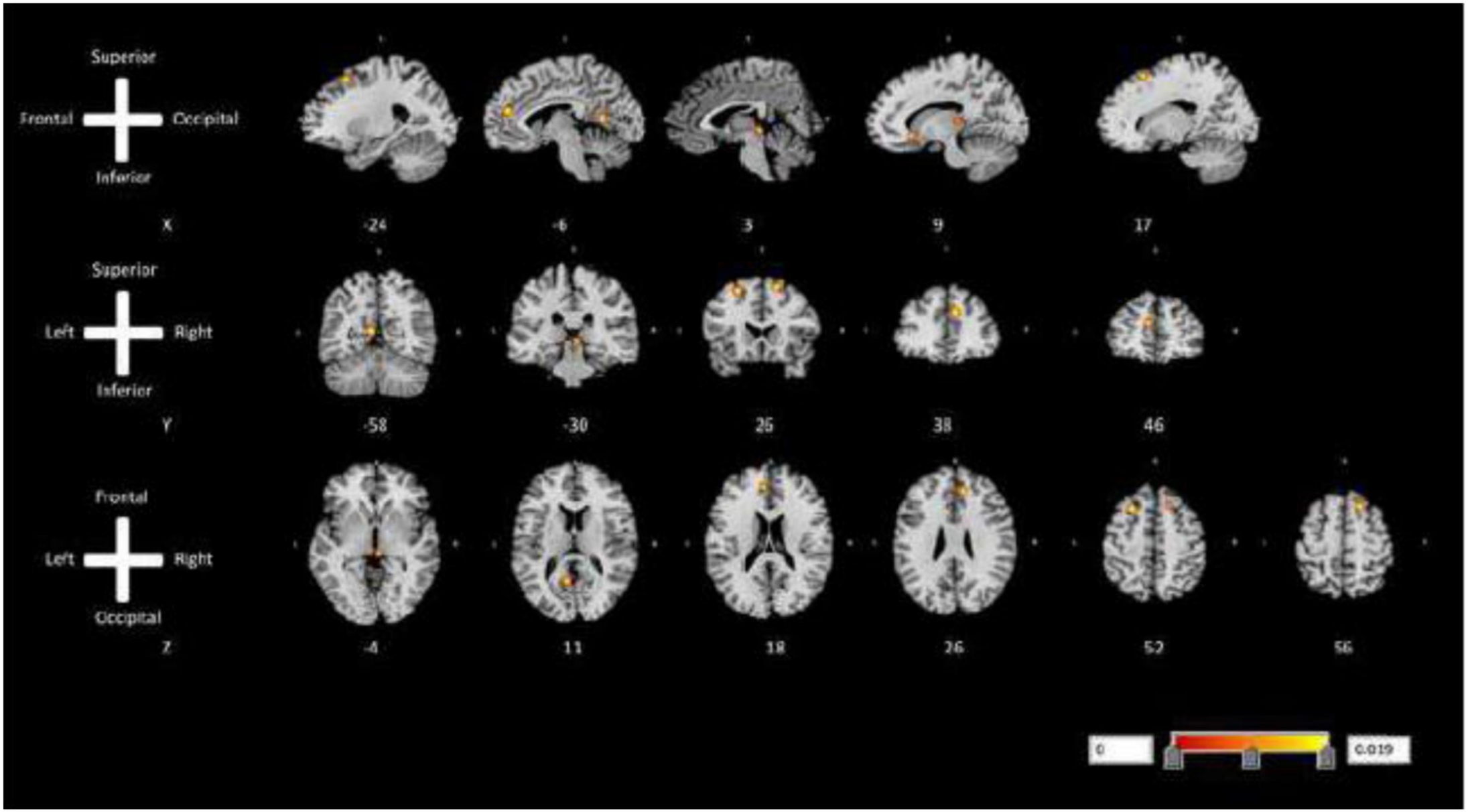

Fig. 3. ALE map investigating differences in functional MRI functional connectivity patterns between patients suffering from TN/TNP and healthy controls
This image summarizes the results of all the papers involved in this meta-analysis on grey matter volume changes. Red color shows increased resting state functional organization (ALE maps were computed at a threshold of $p < 0.001$).

Systematic review VBM Neuropathic pain VS Controls

- January 2000 to March 2014 VBM studies on neuropathic pain compared with healthy controls
- Ten studies comprising 240 patients with neuropathic pain and 263 healthy subjects were systematically included in the present study.
- Compared to healthy controls, the patients showed consistent decreased GM in bilateral anterior insula and thalamus, right superior frontal gyrus and left postcentral gyrus, and increased GM in right medial frontal gyrus and right posterior insula.

Pan PL, Zhong JG, Shang HF, et al. Quantitative meta-analysis of grey matter anomalies in neuropathic pain. *Eur J Pain*. 2015;19(9):1224-1231. doi:10.1002/ejp.670

- The aim of this study was to determine the possible functional and molecular mechanisms taking place in several cortical areas in neuropathic pain, using a mouse model of ION ligation.
- Functional intrinsic imaging of the primary sensory cortex barrel field (S1BF) has allowed us to demonstrate a decreased evoked response to whisker stimulation that is due to an enhanced baseline neuronal activity.

PLOS ONE

RESEARCH ARTICLE

Orofacial Neuropathic Pain Leads to a Hyporesponsive Barrel Cortex with Enhanced Structural Synaptic Plasticity

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Abstract

Chronic pain is a long-lasting debilitating condition that is particularly difficult to treat due to the lack of identified underlying mechanisms. Although several key contributing processes have been described at the level of the spinal cord, very few studies have investigated the supraspinal mechanisms underlying chronic pain. Using a combination of approaches (cortical intrinsic imaging, immunohistochemical and behavioural analysis), our study aimed to decipher the nature of functional and structural changes in a mouse model of orofacial neuropathic pain, focusing on cortical areas involved in various pain components. Our results show that chronic neuropathic orofacial pain is associated with decreased haemodynamic responsiveness to whisker stimulation in the barrel field cortex. This reduced functional activation is likely due to the increased basal neuronal activity (measured indirectly using cFos and phospho-ERK immunoreactivity) observed in several cortical areas, including the contralateral barrel field, motor and cingulate cortices. In the same animals, immunohistochemical analysis of markers for active pre- or postsynaptic elements (Piccolo and phospho-Cofilin, respectively) revealed an increased immunofluorescence in deep cortical layers of the contralateral barrel field, motor and cingulate cortices. These results suggest that long-lasting orofacial neuropathic pain is associated with exacerbated neuronal activity and synaptic plasticity at the cortical level.

ICOP Definitions and Diagnostic Groups
MR Neurrography

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ICOP 2020

MR neurography and trigeminal system

- Abstract
- **Objective:** This tertiary care experience examines the utility of magnetic resonance neurography (MRN) in the management of peripheral trigeminal neuropathies.
- **Materials and methods:** Seventeen patients with clinically suspected peripheral trigeminal neuropathies (inferior alveolar nerve and lingual nerve) were imaged uniformly with 1.5-T examinations. MRN results were correlated with clinical and surgical findings in operated patients and the impact on clinical management was assessed.
- **Results:** Clinical findings included pain (14/17), sensory changes (15/17), motor changes (2/17) and palpable masses (3/17). Inciting events included prior dental surgery (12/17), trauma (1/17) and idiopathic incidents (4/17). Non-affected side nerves and trigeminal nerves in the intracranial and skull base course were normal in all cases. Final diagnoses on affected sides were nerve inflammation (4/17), neuroma in continuity (2/17), LN transection (1/17), scar entrapment (3/17), infectious granuloma (1/17), low-grade injuries (3/17) and no abnormality (3/17). Associated submandibular gland and sublingual gland oedema-like changes were seen in 3/17 cases because of parasympathetic effects. Moderate-to-excellent MRN-surgical correlation was seen in operated (8/17) patients, and neuroma and nerve transection were prospectively identified in all cases.
- **Conclusion:** MRN is useful for the diagnostic work-up of suspected peripheral trigeminal neuropathy patients with significant impact on clinical management and moderate-to-excellent correlation with intra-operative findings.
- **Key points:** • MRN substantially impacts diagnostic thinking and management in peripheral trigeminal neuropathy. • MRN has moderate-to-excellent correlation with intra-operative findings. • MRN should be considered in pre-surgical planning of peripheral trigeminal neuropathy subjects.

- **Keywords:** Inferior alveolar nerve; Lingual nerve; MRN; Neurography; Trigeminal nerve.

Eur Radiol 2016 Oct;26(10):3392-400. doi: 10.1007/s00330-015-4182-5. Epub 2016 Jan 21. Magnetic Resonance Neurography in the Management of Peripheral Trigeminal Neuropathy: Experience in a Tertiary Care Centre Brian Cox [1], John R Zuniga [2], Neeraj Panchal [3], Jonathan Cheng [4], Avneesh Chhabra [5]

MR Neurography PTNP

- **Background and purpose:** Clinical neurosensory testing is an imperfect reference standard to evaluate molar tooth extraction related peripheral trigeminal neuropathy. The purpose was to evaluate the diagnostic accuracy of MR neurography in this domain and correlation with neurosensory testing and surgery.
- **Materials and methods:** In this retrospective study, nerve caliber, T2 signal intensity ratio, and contrast-to-noise ratios were recorded by 2 observers using MR neurography for bilateral branches of the peripheral trigeminal nerve, the inferior alveolar and lingual nerves. Patient demographics and correlation of the MR neurography findings with the Sunderland classification of nerve injury and intraoperative findings of surgical patients were obtained.
- **Results:** Among 42 patients, the mean ± SD age for case and control patients were 35.8 ± 10.2 years and 43.2 ± 11.5 years, respectively, with male-to-female ratios of 1:1.4 and 1:5, respectively. Case subjects (peripheral trigeminal neuropathy or injury) had significantly larger differences in nerve thickness, T2 signal intensity ratio, and contrast-to-noise ratios than control patients for the inferior alveolar nerve and lingual nerve (P = .01 and .0001, .012 and .005, and .01 and .01, respectively). Receiver operating characteristic analysis showed a significant association among differences in nerve thickness, T2 signal intensity ratio, and contrast-to-noise ratios and nerve injury (area under the curve, 0.83-0.84 for the inferior alveolar nerve and 0.77-0.78 for the lingual nerve). Interobserver agreement was good for the inferior alveolar nerve (intraclass correlation coefficient, 0.70-0.79) and good to excellent for the lingual nerve (intraclass correlation coefficient, 0.75-0.85). MR neurography correlations with respect to clinical neurosensory testing and surgical classifications were moderate to good. Pearson correlation coefficients of 0.68 and 0.81 and κ of 0.60 and 0.77 were observed for differences in nerve thickness.
- **Conclusions:** MR neurography can be reliably used for the diagnosis of injuries to the peripheral trigeminal nerve related to molar tooth extractions, with good to excellent correlation of imaging with clinical findings and surgical results.

