NeuroImage: Clinical 20 (2018) 901–912

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

A meta-analytic study of experimental and chronic orofacial pain excluding headache disorders

Lizbeth J. Ayoub[a,d], David A. Seminowicz[b,c], Massieh Moayedi[a,d,e,*]

[a] Faculty of Dentistry, University of Toronto, Toronto, ON, Canada
[b] Department of Neural and Pain Sciences, School of Dentistry, University of Maryland, Baltimore, MD, United States
[c] Center to Advance Chronic Pain Research, University of Maryland Baltimore, Baltimore, MD, United States
[d] Centre for the Study of Pain, University of Toronto, Toronto, ON, Canada
[e] Department of Dentistry, Mount Sinai Hospital, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Pain
VBM
sMRI
MRI
Facial pain
Orofacial pain
Trigeminal
fMRI
Brain
Plasticity
Grey matter volume

ABSTRACT

Chronic orofacial pain (COFP) disorders are prevalent and debilitating pain conditions affecting the head, neck and face areas. Neuroimaging studies have reported functional and grey matter abnormalities, but not all the studies have reported consistent findings. Identifying convergent abnormalities across COFPs provides a basis for future hypothesis-driven research aimed at elucidating common CNS mechanisms. Here, we perform three coordinate-based meta-analyses according to PRISMA guidelines to elucidate the central mechanisms of orofacial pain disorders. Specifically, we investigated consistent patterns of: (1) brain function to experimental orofacial pain in healthy subjects, (2) structural and (3) functional brain abnormalities in COFP. We computed our coordinate-based meta-analyses using GingerALE. The experimental pain meta-analysis revealed 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. The structural COFP meta-analysis identified consistent higher grey matter volume/concentration in the right ventral thalamus and posterior putamen of COFP patients compared to healthy controls. The functional COFP meta-analysis identified a consistent 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. Overall, these findings provide evidence of brain abnormalities in pain-related regions, namely the thalamus and insula, across different COFP disorders. The convergence of thalamic abnormalities in both structure and function suggest a key role for this region in COFP pathophysiology.

1. Introduction

Chronic orofacial pain (COFP) disorders involve the head, face, and neck areas, notably the masticatory muscles, temporomandibular joint and associated structures. COFP is an umbrella term that encompasses several debilitating chronic syndromes affecting the orofacial region (Benoliel and Sharav, 2010). To meet these broad classification terms, the painful syndrome must be present for > 12 weeks or persisting beyond expected healing time. As such, there are few epidemiological studies investigating the prevalence of all COFP disorders. It has been estimated that 7–11% of the population report COFPs (Benoliel and Sharav, 2008; Zakrzewska, 2013).

Pain in the orofacial region is psychologically important, as it is implicated in vital biological functions such as eating, drinking, speech and sexual behavior (Vadivelu et al., 2014). From a systems perspective, there are at least two mechanisms by which pain in the trigeminal system can potentially become chronic: (1) increased nociceptive drive along the trigeminal nociceptive pathway and/or (2) dysfunctional or aberrant descending modulation from supraspinal regions (Davis and Moayedi, 2013; Tracey and Bushnell, 2009). Increased nociceptive drive is associated with increased activity in the trigeminal nociceptive pathway's central projections, including the trigeminal brainstem sensory nuclear complex, the ventroposteriormedial (VPM) and mediodorsal (MD) nuclei of the thalamus, and further cortical projections of the trigeminothalamic tract such as the primary somatosensory cortex (S1), the mid-cingulate cortex (MCC), and the dorsoposterior insula (Sessle, 2000). Additionally, increased nociceptive drive is related to grey matter plasticity in healthy subjects (Teutsch et al., 2008). Over extended periods of time, this nociceptive barrage can drive maladaptive plasticity, and engender central sensitization

* Corresponding author at: Faculty of Dentistry – University of Toronto, 124 Edward Street, Room 260B, Toronto, ON M5G 1G6, Canada.
E-mail address: m.moayedi@dentistry.utoronto.ca (M. Moayedi).

https://doi.org/10.1016/j.nicl.2018.09.018
Received 18 April 2018; Received in revised form 17 September 2018; Accepted 21 September 2018
Available online 25 September 2018

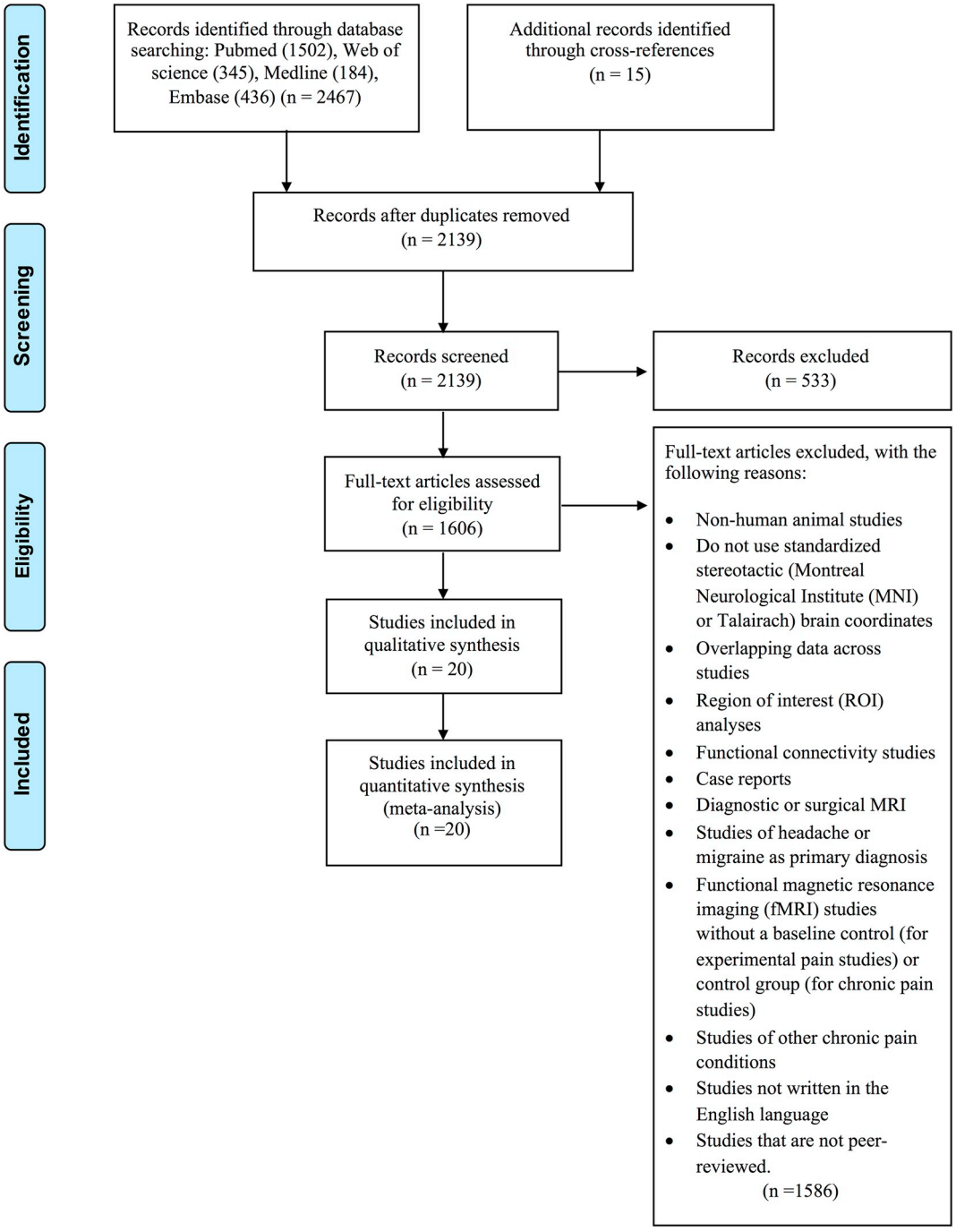

Fig. 1. Article selection for functional studies. Flow diagram according to PRISMA guidelines for functional MRI article selection procedures.

(Kuner and Flor, 2016). These processes lead to a disruption of function, and a diseased state.

Descending modulation of pain involves cortical and subcortical brain structures, typically described as including dorsolateral and medial prefrontal cortices (dlPFC, mPFC), anterior cingulate cortex (ACC), anterior insula, amygdala, and brainstem regions including the periaqueductal grey (PAG), and rostroventromedial medulla (RVM) (Bushnell et al., 2013). Involvement of these descending modulatory circuits has been reported in functional magnetic resonance imaging (fMRI) studies of placebo analgesia (Colloca et al., 2016) and conditioned pain modulation (Bogdanov et al., 2015; Youssef et al., 2016). In the diseased state, it is thought that the pain modulatory circuits become dysfunctional, where endogenous analgesic brainstem changes occur (Mills et al., 2018) and maladaptive pain remains (Sharav and Benoliel, 2015).