AJNR Am J Neuroradiol 2018 Jan;39(1):162-169. doi: 10.3174/ajnr.A5438. Epub 2017 Nov 16. Role of MR Neurography for the Diagnosis of Peripheral Trigeminal Nerve Injuries in Patients With Prior Molar Tooth Extraction R Dessouky[1,2], Y Xi[1], J Zuniga[3], A Chhabra[4]

MR Neurography PTNP

- Abstract
- **Purpose:** The clinical neurosensory testing (NST) is currently the reference standard for the diagnosis of traumatic and nontraumatic peripheral trigeminal neuropathies (PTNs), but exhibits both false-positive and false-negative results compared with surgical findings and frequently results in treatment decision delays. We tested the hypothesis that magnetic resonance neurography (MRN) of PTNs can serve as a diagnostic modality by correlating the NST, MRN, and surgical findings.
- **Materials and methods:** Sixty patients with traumatic and nontraumatic PTN of varying etiologies and Sunderland classifications underwent NST, followed by MRN using 1.5T and 3.0T scanners. The protocol included 2-dimensional and 3-dimensional (3D) imaging, including diffusion imaging and isotropic 3D PSIF. The MRN findings were read by 2 readers in consensus with the clinical findings but without knowing the side of abnormality. The MRN results were summarized using the Sunderland classification. In 26 patients, surgery was performed, and the Sunderland classification was assigned using the surgical photographs. Agreement between the MRN findings and NST/surgical classification was evaluated using kappa statistics. Pearson's correlation coefficient was used to assess the correlation between continuous measurements of MRN/NST and surgical classification.
- **Results:** Of the 60 patients, 19 males and 41 females, mean age 41 years (range 12 to 75), with 54 complaints of altered sensation of the lip, chin, or tongue, including 16 with neuropathic pain and 4 with no neurosensory complaint, were included. Third molar surgery (n = 29) represented the most common cause of traumatic PTN. Assuming 1 nerve abnormality per patient, the lower class was accepted, a kappa of 0.57 was observed between the MRN and NST classification. A kappa of 0.5 was found between MRN and surgical findings with a Pearson correlation coefficient of 0.67.
- **Conclusions:** MRN anatomically maps PTNs and stratifies the nerve injury and neuropathies with moderate to good agreement with NST and surgical findings for clinical use.

J Oral Maxillofac Surg 2018 Apr;76(4):725-736. doi: 10.1016/j.joms.2017.11.007. Epub 2017 Nov 16. Magnetic Resonance Neurography of Traumatic and Nontraumatic Peripheral Trigeminal Neuropathies John R Zuniga [1], Cyrus Mistry [2], Igor Tikhonov [2], Riham Dessouky [3], Avneesh Chhabra [4]

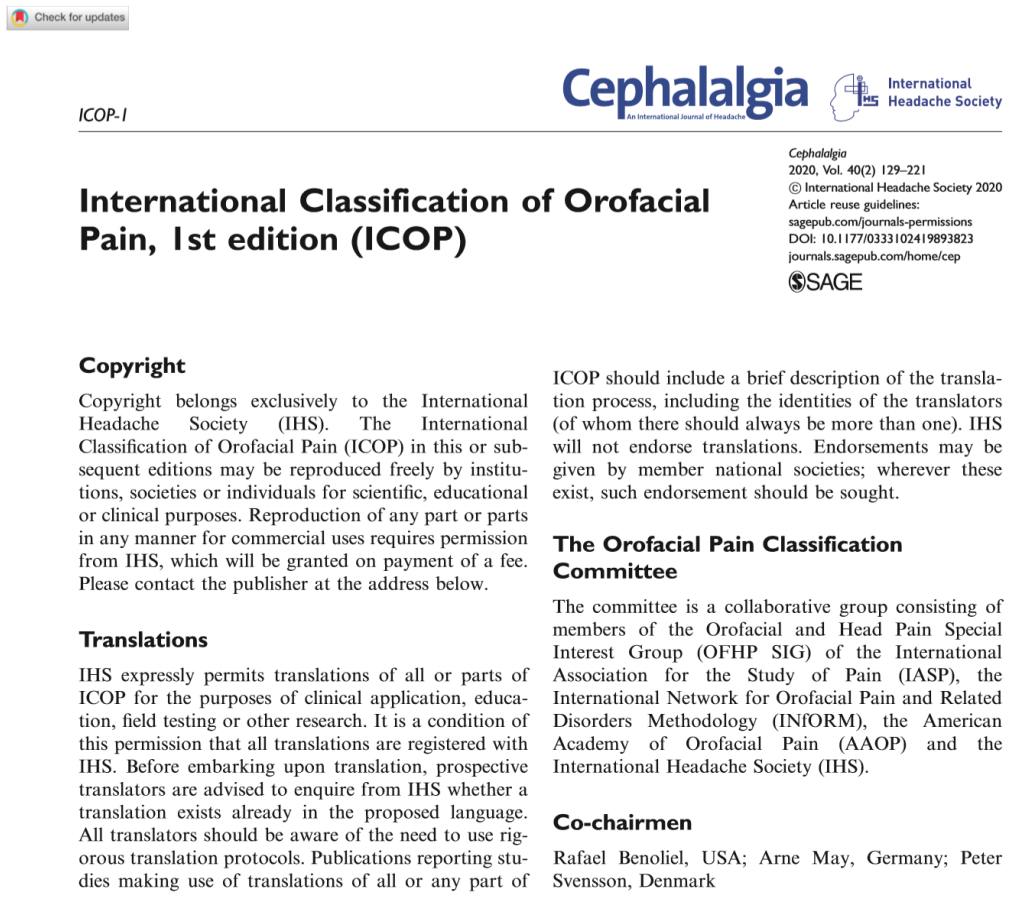
MR Neurography PTNP

- Abstract
- **Objectives:** To perform a systematic review of published studies on diagnostic accuracy of magnetic resonance neurography (MRN) *vs* clinical neurosensory testing (NST) for post-traumatic trigeminal neuropathy (PTTN) 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:** 8 studies met eligibility criteria of which 7 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. T_2 weighted 3 T 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, PTTN 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 PTTN. Methodological issues underline the importance for prospective blinded studies with standardization of signal intensity calculation and rigorous reporting of MRI acquisition parameters.

Van der Cruyssen F, Peeters F, Croonenborghs TM, et al. 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 [published online ahead of print, 2020 May 27]. *Dentomaxillofac Radiol*. 2020;20200103. doi:10.1259/dmfr.20200103

Frederic Van der Cruyssen [1,2], Frederik Peeters [1,2], Tomas-Marijn Croonenborghs [1,2], Jasper Fransen [1,2], Tara Renton [3], Constantinus Politis [1,2], Jan Casselman [4,5], Reinhilde Jacobs [2,6,7]

ICOP Definitions and Diagnostic Groups



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International Classification of Orofacial Pain, 1st edition (ICOP)

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Co-chairmen

Rafael Benoliel, USA; Arne May, Germany; Peter Svensson, Denmark

1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures
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ICOP 2020

Migraine GM changes Meta analysis

- Methods
  - January 1985 and November 2015, and examined the references within relevant primary articles. Following exclusion of unsuitable studies, meta-analysis were performed using activation likelihood estimation (ALE).
  - **8** clinical studies were analyzed for structural changes, containing a total of 390 subjects (191 patients and 199 controls).
  - 5 functional studies were enrolled, containing 93 patients and 96 controls.
- Results
  - ALE showed that the migraineurs had concordant decreases in the GM volume (GMV) in the bilateral inferior frontal gyri, the right precentral gyrus, the left middle frontal gyrus and the left cingulate gyrus.
  - GMV decreases in right claustrum, left cingulated gyrus, right anterior cingulate, amygdala and left parahippocampal gyrus are related to estimated frequency of headache attack.
  - Activation was found in the somatosensory, cingulate, limbic lobe, basal ganglia and midbrain in migraine patients.
- The limbic regions may be accumulated damage due to the repetitive occurrence of pain-related processes. Increased activation in precentral gyrus and cingulate opposed to GMV decrease might suggest increased effort duo to disorganization of these areas and/or the use of compensatory strategies involving pain processing in migraine

Neuroimage Clin. 2017 Jan 19;14:130-140. doi: 10.1016/j.nicl.2017.01.019. eCollection 2017. **Grey Matter Alterations in Migraine: A Systematic Review and Meta-Analysis** Zhihua Jia [1], Shengyuan Yu [1]

Table 1 Socio-demographic and clinical characteristics of three groups (% frequency)

	Migraine without aura (Mean±SD)	Migraine with aura (Mean±SD)	Health Control (Mean±SD)	p
N. patients	14	14	14	
Age	43.5±3.25	42.36±2.95	42.5±5.17	0.70[±]
Education	12.96±3.49	13.45±3.28	13.46±3.75	0.91[±]
Disease Duration (year)	6.78±3.66	5.21±1.31	–	0.14[¥]
Attacks per year	22.75±10.03	29.83±11.9	–	0.10[¥]
Frequency of attacks (mounth)	1.89±1.18	2.48±1.40	–	0.24[¥]
Duration of headache attacks (hours)	2.5±1.2	3.3±1.9	–	0.19[¥]
VBM analysis				
Grey Matter	793.83±47.10	814.73±29.10	850.98±46.11	0.003[*±]

[*] $p < 0.05$
[¥] unpaired t-test
[±] one-way Anova
SD Standard Deviation, *HAM-A* Hamilton Rating Scale for Anxiety, *BDI-II* Beck Depression Inventory

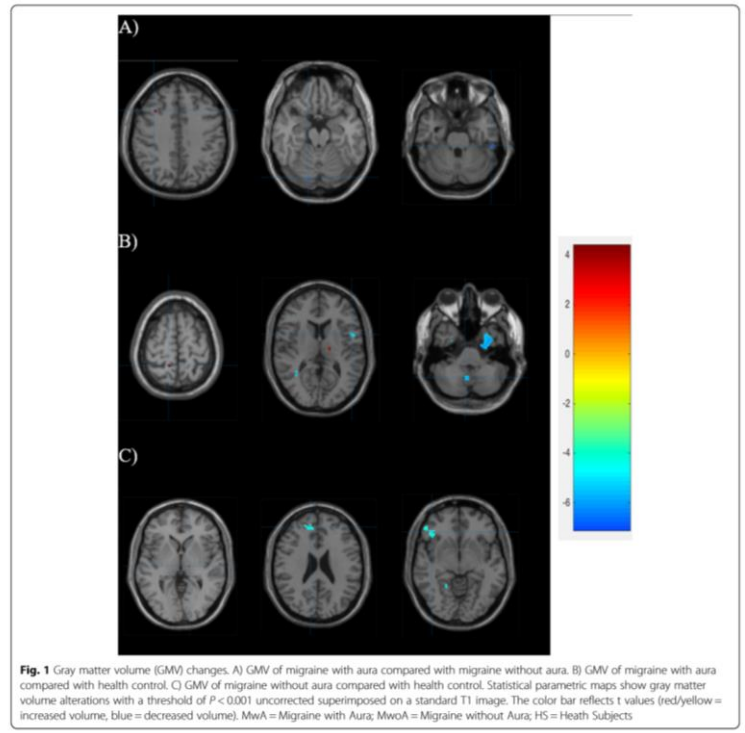

Fig. 1 Gray matter volume (GMV) changes. A) GMV of migraine with aura compared with migraine without aura. B) GMV of migraine with aura compared with health control. C) GMV of migraine without aura compared with health control. Statistical parametric maps show gray matter volume alterations with a threshold of $P < 0.001$ uncorrected superimposed on a standard T1 image. The color bar reflects t values (red/yellow = increased volume, blue = decreased volume). MwA = Migraine with Aura; MwoA = Migraine without Aura; HS = Heath Subjects

Table 2
Technique details of structural changes in migraine.