Here, we provide a quantitative meta-analysis of orofacial pain in health and in disease. COFPs investigated are non-odontogenic in origin and include musculoskeletal pain disorders (e.g., temporomandibular disorders (TMD)) and neuropathic orofacial pain disorders (e.g., trigeminal neuropathic pain (TNP), burning mouth syndrome (BMS)), as well as a number of other orofacial syndromes. A meta-analysis of experimental pain in healthy subjects can provide an understanding of spatially consistent brain activations in response to acute nociceptive stimulation in the orofacial region. Furthermore, separate meta-analyses of COFP structure and function may highlight consistent structural and functional abnormalities, respectively, in chronic pain. A recent meta-analysis of experimental dental pain found consistent activation in the dlPFC (Lin et al., 2014). Another meta-analysis investigating

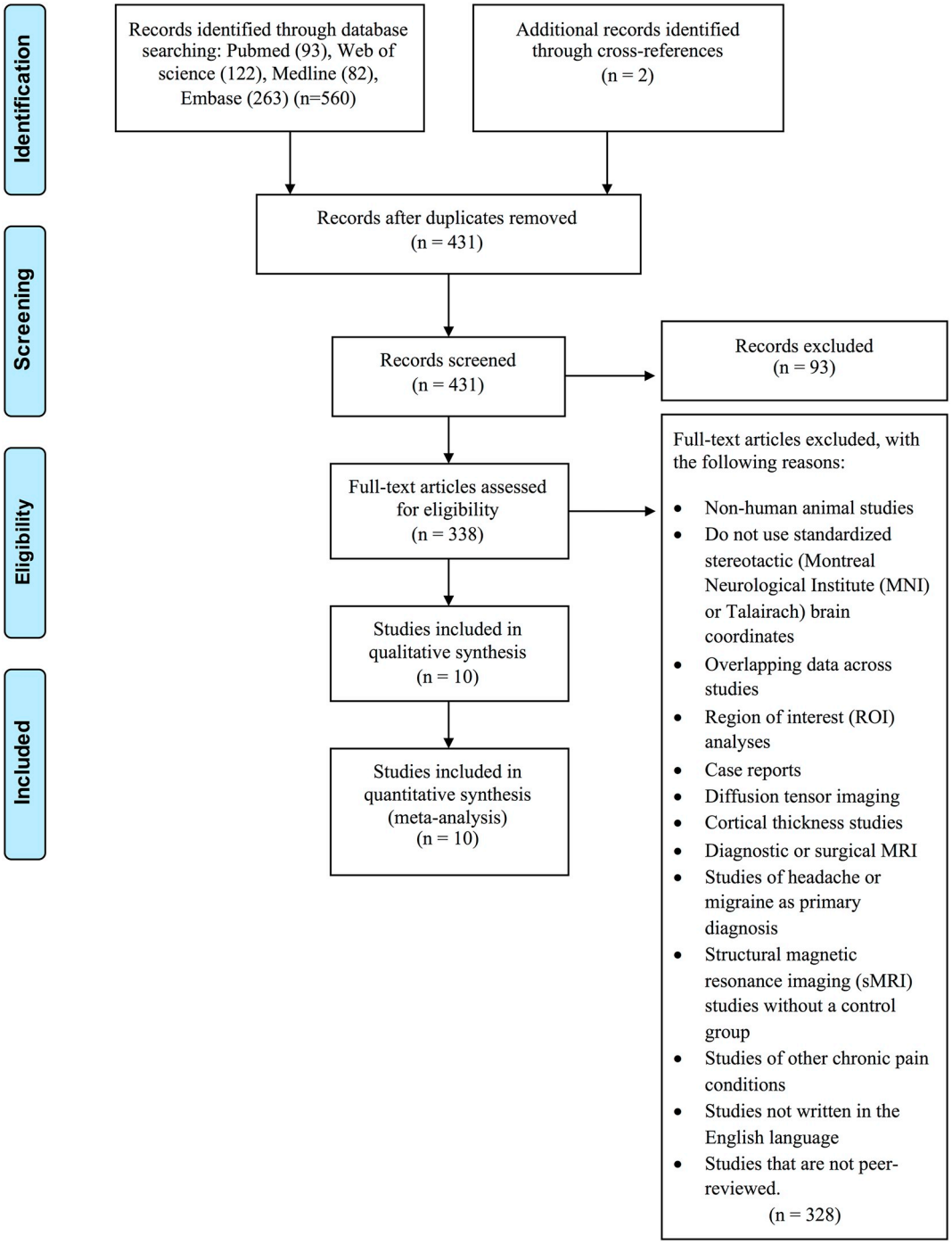

Fig. 2. Article selection for structural studies. Flow diagram according to PRISMA guidelines for structural MRI (grey matter) article selection procedures.

TMD and TNP found consistent structural and functional abnormalities in the thalamus and S1 (Lin, 2014). Several studies have found structural and functional abnormalities in COFP, but their findings are divergent. As such, a quantitative meta-analysis including phenotypically different COFP disorders can provide a directionality for future studies investigating pain mechanisms in COFP.

Therefore, the aim of the current study was to perform three coordinate-based meta-analyses: (1) functional response to experimental pain in the orofacial region in healthy subjects; (2) functional and (3) structural abnormalities in COFP disorders. We hypothesized that the brain activations during experimental orofacial pain, compared to baseline conditions, would show consistent activation along the trigeminal nociceptive pathways, and descending modulatory pathways. In our functional and structural meta-analysis of COFP, we hypothesized that trigeminal nociceptive and pain modulatory brain regions would show consistent abnormalities across COFP disorders, in COFP patients compared to healthy controls.

2. Methods

Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 guidelines and the PRISMA checklist is reported in Supplementary Table A.1 (Moher et al., 2015).

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.

2.1. Article selection criteria