First author (year)	MRI scanner	Region studied	Timing	Methods	Main findings
Rocca MA (2006) (Rocca et al., 2006)	3.0T	Whole brain	Interictal	VBM	Reduced GM density located in the frontal and temporal lobes, increased PAG density; reduced GM density was strongly related to age, disease duration
Kim JH (2008) (Kim et al., 2008)	1.5T	Whole brain	Interictal	VBM	GMV reductions in the bilateral insula, motor/premotor, prefrontal, cingulated cortex, right posterior parietal cortex, and orbitofrontal cortex; GMV changes were negatively correlated with headache duration and lifetime headache frequency
Schmidt-Wilcke T (2008) (Schmidt-Wilcke et al., 2008)	1.5T	Whole brain (cingulate cortex, anterior insulae, thalamus, brainstem)	Interictal	VBM	Reduced grey matter density in the anterior and posterior part of the cingulate cortex and the right insular cortex
Schmitz N (2008) (Schmitz et al., 2008a)	3.0T	Whole brain	Interictal	VBM, DTI	Frontal GM density reduction; reduced FA values in the superior frontal lobe, the medial frontal lobe, the brainstem and the cerebellum; high attack frequency show reduced left parahippocampal, left superior frontal gyrus and the inferior parietal lobe GM density; long disease duration(>15 years) showed decreased GM density in the basal ganglia and the brainstem (medulla), decreased FA in the right frontal lobe
Schmitz N (2008) (Schmitz et al., 2008b)	3.0T	Whole brain	Interictal	VBM	Reduced GM density in the right middle frontal and left inferior parietal lobe
Valfre W (2008) (Valfre et al., 2008)	1.0T	Whole brain	Interictal	VBM	Grey matter reduction in the Right Superior Temporal, Right Inferior Frontal and Left Precentral Gyrus. Chronic migraine compared to episodic, showed a grey matter decrease in the bilateral Anterior Cingulate Cortex. A significant correlation between grey matter reduction in anterior cingulated cortex and frequency of migraine attacks was found.
Maleki N (2012) (Maleki et al., 2012a)	3.0T	Whole brain	Interictal	Cortical thickness, volumetric comparisons	HF patients showed higher thickness in the post-central Gyrus, temporal; smaller cortical volume was observed in the cingulate cortex, insula
Jin C (2013) (Jin et al., 2013)	3.0T	Whole brain	Interictal	VBM, FC	Decreased grey matter volume in: the left medial prefrontal cortex(MPFC), dorsal anterior cingulate cortex (dACC), right occipital lobe, cerebellum and

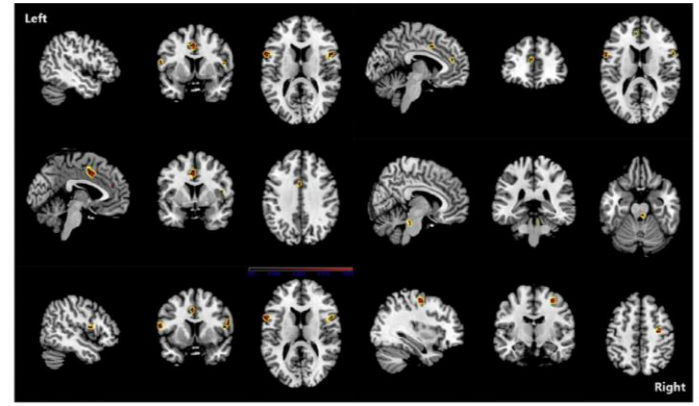

Fig. 2. ALE map investigating differences in GMV between migraine patients and HC. This image summarizes the results of all the papers involved in this meta-analysis. Red colour show grey matter decreases, they include bilateral inferior frontal gyri, right precentral gyrus, right cerebellar culmen, left middle frontal gyrus and left cingulate gyrus. (ALE maps were computed at a threshold of $p < 0.001$, with a minimum cluster size of $K > 100$ mm3 and visualized using MRIcron). Talairach coordinates of clusters showed in this image are reported in Table 5.

Table 4
Technique details of functional changes in migraine.

Study	MRI scanner	Region studied	Timing	Stimulus	Main findings
Moulton et al. (2011)	3.0T	Whole brain	Interictal	Heat	Increased activation in migraine patients in the contralateral anterior temporal pole, the ipsilateral parahippocampal gyrus, pulvinar nucleus, periaqueductal grey and decreases in the dorsolateral prefrontal cortex
Stankewitz et al. (2011)	3.0T	Whole brain	Interictal	Ammonia	Controls showed significantly stronger activation in a brainstem area corresponding to the trigeminal nuclei
Maleki et al. (2012)	3.0T	Whole brain	Interictal	Heat	Female migraineurs showed significant increased activation in paracingulate, ipsilateral superior frontal gyrus, contralateral hippocampus, parahippocampal and precentral gyrus
Russo et al. (2012)	3.0T	Whole brain	Interictal	Heat	Stronger activation in anterior cingulate cortex; and weaker activation in secondary somatosensory cortex and pons in episodic migraineurs than in healthy controls
Schwedt et al. (2014)	3.0T	Whole brain	Interictal	Heat	Greater activation of lentiform nucleus, fusiform gyrus, subthalamic nucleus, hippocampus, middle cingulate cortex, premotor cortex, somatosensory cortex and dorsolateral prefrontal cortex, and less

Migraine episodic vs chronic: global or focal gray or white matter alterations

- **Protocol**
  - **27** migraine right-handed patients and **27** healthy controls were selected for the study.
  - 16 patients fulfilled the HIS criteria for episodic migraine and 11 for chronic migraine.
  - Voxel based morphometry (VBM), a fully automated method of analyzing changes in brain structure.
- Migraineurs presented a significant focal gray matter reduction in the
  - Right Superior Temporal Gyrus,
  - Right Inferior Frontal Gyrus,
  - Left Precentral Gyrus.
  - Chronic migraine patients, compared to episodic, showed a focal gray matter decrease in the bilateral Anterior Cingulate Cortex, Left Amygdala, Left Parietal Operculum, Left Middle and Inferior Frontal Gyrus, Right Inferior Frontal Gyrus, and bilateral Insula.
  - Considering all the migraine patients, a significant correlation between gray matter reduction in anterior cingulate cortex and frequency of migraine attacks was found.

Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache*. 2008;48(1):109-117. doi:10.1111/j.1526-4610.2007.00723.x

Migraine: brain morphologic differences

- Cohorts
  - migraine patients, 14 with aura (MwA) [the mean (SD) age was 42.36 (2.95) years (range, 37-47)]
  - 14 without aura (MwoA) [the mean (SD) age was 43.5 (3.25) years (range, 39-50)] during episodic attack
  - compared with health subjects balanced (HS) [the mean (SD) age was 42.5 (5.17) years (range, 34-51)].
- Magnetic Resonance Imaging (MRI) examination with a scanner operating at 3.0 T and voxel based morphometry (VBM) approach was used to examine the gray matter volume (GMV). The statistical analysis to compare clinical characteristics was performed using unpaired t-test an one-way Anova.
- Results
  - Total cerebral GMV showed a significant difference between MwA and HS ($p = 0.02$), and between MwoA and HS ($p = 0.003$).
  - In addition, not significative differences were found between MwA and MwoA groups ($p = 0.17$).
  - We found three clusters of regions which showed significant GMV reduction in MwA compared with MwoA.
  - MwA subjects showed a less of GMV in 4 clusters if compared with HS, and MwoA subjects showed a less of GMV in 3 clusters if compared with HS.
  - We observed that MwA and MwoA patients had a significant reduction of GMV in the frontal and temporal lobe and the cerebellum, if compared to HS. The bilateral fusiform gyrus and the cingulate gyrus were increase in MwoA patients compared with HS.

Bonanno L, Lo Buono V, De Salvo S, et al. Brain morphologic abnormalities in migraine patients: an observational study. *J Headache Pain*. 2020;21(1):39. Published 2020 Apr 25. doi:10.1186/s10194-020-01109-2

Migraine Brain anomalies using VBM

- **Methods:** A systematic search of VBM studies of patients with migraine and healthy controls (HC) published in PubMed and Embase databases from January 2000 to March 2014 was conducted.
- 9 studies comprising 222 patients with migraine and 230 HC subjects were included in the present study.
- Results
- Compared to HC subjects, the patients group showed consistent decreased GM in the posterior insular-opercular regions, the prefrontal cortex, and the anterior cingulate cortex.
- Results remained largely unchanged in the following jackknife sensitivity analyses.
- Meta-regression analysis showed that a higher percentage of females in the patient sample was associated with decreased GM in the right dorsolateral prefrontal cortex.
- This is the first quantitative whole-brain VBM meta-analysis in migraine showing strong evidence of brain GM anomalies within the pain-processing neural network.

Dai Z, Zhong J, Xiao P, et al. Gray matter correlates of migraine and gender effect: A meta-analysis of voxel-based morphometry studies. *Neuroscience*. 2015;299:88-96. doi:10.1016/j.neuroscience.2015.04.066

ICOP Definitions and Diagnostic Groups

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BMS brain anatomical and functional changes

Methods

- Fifty-three patients (26 BMS patients and 27 gender- and age-matched controls) were recruited. Demographic information was collected *via* interviews. Visual analogue scale (VAS), anxiety, and depression scale were administered.
- Participants underwent an MRI scan (including one high-resolution structural scan, one diffusion tensor image, and one session of resting state scan) on the same day.

Results

- BMS patients had higher depression and anxiety levels than controls.
- BMS patients showed lower gray matter volume (GMV) in the bilateral ventromedial prefrontal cortex (VMPFC)
- BMS patients had increased functional connectivity between this region and the bilateral amygdala.
- Region of interest (ROI) analysis suggested that the functional connectivity between the bilateral VMPFC and amygdala correlated with the years of BMS illness in patients.
- The brain measures could predict the years of symptoms in the BMS group.

Tan Y, Wu X, Chen J, Kong L, Qian Z. Structural and Functional Connectivity Between the Amygdala and Orbital Frontal Cortex in Burning Mouth Syndrome: An fMRI Study. *Front Psychol*. 2019;10:1700. Published 2019 Jul 25. doi:10.3389/fpsyg.2019.01700

- On all three measures, patients showed higher scores than controls, suggesting that BMS patients had significantly higher trait and state anxiety and depression.
- VBM results suggested that there were two clusters (Table 2; Figures 1A,B) showing significantly lower gray matter volume in patients than in controls, including the left and right ventromedial prefrontal cortex (VMPFC). No region showed significantly higher GMV in patients than in controls. ROI analysis suggested that the GMV in the bilatera VMPFC correlated with the years of BMS illness in patients [left: $r(26) = -0.81$, $p < 0.001$; right: $r(26) = -0.80$, $p < 0.001$].
- Tract-Based Spatial Statistics Results TBSS did not reveal any significant difference between patients and controls with regard to FA and MD.
- Functional Connectivity Results Using the left and right VMPFC as the seed region, wholebrain connectivity analysis suggested that the bilateral amygdala had increased functional connectivity with the bilateral VMPFC region (Table 2; Figures 1C,D) in patients than in controls. There was no decreased functional connectivity in patients compared to controls. ROI analysis suggested that the functional connectivity between the bilateral VMPFC and amygdala correlated with the years of BMS illness in patients [left: $r(26) = 0.71$, $p < 0.001$; right: $r(26) = 0.68$, $p < 0.001$].
- These results replicated those of previous studies on the mood problems in BMS patients (Grushka, 1987; Bergdahl and Bergdahl, 1999; Forssell et al., 2002; Grushka et al., 2002; Scala et al., 2003; Khan et al., 2014; Sinding et al., 2016). In our study, depression, trait anxiety, and state anxiety were all higher in BMS patients thar in controls. Although the scores of the BMS group were comparable to those found in previous studies (Khan et al., 2014), we found even lower anxiety scores in the controls. This may be because our sample was from a nearby community, while previous studies only recruited controls from other departments of the hospital. Additionally, our results suggested that BMS patients had lower GMV in the bilateral VMPFC region, and the GM of this region was inversely correlated with the severity of BMS. These results partially replicated the results of Khan et al. (2014) but were not consistent with a later study by Sinding et al. (2016). The inconsistency may be partially due to the smaller sample size used in the previous studies. Decreased GMV in
- the VMPFC has been reported previously in other chronic pain populations (Ploghaus et al., 2003; Kong et al., 2010; Yu et al., 2014). Besides chronical and social pain (Ploghaus et al., 2003; Masten et al., 2011), this region is known to be involved in many other functions, such as decision making (Koritzky et al., 2013; Zhu et al., 2018; He et al., 2019; Huang et al., 2019), stress regulation and inhibition (Dickie et al., 2011; Conner et al., 2012; Shvil et al., 2014), and emotion processing (Northoff et al., 2004; Grimm et al., 2006; Moll and de Oliveira-Souza, 2007 The decreased GMV in the bilateral VMPFC may be a neuromarker for the diagnosis and treatment of BMSOur results further indicated that the functional connectivity between the VMPFC and amygdala was increased in BM patients, and this phenomenon was associated with the severity of BMS. This is consistent with previous studies (Hawker et al., 2011) showing functional connectivity enhancement between the mPFC and amygdala for more severe conditions (comparable to our afternoon session). The amygdala has long been linked to emotional processing (Morris et al., 1998; Davis and Whalen, 2001; Hamann and Mao, 2002; LeDoux, 2003), especially fear (LeDoux, 2003). The amygdala has also been linked to substance addiction and behavior addiction, such as social media addiction (He et al., 2017; Zhu et al., 2017a). Previous reports have suggested that the functional connectivity between the amygdala and medial PFC is associated with anxiety (Kim et al., 2011), emotion regulation (Banks et al., 2007; Zhu et al., 2017b), emotional learning (Sakaki et al., 2016), and sleep (Yoo et al., 2007). In summary, the increased functional connectivity between the amygdala and VMPFC may be another neuromarker for the diagnosis and treatment of BMS.

TABLE 1 | Demographic characteristics and clinical measures of participants ($M \pm SD$).

	BMS patients	Healthy controls	Statistics
n (females)	26 (21)	27 (25)	$\chi^2(1) = 1.62$, $p = 0.20$
Age (years)	52.12 ± 8.81	51.11 ± 5.42	$t(51) = 0.50$, $p = 0.62$
Depression (BDI)	11.27 ± 6.50	2.59 ± 2.06	$t(51) = 6.60$, $p < 0.001$
Trait anxiety (STAI)	38.23 ± 14.30	24.30 ± 4.59	$t(51) = 4.82$, $p < 0.001$
State anxiety (STAI)	36.12 ± 13.35	24.11 ± 4.71	$t(51) = 4.40$, $p < 0.001$
BMS history (months)	8.61 ± 9.93	–	–
VAS pain rating	4.19 ± 1.60	–	–

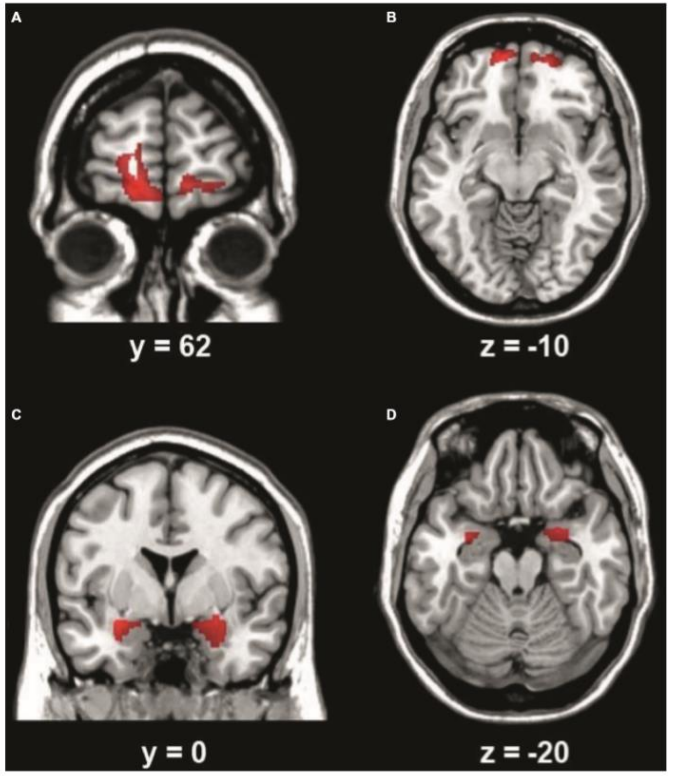

FIGURE 1 | The left **(A)** and right **(B)** VMPFC showed lower gray matter volume in BMS patients than in controls. The left **(C)** and right **(D)** amygdala showed increased functional connectivity in BMS patients than in controls. The results were mapped onto the standard brain for visual display, with the left side representing the right hemisphere.

BMS Gray matter changes

Methods

- 12 subjects using voxel-based morphometry. +/- dysgeusia

Results

- a major part of the 'pain matrix' presented modifications of the grey matter concentration in subjects with BMS.
- Six regions out of eight were affected [anterior and posterior cingulate gyrus, lobules of the cerebellum, insula/frontal operculum, inferior temporal area, primary motor cortex, dorsolateral pre-frontal cortex (DLPFC)].
- In the anterior cingulate gyrus, the lobules of the cerebellum, the inferior temporal lobe and the DLPFC, pain intensity correlated with grey matter concentration.
- Dysgesia also presented changes in grey matter concentration but in different areas of the brain.
- Our results suggest that a deficiency in the control of pain could in part be a cause of BMS and that BMS and dysgeusia conditions are not linked to similar structural changes in the brain.

Sinding C, Gransjøen AM, Schlumberger G, Grushka M, Frasnelli J, Singh PB. Grey matter changes of the pain matrix in patients with burning mouth syndrome. *Eur J Neurosci*. 2016;43(8):997-1005. doi:10.1111/ejn.13156

BMS vs controls: Gray matter volume

Methods

- voxel-based morphometry (VBM), white matter fractional anisotropy (FA) with diffusion tensor imaging (DTI), and functional connectivity in resting state functional MRI (rsfMRI)
- 9 female, postmenopausal/perimenopausal BMS patients
- 9 matched healthy control subjects. Patients underwent 2 scanning sessions in the same day: in the morning, when ongoing pain/burning was low, and in the afternoon, when pain/burning was significantly higher.

Results Patients had

- increased GMV and lower FA in the hippocampus (Hc),
- decreased GMV in the medial prefrontal cortex (mPFC).
- rsfMRI revealed altered connectivity patterns in different states of pain/burning, with increased connectivity between mPFC (a node in the default mode network) and anterior cingulate cortex, occipital cortex, ventromedial PFC, and bilateral Hc/amygdala in the afternoon compared with the morning session.
- Furthermore, mPFC-Hc connectivity was higher in BMS patients than control subjects for the afternoon but not the morning session. mPFC-Hc connectivity was related to Beck depression inventory scores both between groups and between burning states within patients, suggesting that depression and anxiety partially explain pain-related brain dysfunction in BMS..

Khan SA, Keaser ML, Meiller TF, Seminowicz DA. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. *Pain*. 2014;155(8):1472-1480. doi:10.1016/j.pain.2014.04.022
Later comment Pain 2014 Aug;155(8):1424-5. doi: 10.1016/j.pain.2014.05.020. Epub 2014 May 23. Altered Structure and Function in Hippocampus and Medial Frontal Cortex in Patients With Burning Mouth Syndrome Eli Eliav[1]

BMS vs controls: brain network using probabilistic tractography and graph analysis

Methods: 14 BMS patients and 14 age-matched healthy controls underwent 1.5T MRI. Structural connectivity was calculated in 83 anatomically defined regions with probabilistic tractography of 60-axis diffusion tensor imaging and 3D T1-weighted imaging. Graph theory network analysis was used to evaluate the brain network at local and global connectivity.

Results: In BMS brain,

- a significant difference of local brain connectivity was recognized at the bilateral rostral anterior cingulate cortex, right medial orbitofrontal cortex, and left pars orbitalis which belong to the medial pain system;
- however, no significant difference was recognized at the lateral system including the somatic sensory cortex.
- A strengthened connection of the anterior cingulate cortex and medial prefrontal cortex with the basal ganglia, thalamus, and brain stem was revealed.