We selected articles using the following exclusion criteria: 1) non-human animal studies; 2) absence of standardized stereotactic (i.e. Montreal Neurological Institute (MNI) or Talairach (Talairach and Tournoux, 1988)) brain coordinates; 3) overlapping data across studies, such as reviews 4) region of interest (ROI) analyses; 5) case reports; 6) diagnostic or surgical MRI; 7) diffusion tensor imaging; 8) studies of headache or migraine as primary disorders; 9) studies of other chronic pain conditions; 10) studies without a baseline for experimental pain studies or control groups for COFP studies; 11) studies not written in the English language; and 12) not peer-reviewed studies. We also excluded functional connectivity and cortical thickness analyses. Hence, only voxel-based morphometry (VBM) and fMRI, including blood-oxygen-level-dependent (BOLD) and positron-emission tomography (PET) studies reporting standardized whole-brain coordinates were used for the purpose of this study. Studies of headache and/or migraine were excluded because our meta-analyses focused on musculoskeletal and neuropathic orofacial pain, rather than craniofacial pain. In addition to our exclusion criteria that are meant to reduce experimental bias, we carefully screened for the risk of bias in terms of conflicts of interest on an individual study scale. All authors of the studies included in our study have no conflict of interests. Risk of bias across studies may affect our ALE analyses since some authors share the same collaborations and data might have been transferred from one study to the other. Authors do not claim such data transfers, and we could not have excluded such articles based on these assumptions. We assigned a quality score for each article selected based on a modified version of Downs and Black's checklist for quality assessment (Downs and Black, 1998; Supplementary Table A.2) as reported by Burns and colleagues (Burns et al., 2016). A maximum quality score based on external and internal validity is 20. Finally, two investigators (LA, MM) independently reviewed the exclusion criteria for article eligibility.

2.2. Database search

A summary of our article selection from the database search on 22 March 2018 is provided according to the PRISMA guidelines (see Figs. 1 and 2). We performed two separate systematic searches across four literary databases through all articles until 22 March 2018: ISI Web of Science, PubMed, Embase and Medline. We used the following keyword search expression for functional studies of experimental pain and COFP disorders across all databases: *"((orofacial OR (trigeminal OR masseter OR burning mouth syndrome OR BMS OR temporomandibular OR TMD)) AND pain AND (fMRI OR functional magnetic resonance imaging OR functional MRI OR (BOLD OR blood oxygen level dependent) OR (PET OR*