Wada A, Shizukuishi T, Kikuta J, et al. Altered structural connectivity of pain-related brain network in burning mouth syndrome-investigation by graph analysis of probabilistic tractography. *Neuroradiology*. 2017;59(5):525-532. doi:10.1007/s00234-017-1830-2

BMS vs controls: GMV and CBf

Methods

- 12 patients with BMS and 14 healthy controls. Volumetric T1-weighted magnetization-prepared rapid gradient-echo imaging and pseudo-continuous ASL were performed to obtain GMV and CBF, respectively.

Results:

- The GMV was smaller in the left thalamus and left middle temporal gyrus in the BMS group when compared to controls.
- Regional CBF in the BMS group was significantly decreased in the left middle temporal gyrus, left insula, right middle temporal gyrus, and right insula compared with controls.
- In BMS patients, there was a significant correlation between GMV and pain severity in the left middle temporal gyrus.
- Pathogenesis of BMS may be associated with atrophy of the brain structures associated with thalamocortical processing.

Lee YC, Jahng GH, Ryu CW, Byun JY. Change in gray matter volume and cerebral blood flow in patients with burning mouth syndrome. *J Oral Pathol Med*. 2019;48(4):335-342. doi:10.1111/jop.12838

BMD vs controls: thermal stimulation cerebral activation

Methods

- 8 eight female patients with BMD (mean age 49.1+/-10.1) were mapped using fMRI and compared with those of eight matched pain-free volunteers (mean age 50.3+/-12.3).

Results

- Qualitative and quantitative differences in brain activation patterns between the two study groups were demonstrated.
- BMD patients displayed greater fractional signal changes in the right anterior cingulate cortex (BA 32/24) and bilateral precuneus than did controls ($p<0.005$).
- The control group showed **larger fractional signal changes in the bilateral thalamus, right middle frontal gyrus, right pre-central gyrus, left lingual gyrus, and cerebellum than did the BMD patients** ($p<0.005$).
- In addition, BMD patients had **less volumetric activation throughout the entire brain compared** to the control group.
- Overall, BMD patients displayed brain activation patterns similar to those of patients with other neuropathic pain conditions and appear to process thermal painful stimulation to the trigeminal nerve qualitatively and quantitatively different than pain-free individuals.

Pain .2006 Jun;122(3):223-34. doi: 10.1016/j.pain.2006.01.020. Epub 2006 Apr 24. Cerebral Activation During Thermal Stimulation of Patients Who Have Burning Mouth Disorder: An fMRI Study Romulo J C Albuquerque [1], Reny de Leeuw, Charles R Carlson, Jeffrey P Okeson, Craig S Miller, Anders H Andersen

Pain 2007 Apr;128(3):290-1; author reply 291-2. doi: 10.1016/j.pain.2006.11.009. Epub 2007 Jan 2.
BMD, fMRI Study and Brain Hypoactivity Antonella Costa, Vincenzo Branca, Paolo D Pigatto, Gianpaolo Guzzi

BMS vs controls: brain response to noxious stimulus

Methods

- 16 right-handed women with primary BMS and 15 sex- and age-matched right-handed healthy female controls.
- A thermal stimulus sequence of 32 °C to 40 °C to 32 °C to 49 °C was repeated 4 times in a cycle. Warm and noxious heat stimuli were delivered with a Peltier thermode placed on the right palm or right lower lip for 32 s each in a session. Functional magnetic resonance imaging data were obtained by recording echoplanar images with a block design.

Results

- Repetition of noxious heat stimulus on the lower lip but not on the palm induced habituation in brain activity in the cingulate cortex without reduction in pain perception.
- Multiple regression analysis revealed a correlation between perceived pain intensity and suppression of brain activity in the anterior cingulate cortex when the repeated thermal sequence was applied at the lower lip.
- Furthermore, the response of the parahippocampal area differed in BMS patients and controls when the same repeated thermal sequence was applied at the palm.
- findings indicate that BMS patients show specific brain responses due to impaired function of the central and peripheral nervous systems

T Shinozaki [1], Y Imamura [2], R Kohashi [3], K Dezawa [3], Y Nakaya [3], Y Sato [3], K Watanabe [3], Y Morimoto [4], T Shizukuishi [5], O Abe [5], T Haji [6], K Tabei [7], M Taira [8] **Spatial and Temporal Brain Responses to Noxious Heat Thermal Stimuli in Burning Mouth Syndrome.** J Dent Res 2016 Sep;95(10):1138-46. doi: 10.1177/0022034516653580. Epub 2016 Jun 14.

BMS: thermal stimulation

(2 ? Salami publishing?)

Methods

- investigate the pain modulating system in patients with BMS. The thermal stimulation sequence baseline (32°C, 40 s) to warm (40°C, 32 s) to baseline (32°C, 40 s) to hot (49°C, 32 s), which was repeated four times using a Peltier thermode. These warm and hot stimuli were applied on the right palm and right lower lip in two separate sessions.
- Functional magnetic resonance imaging data were acquired by recording echo-planar images with a block design.

Results

- Brain activity induced by purely hot stimulation (49°C vs. 40°C) applied to the palm was more pronounced than that induced by lip stimulation and in patients with BMS compared with controls.
- Comparison of brain activity between the first 16 s and second 16 s of the stimulus revealed pronounced time-dependent facilitation in patients with BMS during lip stimulation.
- These findings indicate that the pain modulating system in patients with BMS is dysregulated

J Oral Sci 2020;62(2):170-174. doi: 10.2334/josnusd.18-0431. Time-dependent Responses in Brain Activity to Ongoing Hot Stimulation in Burning Mouth Syndrome. Ryutaro Kohashi [1], Takahiro Shinozaki [1 2], Naohiko Sekine [1], Kosuke Watanabe [1], Daiki Takanezawa [1], Chisa Nishihara [1], Kana Ozasa [1], Mariko Ikeda [1], Noboru Noma [1 2], Akiko Okada-Ogawa [1 2], Yoshiki Imamura [1 2]

BMS: brain activation to intra oral tactile stimuli

Methods

- We examined activation of brain regions in response to intraoral tactile stimuli when modulated by angry facial expressions. We performed functional magnetic resonance imaging on a group of 27 BMS patients and 21 age-matched healthy controls.
- Tactile stimuli were presented during different emotional contexts, which were induced *via* the continuous presentation of angry or neutral pictures of human faces.

Results

- BMS patients exhibited higher tactile ratings and **greater activation in the postcentral gyrus during the presentation of tactile stimuli involving angry faces relative to controls**.
- Significant positive correlations between changes in brain activation elicited by angry facial images in the postcentral gyrus and changes in tactile rating scores by angry facial images were found for both groups.
- For BMS patients, there was a significant positive correlation between changes in tactile-related activation of the postcentral gyrus elicited by angry facial expressions and pain intensity in daily life.
- Findings suggest that neural responses in the postcentral gyrus are more strongly affected by angry facial expressions in BMS patients, which may reflect one possible mechanism underlying impaired somatosensory system function in this disorder.

Yoshino A, Okamoto Y, Doi M, et al. Functional Alterations of Postcentral Gyrus Modulated by Angry Facial Expressions during Intraoral Tactile Stimuli in Patients with Burning Mouth Syndrome: A Functional Magnetic Resonance Imaging Study. *Front Psychiatry*. 2017;8:224. Published 2017 Nov 6.

Summary

Summary of changes seen in orofacial pain? Regional function

The available studies implied that the

- **anterior cingulate cortex plays a role in the emotional-affective component of pain**, as well as in **pain-related attention and anxiety**.
- The **somatosensory cortices may be involved in encoding spatial, temporal, and intensity aspects of noxious input.**
- The insula may **mediate both affective and sensory-discriminative aspects of the pain experience**.
- The thalamus **appears to be a multifunctional relay system**.
- The prefrontal cortex has been **implied in the pain-related attention processing; it does not have intensity encoding properties.**
- Chronic pain conditions were associated with increased activity in the somatosensory cortices, anterior cingulate cortex, and the prefrontal cortex, and with decreased activity in the thalamus.
- Few neuroimaging studies used experimental stimuli to the trigeminal system or included orofacial pain patients.
- Overall, the available data suggest that chronic (orofacial) pain states may be related to a dysfunctional brain network and may involve a compromised descending inhibitory control system. The somatosensory cortices, anterior cingulate cortex, thalamus, and prefrontal cortex may play a vital role in the pathophysiology of chronic pain and should be the main focus of future neuroimaging studies in chronic pain patients.

de Leeuw R, Albuquerque R, Okeson J, Carlson C. **The contribution of neuroimaging techniques to the understanding of supraspinal pain circuits: implications for orofacial pain**. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100(3):308-314. doi:10.1016/j.tripleo.2004.11.014

Summary TMD

- (1) TNP and TMD patients showed consistent functional/structural changes in the thalamus and the primary somatosensory cortex, indicating the thalamocortical pathway as the major site of plasticity.
- (2) The TNP patients showed more alterations at the thalamocortical pathway, and the two disorders showed distinct patterns of thalamic and insular connectivity.
- Additionally, **functional and structural changes were frequently reported in the prefrontal cortex and the basal ganglia**, suggesting the role of cognitive modulation and reward processing in chronic orofacial pain.

Lin CS. Brain signature of chronic orofacial pain: a systematic review and meta-analysis on neuroimaging research of trigeminal neuropathic pain and temporomandibular joint disorders. *PLoS One*. 2014;9(4):e94300. Published 2014 Apr 23. doi:10.1371/journal.pone.0094300

Summary TMD gray matter

- patients with TMD have cortical thickening in the primary somatosensory cortex (S1), frontal polar and the ventrolateral prefrontal cortex (PFC).
- These findings provide a structural basis for previous findings of TMD pain and cognitive sluggishness in TMD.
- We then examined the contribution of TMD characteristics to GM abnormalities. We found that
  - 1) GM in the sensory thalamus positively correlated to TMD duration,
  - 2) cortical thickness in the primary motor (M1) and the anterior mid-cingulate cortices (aMCC) were negatively correlated to pain intensity, and
  - 3) pain unpleasantness was negatively correlated to cortical thickness in the orbitofrontal cortex (OFC).
  - 4) . there was an abnormal positive correlation between neuroticism and OFC thickness, in contrast to the negative correlation found in the healthy controls.

  These findings suggest that an individual's TMD pain history contributes to GM in the brainTherefore, neuroticism may contribute to TMD pathophysiology. In sum, our data suggest that GM in the brain of patients with chronic TMD pain can be shaped by both personality and pain characteristics.

Moayedi M, Weissman-Fogel I, Crawley AP, et al. Contribution of chronic pain and neuroticism to abnormal forebrain gray matter in patients with temporomandibular disorder. *Neuroimage*. 2011;55(1):277-286. doi:10.1016/j.neuroimage.2010.12.013

Summary TMD spectroscopy

- Results
  - **significantly higher total creatine levels within the posterior insula in patients with rTMD or gTMD pain than in HI** (p=0.029).
  - **choline** was negatively correlated to maximum mouth opening capacity with or without pain (rs=-0.42, n=28, p=0.031 and rs=-0.48, n=28, p=0.034, respectively) as well as pressure-pain threshold on the hand (rs=-0.41, n=28, p=0.031).
  - **Glutamate was positively correlated to temporal summation to painful mechanical stimuli**

Harfeldt K, Alexander L, Lam J, et al. Spectroscopic differences in posterior insula in patients with chronic temporomandibular pain. *Scand J Pain*. 2018;18(3):351-361. doi:10.1515/sjpain-2017-0159

- Patients with TMD, **left-insular Glutamine** levels were related to reported pain, left posterior insular **N-acetylaspartate (NAA) and Choline levels were significantly higher at baseline than in control** and significantly correlated with pain-symptom duration, suggesting adaptive changes.

Gerstner GE, Gracely RH, Deebajah A, et al. Posterior insular molecular changes in myofascial pain. *J Dent Res*. 2012;91(5):485-490. doi:10.1177/0022034512443366

Summary TMD activity

TMD patients displayed different brain activations in the fronto-insulo-thalamo-parietal network under both innocuous and painful stimulus compared with healthy controls, reflecting the involvement of aberrant central pain processing in TMD. Multivariate analysis techniques like SVM may help distinguish the subtypes of TMD patients, i.e. identify whose pain has a more peripheral or a central etiology,

Gerstner GE, Gracely RH, Deebajah A, et al. Posterior insular molecular changes in myofascial pain. *J Dent Res*. 2012;91(5):485-490. doi:10.1177/0022034512443366

Summary TN GM

- < GM
- Hum Brain Mapp. 2018 Feb;39(2):609-621. doi: 10.1002/hbm.23696. Epub 2017 Nov 6. **Altered Structure and Functional Connection in Patients With Classical Trigeminal Neuralgia.** Yuan-Hsiung Tsai [1], Rui Yuan [2], Dharni Patel [2], Subhashini Chandrasekaran [2], Hsu-Huei Weng [1], Jen-Tsung Yang [3], Ching-Po Lin [4], Bharat B Biswal [2]

Obermann M, Rodriguez-Raecke R, Naegel S, et al. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. *Neuroimage*. 2013;74:352-358. doi:10.1016/j.neuroimage.2013.02.029

Li M, Yan J, Li S, et al. Reduced volume of gray matter in patients with trigeminal neuralgia. *Brain Imaging Behav*. 2017;11(2):486-492. Brain Imaging Behav

Yuan Wang [1], Dong-Yuan Cao, Bethany Remeniuk, Samuel Krimmel, David A Seminowicz, Ming Zhang **Altered Brain Structure and Function Associated With Sensory and Affective Components of Classic Trigeminal Neuralgia.** Pain 2017 Aug;158(8):1561-1570. doi: 10.1097/j.pain.0000000000000951.

Henssen D, Dijk J, Knepflé R, Sieffers M, Winter A, Vissers K. Alterations in grey matter density and functional connectivity in trigeminal neuropathic pain and trigeminal neuralgia: A systematic review and meta-analysis. *Neuroimage Clin*. 2019;24:102039. doi:10.1016/j.nicl.2019.102039

- > GM
  - TN patients had increased GM volume in the sensory thalamus, amygdala, periaqueductal gray, and basal ganglia (putamen, caudate, nucleus accumbens) compared to healthy controls

Desouza DD, Moayedi M, Chen DQ, Davis KD, Hodaie M. Sensorimotor and Pain Modulation Brain Abnormalities in Trigeminal Neuralgia: A Paroxysmal, Sensory-Triggered Neuropathic Pain. *PLoS One*. 2013;8(6):e66340. Published 2013 Jun 18. doi:10.1371/journal.pone.0066340

TN metanalysis of consistent and replicable Gray Matter volume abnormalities using effect-size signed differential mapping (ES-SDM).

- And meta-regression to explore the potential effects of clinical characteristics on GM volume alterations in patients with TN.
- 13 studies with 15 datasets, representing 407 TN patients and 376 healthy individuals
- TN patients had GM volume abnormalities mainly in the basal ganglia, including the putamen, nucleus accumbens (NAc), caudate nucleus and amygdala, as well as the cingulate cortex (CC), thalamus, insula and superior temporal gyrus (STG).
- The meta-regression analysis showed that **verbal rating scale (VRS) scores were negatively correlated with decreased GM volume** in the left striatum and that illness duration was negatively correlated with decreased GM volume in the left STG and left insula..

Tang Y, Wang M, Zheng T, et al. Grey matter volume alterations in trigeminal neuralgia: A systematic review and meta-analysis of voxel-based morphometry studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;98:109821. doi:10.1016/j.pnpbp.2019.109821

Summary TN connectivity

- CTN had enhanced functional connectivity between the right insula/S2 and ACC, medial prefrontal cortex, posterior cingulate cortex, and bilateral dorsolateral prefrontal cortex.

Yuan Wang [1], Dong-Yuan Cao, Bethany Remeniuk, Samuel Krimmel, David A Seminowicz, Ming Zhang **Altered Brain Structure and Function Associated With Sensory and Affective Components of Classic Trigeminal Neuralgia.** Pain 2017 Aug;158(8):1561-1570. doi: 10.1097/j.pain.0000000000000951.

Summary Migraine
Gray matter

- < GM
  - ALE showed that the migraineurs had concordant decreases in the GM volume (GMV) in the bilateral inferior frontal gyri, the right precentral gyrus, the left middle frontal gyrus and the left cingulate gyrus.
  - GMV decreases in right claustrum, left cingulated gyrus, right anterior cingulate, amygdala and left parahippocampal gyrus are related to estimated frequency of headache attack.
  - Activation was found in the somatosensory, cingulate, limbic lobe, basal ganglia and midbrain in migraine patients.

Neuroimage Clin. 2017 Jan 19;14:130-140. doi: 10.1016/j.nicl.2017.01.019. eCollection 2017. **Grey Matter Alterations in Migraine: A Systematic Review and Meta-Analysis** Zhihua Jia [1], Shengyuan Yu [1]

Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache*. 2008;48(1):109-117. doi:10.1111/j.1526-4610.2007.00723.x

Bonanno L, Lo Buono V, De Salvo S, et al. Brain morphologic abnormalities in migraine patients: an observational study. *J Headache Pain*. 2020;21(1):39. Published 2020 Apr 25. doi:10.1186/s10194-020-01109-2

Meta-regression analysis showed that a higher percentage of females in the patient sample was associated with decreased GM in the right dorsolateral prefrontal cortex.

Dai Z, Zhong J, Xiao P, et al. Gray matter correlates of migraine and gender effect: A meta-analysis of voxel-based morphometry studies. *Neuroscience*. 2015;299:88-96. doi:10.1016/j.neuroscience.2015.04.066

Summary BMS < GM

- BMS patients showed lower gray matter volume (GMV) in the bilateral ventromedial prefrontal cortex (VMPFC)
- BMS patients had increased functional connectivity between this region and the bilateral amygdala.
- Region of interest (ROI) analysis suggested that the functional connectivity between the bilateral VMPFC and amygdala correlated with the years of BMS illness in patients

Tan Y, Wu X, Chen J, Kong L, Qian Z. Structural and Functional Connectivity Between the Amygdala and Orbital Frontal Cortex in Burning Mouth Syndrome: An fMRI Study. *Front Psychol*. 2019;10:1700. Published 2019 Jul 25. doi:10.3389/fpsyg.2019.01700

- increased GMV and lower FA in the hippocampus (Hc),
- decreased GMV in the medial prefrontal cortex (mPFC).
- rsfMRI revealed altered connectivity patterns in different states of pain/burning, with increased connectivity between mPFC (a node in the default mode network) and anterior cingulate cortex, occipital cortex, ventromedial PFC, and bilateral Hc/amygdala in the afternoon compared with the morning session.

Khan SA, Keaser ML, Meiller TF, Seminowicz DA. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. *Pain*. 2014;155(8):1472-1480. doi:10.1016/j.pain.2014.04.022

- The GMV was smaller in the left thalamus and left middle temporal gyrus in the BMS group when compared to controls.
  - Regional CBF in the BMS group was significantly decreased in the left middle temporal gyrus, left insula, right middle temporal gyrus, and right insula compared with controls.

Lee YC, Jahng GH, Ryu CW, Byun JY. Change in gray matter volume and cerebral blood flow in patients with burning mouth syndrome. *J Oral Pathol Med*. 2019;48(4):335-342. doi:10.1111/jop.12838

Summary BMS connectivity/ activity

- a significant difference of local brain connectivity was recognized at the bilateral rostral anterior cingulate cortex, right medial orbitofrontal cortex, and left pars orbitalis which belong to the medial pain system

Wada A, Shizukuishi T, Kikuta J, et al. Altered structural connectivity of pain-related brain network in burning mouth syndrome-investigation by graph analysis of probabilistic tractography. *Neuroradiology*. 2017;59(5):525-532. doi:10.1007/s00234-017-1830-2

- The control group showed **larger fractional signal changes in the bilateral thalamus, right middle frontal gyrus, right pre-central gyrus, left lingual gyrus, and cerebellum than did the BMD patients** ($p<0.005$).
- In addition, BMD patients had **less volumetric activation throughout the entire brain compared** to the control group

Pain .2006 Jun;122(3):223-34. doi: 10.1016/j.pain.2006.01.020. Epub 2006 Apr 24. Cerebral Activation During Thermal Stimulation of Patients Who Have Burning Mouth Disorder: An fMRI Study Romulo J C Albuquerque [1], Reny de Leeuw, Charles R Carlson, Jeffrey P Okeson, Craig S Miller, Anders H Andersen

Summary overall experimental OFP

- (1) brain function to experimental orofacial pain in healthy subjects
  - **Results increased brain activity in bilateral thalami, posterior mid-cingulate cortices, and secondary somatosensory cortices, the right posterior parietal cortex extending to the orofacial region of the right primary somatosensory cortex and the right insula,**
  - **and decreased activity in the right somatomotor regions**.
- (2) structural
  - **identified consistent higher grey matter volume/concentration in the right ventral thalamus and posterior putamen of COFP patients compared to healthy controls**.
- (3) functional brain abnormalities in COFP
  - **increase in brain activity in the left medial and posterior thalamus and lesser activity in the left posterior insula in COFP, compared to healthy controls**.

The convergence of thalamic abnormalities in both structure and function suggest a key role for this region in COFP pathophysiology

Ayoub LJ, Seminowicz DA, Moayedi M. A meta-analytic study of experimental and chronic orofacial pain excluding headache disorders. *Neuroimage Clin*. 2018;20:901-912. doi:10.1016/j.nicl.2018.09.018

Additional studies

- Facial expressions of pain are composed of a subset of pain-indicative muscle movements. Amongst this subset, contracting the muscles surrounding the eyes (orbicularis oculi muscle) is the most frequent response and has been linked specifically to pain intensity, a fundamental aspect of the sensory dimension of pain. To further explore this link, the present study used functional magnetic resonance imaging (fMRI) to test the hypothesis that orbicularis oculi activation during pain reflects the magnitude of brain responses in areas being involved in processing the sensory dimension of pain.
- Facial and brain (BOLD) responses to experimentally-induced heat pain applied to the left lower leg were assessed in twenty-two healthy participants after verbal suggestions were given to specifically increase perceived pain intensity and in control conditions involving no suggestion. Increases in pain intensity produced the expected changes in facial responses characterized by a stronger contraction of the orbicularis oculi muscle. A regression model further demonstrated that stronger increases in orbicularis oculi activity reflected a larger increase in the BOLD response to the noxious stimulus in the leg area of the primary somatosensory cortex (S1) and a larger decrease in medial prefrontal activity consistent with previous finding suggesting disinhibition. Importantly, the positive coupling of orbicularis oculi with S1 activity was not accounted for by changes in other facial muscles. These results are consistent with the notion that facial expressions of pain differentially encode the multi-dimensional pain experience and reflect, at least partly, the activity of the spino-thalamo-cortical pathway targeting the primary somatosensory cortex.

Neuroimage. 2020 Aug 15;217:116885. doi: 10.1016/j.neuroimage.2020.116885. Epub 2020 May 1. **Keeping an Eye on Pain Expression in Primary Somatosensory Cortex** Miriam Kunz [1], Jen-I Chen [2], Pierre Rainville [2]

- Complex regional pain syndrome (CRPS) is one of the most challenging chronic pain conditions and is characterized by burning pain, allodynia, hyperalgesia, autonomic changes, trophic changes, edema, and functional loss involving mainly the extremities. Until recently, very few reports have been published concerning CRPS involving the orofacial area.
- We report on a 50-year-old female patient who presented with unbearable pain in all of her teeth and hypersensitivity of the facial skin. She also reported intractable pain in both extremities accompanied by temperature changes and orofacial pain that increased when the other pains were aggravated.
- In the case of CRPS with trigeminal neuropathic pain, protocols for proper diagnosis and prompt treatment have yet to be established in academia or in the clinical field. We performed functional magnetic resonance imaging for a thorough analysis of the cortical representation of the affected orofacial area immediately before and immediately after isolated light stimulus of the affected hand and foot and concluded that CRPS can be correlated with trigeminal neuropathy in the orofacial area. Furthermore, the patient was treated with carbamazepine administration and stellate ganglion block, which can result in a rapid improvement of pain in the trigeminal region.

Lee YH, Lee KM, Kim HG, et al. Orofacial complex regional pain syndrome: pathophysiologic mechanisms and functional MRI. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;124(2):e164-e170. doi:10.1016/j.oooo.2017.03.006

Overview imaging in OFP

- **Imaging modalities:** Following a thorough history and clinical examination, imaging is often required to narrow the differential diagnosis or answer a specific query related to the final diagnosis. A range of imaging modalities can be used to evaluate orofacial pain including dental panoramic tomography (DPT), intraoral radiographs, Cone Beam Computed Tomography (CBCT), Multidetector Computed Tomography (MDCT), Ultrasonography (US), Magnetic Resonance Imaging (MRI), and Nuclear Medicine.
- **Imaging protocols:** This paper provides a guideline outlining imaging protocols for categories of facial pain divided into: (i) unilateral odontalgia; (ii) unilateral facial pain; (iii) combined unilateral odontalgia and facial pain; (iv) trigeminal neuralgia; (v) trigeminal neuropathic pain with or without other sensory, autonomic or motor features; (vi) temporomandibular joint disorders and associated pain; (vii) referred pain and (viii) non-specific orofacial pain.
- **Conclusion:** Imaging for orofacial pain should be tailored to answer a specific query related to the aetiology of the reported pain. This should result in a specific diagnosis or narrowing of the differential diagnosis as possible causes of orofacial pain are eliminated. Choosing the correct imaging modality and protocol based on the pain category is important for efficient and effective pain diagnosis and management.

Whyte A, Matias MATJ. Imaging Of Orofacial Pain [published online ahead of print, 2020 Jun 12]. *J Oral Pathol Med*. 2020;10.1111/jop.13063. doi:10.1111/jop.13063

Retained maxillary third molars cause chronic orofacial pain!!!!!

- **Objectives:** To examine the association between third molars and orofacial pain. We hypothesized that impacted third molars are a cause of orofacial pain.
- **Methods:** Magnetic resonance images of 1808 participants from two population-based cohorts from Northeastern Germany were analysed to define the status of third molars according to the Pell and Gregory classification. A self-reported questionnaire and a clinical dental examination were used to detect chronic and acute complaints of orofacial pain, masticatory muscle pain, migraine and other types of headache. Logistic regression models were used to analyse the associations between third molar status and orofacial pain.
- **Results:** Individuals with impacted third molars in the maxilla had a higher chance of chronic orofacial pain than those with erupted third molars (odds ratio 2.19; 95% CI 1.19-4.02). No such association was detected for third molars in the lower jaw. Third molars were not associated with masticatory muscle pain, migraine or other types of headache.
- **Conclusions:** Impacted maxillary third molars might be a cause of chronic orofacial pain. Thus, physicians should consider the eruption/impaction status of third molars in their decision-making process when treating patients who complain of orofacial pain.

Community Dent Oral Epidemiol. 2020 May 18. doi: 10.1111/cdoe.12540. Online ahead of print. **Are Third Molars Associated With Orofacial Pain? Findings From the SHIP Study** Maria Mksoud [1], Till Ittermann [2], Amro Daboul [3], Philipp Schneider [1], Olaf Bernhardt [4], Thomas Koppe [5], Robin Bülow [6], Hans-Robert Metelmann [1], Henry Völzke [2], Stefan Kindler [1]

Overview Glial cell involvement in NePain

This article provides a brief overview of the neural mechanisms underlying orofacial pain and then highlights recent findings indicating that nonneural cells, specifically satellite cells in the sensory ganglia and astroglia and microglia cells in the central nervous system, are important players in both acute and chronic inflammatory and neuropathic orofacial pain conditions and may offer new targets for management of these conditions.

Neuroscientist. 2011 Jun;17(3):303-20. doi: 10.1177/1073858410386801. Epub 2011 Apr 21. **Role of Glia in Orofacial Pain** Chen-Yu Chiang [1], Jonathan O Dostrovsky, Koichi Iwata, Barry J Sessle

Glial cell-neuron cross talk in Nepain

Neuropathic orofacial pain (NOP) is a debilitating condition. Although the pathophysiology remains unclear, accumulating evidence suggests the involvement of multiple mechanisms in the development of neuropathic pain. Recently, glial cells have been shown to play a key pathogenetic role. Nerve injury leads to an immune response near the site of injury. Satellite glial cells are activated in the peripheral ganglia. Various neural and immune mediators, released at the central terminals of primary afferents, lead to the sensitization of postsynaptic neurons and the activation of glia. The activated glia, in turn, release pro-inflammatory factors, further sensitizing the neurons, and resulting in central sensitization.

- Recently, we observed the involvement of glia in the alteration of orofacial motor activity in NOP. Microglia and astroglia were activated in the trigeminal sensory and motor nuclei, in parallel with altered motor functions and a decreased pain threshold. A microglial blocker attenuated the reduction in pain threshold, reduced the number of activated microglia, and restored motor activity. We also found an involvement of the astroglial glutamate-glutamine shuttle in the trigeminal motor nucleus in the alteration of the jaw reflex. Neuron-glia crosstalk thus plays an important role in the development of pain and altered motor activity in NOP.

Hossain MZ, Unno S, Ando H, Masuda Y, Kitagawa J. Neuron-Glia Crosstalk and Neuropathic Pain: Involvement in the Modulation of Motor Activity in the Orofacial Region. *Int J Mol Sci*. 2017;18(10):2051. Published 2017 Sep 26. doi:10.3390/ijms18102051

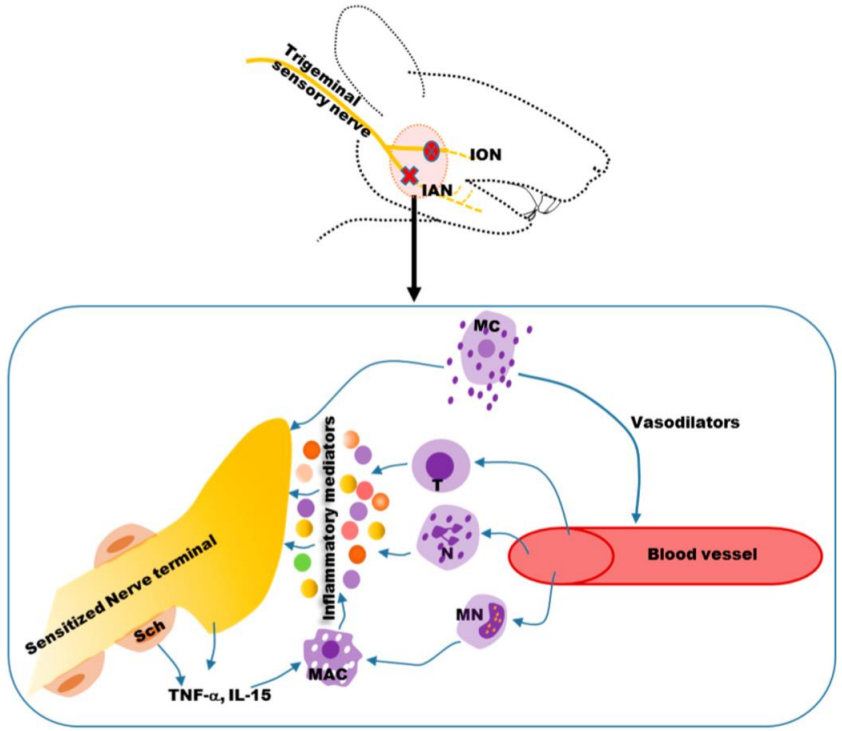

Figure 1. The immune response near the site of a nerve injury sensitizes the nerve terminals. Resident mast cells (MC) are activated and release vasodilators that act on blood vessels, leading to infiltration of immune cells, such as neutrophils, monocytes and T-lymphocytes. Monocytes differentiate into macrophages. These immune cells release inflammatory mediators that sensitize terminals of injured and uninjured nerves. Schwann cells (Sch) that cover the myelinated nerves release cytokines (e.g., TNF-α, IL-15) that also facilitate the recruitment and activation of macrophages. ION: Inferior orbital nerve; IAN: Inferior alveolar nerve; MC: Mast cell; T: T-lymphocyte; N: Neutrophil; MN: Monocyte; MAC: Macrophage; TNF-α: Tumor necrosis factor alpha; IL-15: Interleukin 15.

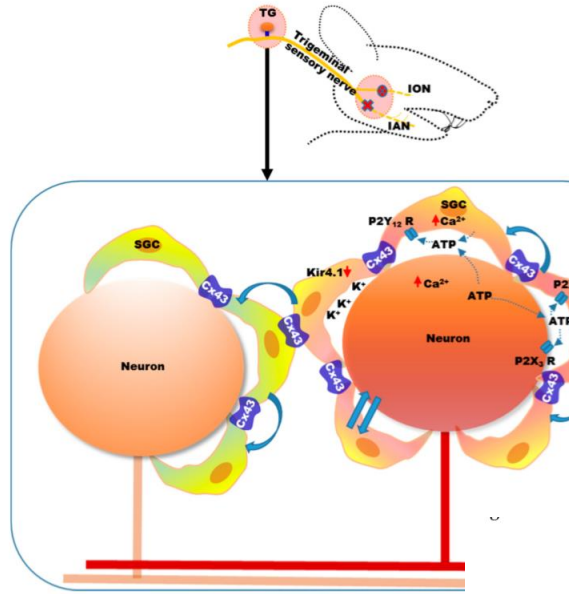

Figure 2. Satellite glial cells (SGCs) surrounding the cell bodies o
an important role in the development of neuropathic pain. Nerve
and proliferation of SGCs in the sensory ganglia. They interact wi
signaling. ATP, released from SGCs as well as from injured neurons
resulting in the mutual activation of neurons and SGCs (indicated in t
Purinergic receptors, P2Y12 and P2X3, are upregulated in the trigeminal
SGCs express the inwardly rectifying potassium channel, Kir4.1, which
potassium homeostasis. Following nerve injury, expression of Kir4.1 is c
ganglion, thereby increasing extracellular potassium and neuronal excit
the SGCs also increases (indicated in the diagram by solid curved
increase in expression of the common gap junction protein, connexi
ganglion following nerve injury. This communication spreads to the SG
turn sensitizes these cells. ATP: Adenosine triphosphate; P2Y12: Pu
P2X3: Purinergic receptor subtype X3; Kir4.1: Inwardly rectifying pc
Trigeminal ganglion.

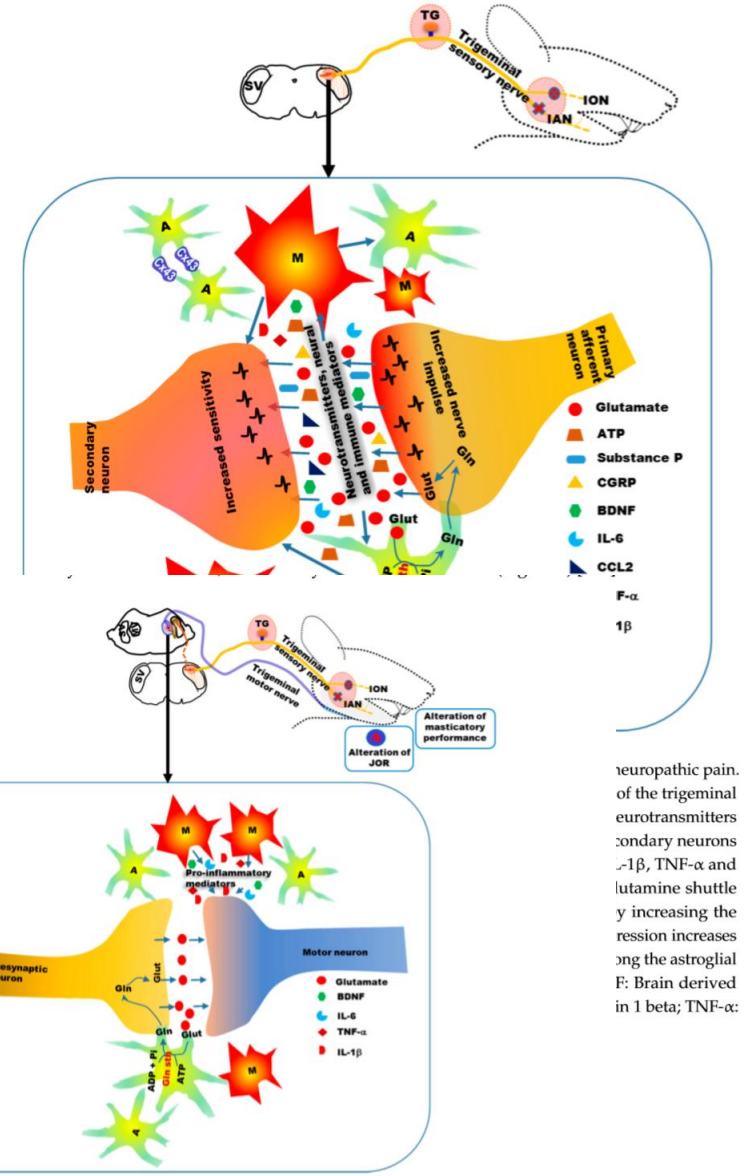

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Figure 5. Schematic showing the involvement of glia in the trigeminal motor nucleus in the change in orofacial motor activity following nerve injury. Activated microglia and astroglia are observed in the motor trigeminal nucleus following nerve injury. Similar to sensory nuclei, pro-inflammatory mediators might be released from hyperactive microglia, and these mediators may alter the sensitivity of motor neurons. The astroglial glutamate–glutamine shuttle might also participate in the modulation of motor neuronal activity. BDNF: Brain derived neurotrophic factor; IL-6: Interleukin 6; IL-1β: Interleukin 1 beta; TNF-α: Tumor necrosis factor alpha; Glut: Glutamate; Gln: Glutamine; Gln sth: glutamine synthetase;

PTNP-mouse model

- A combination of approaches (cortical intrinsic imaging, immunohistochemical and behavioural analysis), our study aimed to decipher the nature of functional and structural changes in a **mouse model of orofacial neuropathic pain**, focusing on cortical areas involved in various pain components.
- Our results show that chronic neuropathic orofacial pain is associated with decreased haemodynamic responsiveness to whisker stimulation in the barrel field cortex.
- This reduced functional activation is likely due to the increased basal neuronal activity (measured indirectly using cFos and phospho-ERK immunoreactivity) observed in several cortical areas, including the contralateral barrel field, motor and cingulate cortices.
- In the same animals, immunohistochemical analysis of markers for active pre- or postsynaptic elements (Piccolo and phospho-Cofilin, respectively) revealed an increased immunofluorescence in deep cortical layers of the contralateral barrel field, motor and cingulate cortices. These results suggest that long-lasting orofacial neuropathic pain is associated with exacerbated neuronal activity and synaptic plasticity at the cortical level.

Thibault K, Rivière S, Lenkei Z, Férézou I, Pezet S. Orofacial Neuropathic Pain Leads to a Hyporesponsive Barrel Cortex with Enhanced Structural Synaptic Plasticity. *PLoS One*. 2016;11(8):e0160786. Published 2016 Aug 22. doi:10.1371/journal.pone.0160786

BMS experimental study overview

- **Abstract**
- Burning mouth syndrome (BMS) is one of the most frequently seen idiopathic pain conditions in a dental setting. Peri- and postmenopausal women are most frequently affected, and patients who experience BMS complain of persistent burning pain mainly at the tip and the bilateral border of the tongue. Recent studies have assessed whether BMS is a neuropathic pain condition, based on morphologic changes in biopsied tongue specimens, and whether there are abnormal pain responses in patients with this disease. Somatosensory studies have reported some abnormal findings in sensory and pain detection thresholds with inconsistency; however, the most distinct finding was exaggerated responses to painful stimuli. Imaging and electrophysiologic studies have suggested the possibility of dysregulation of the pain-modulating system in the central nervous system, which may explain the enhanced pain responses despite the lack of typical responses toward quantitative sensory tests. Basic studies have suggested the possible involvement of neuroprotective steroids, although the underlying mechanisms of this condition have not been elucidated. Experimental studies are looking for preferable supportive therapies for BMS patients despite the obscure pathogenesis.

Yoshiki Imamura[1,2], Akiko Okada-Ogawa[1,2], Noboru Noma[1,2], Takahiro Shinozaki[1,2], Kosuke Watanabe[1], Ryutaro Kohashi[3], Masamichi Shinoda[4,5], Akihiko Wada[6], Osamu Abe[7], Koichi Iwata[4,5] **A Perspective From Experimental Studies of Burning Mouth Syndrome.** Oral Sci. 2020 Mar 28;62(2):165-169.doi: 10.2334/josnusd.19-0459. Epub 2020 Mar 11.

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Sensorimotor and Pain Modulation Brain Abnormalities in Trigeminal Neuralgia: A Paroxysmal, Sensory-Triggered Neuropathic Pain

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Abstract

Objective: Idiopathic trigeminal neuralgia (TN) is characterized by paroxysms of severe facial pain but without the major sensory loss that commonly accompanies neuropathic pain. Since neurovascular compression of the trigeminal nerve root entry zone does not fully explain the pathogenesis of TN, we determined whether there were brain gray matter abnormalities in a cohort of idiopathic TN patients. We used structural MRI to test the hypothesis that TN is associated with altered gray matter (GM) in brain areas involved in the sensory and affective aspects of pain, pain modulation, and motor function. We further determined the contribution of long-term TN on GM plasticity.

Methods: Cortical thickness and subcortical GM volume were measured from high-resolution 3T T1-weighted MRI scans in 24 patients with right-sided TN and 24 healthy control participants.

Results: TN patients had increased GM volume in the sensory thalamus, amygdala, periaqueductal gray, and basal ganglia (putamen, caudate, nucleus accumbens) compared to healthy controls. The patients also had greater cortical thickness in the contralateral primary somatosensory cortex and frontal pole compared to controls. In contrast, patients had thinner cortex in the pregenual anterior cingulate cortex, the insula and the orbitofrontal cortex. No relationship was observed between GM abnormalities and TN pain duration.

Conclusions: TN is associated with GM abnormalities in areas involved in pain perception, pain modulation and motor function. These findings may reflect increased nociceptive input to the brain, an impaired descending modulation system that does not adequately inhibit pain, and increased motor output to control facial movements to limit pain attacks.

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