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* medial prefrontal cortex, *MTG* middle temporal gyrus, *NAc* nucleus accumens, *OFC* orbitofrontal cortex, *pACC* pregenual anterior cingulate cortex, *ParaHc* parahippocampal gyrus, *PCC* posterior cingulate cortex, *PCL* paracentral lobule, *PCu* precuneus, *PFC* prefrontal cortex, *pINS* posterior insular cortex, *PIFP* persistent idiopathic facial pain, *PMC* premotor cortex, *pre-SMA* pre supplementary motor area, *PTN* painful trigeminal neuropathy, *Pu* putamen, *R* right, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *sACC* subgenual anterior cingulate cortex, *SMA* supplementary motor area, *SPL* superior parietal lobule, *STG* superior temporal gyrus, *Thal* thalamus, *Ti* inferior temporal area, *TMD* temporomandibular disorder, *TN* trigeminal neuralgia, *VP* ventral posterior thalamus, *VL* ventral lateral thalamus, *vlPFC* ventrolateral prefrontal cortex, *VMN* trigeminal motor nucleus, *VMSN* trigeminal sensory nucleus, VS ventral striatum.

positron emission tomography) OR (ASL OR arterial spin labelling)))". In addition, we used the following keyword search terms to identify structural studies of COFP across all databases: "*((orofacial OR (trigeminal OR masseter OR burning mouth OR BMS OR temporomandibular OR TMD)) AND Pain AND (DBM OR deformation based morphometry OR (VBM OR voxel-based morphometry OR DARTEL) OR grey matter OR gray matter OR sMRI))"*.

2.3. Activation/anatomical likelihood of estimation (ALE) meta-analysis

Our activation/anatomical likelihood estimation (ALE) based meta-analysis was performed using the GingerALE software (v2.3.6). Briefly, the purpose of the ALE algorithm is to compute whole-brain standardized coordinates into a voxel-based statistical value, which projects the probability of activation or anatomical alterations of brain regions (Eickhoff et al., 2012).

2.4. Dataset foci

Peak voxel brain coordinates (X, Y, Z) of healthy subjects under noxious stimuli and pain-free baseline condition, and COFP patients reporting abnormal grey matter structure and brain region activation, were used as data. Our structural meta-analysis included foci from studies investigating grey matter volume and concentration (GMV/GMC). Our functional meta-analysis included foci from studies investigating cerebral blood flow.

All data were extracted manually from each study and organized in text files according to its specific contrast and subject number (Eickhoff et al., 2009). First, all brain coordinates (foci) reported in Talairach space were converted into MNI space using the algorithm "Brett: Talairach to MNI" (Brett et al., 2002). Each group of foci included the number of subjects for smoothing estimation purposes (Eickhoff et al., 2012). Furthermore, foci were organized into six separate datasets according to subject group and their findings in terms of brain region activity and GMV/GMC as follows: (1) greater brain region activation in response to experimental pain compared to baseline control in healthy subjects; (2) lesser brain region activation in response to experimental pain compared to baseline control in healthy subjects; (3) GMV/GMC increase in COFP patients compared to a control group; (4) GMV/GMC increase in COFP patients compared to a control group; (5) greater brain region activity in COFP patients compared to a control group; (6) lesser brain region activity in COFP patients compared to a control group. Data was confirmed by two investigators, independently (LA, MM). Therefore, datasets 1 and 2 identify consistent brain region of activation in response to acute experimental orofacial pain; datasets 3 and 4 identify consistent GMV/GMC abnormalities between COFP and healthy participants; and datasets 5 and 6 identify consistent brain activity abnormalities between COFP and healthy participants.

2.5. Dataset analysis

We used the single dataset analysis module in the GingerALE software to compute each of the contrasts, as described elsewhere (Eickhoff et al., 2012). A total of six single dataset analyses were performed. We employed the revised Eickhoff algorithm (Eickhoff et al., 2009) for the functional and structural COFP meta-analyses. For the acute experimental pain meta-analysis, we used Turkeltaub's Non-Additive algorithm to potentially minimize effects within a subject group and between experiments (Turkeltaub et al., 2012). Briefly, each analysis consisted of four steps performed automatically by the GingerALE software: 1) calculating ALE scores, 2) deriving a null distribution, 3) statistical thresholding and 4) correction for multiple comparisons using cluster-based thresholding. An ALE score was generated for each of the foci to produce a Modeled Activation (MA) map. All MA maps were calculated by finding the maximum value with the "random effects" selection, which permits the generalization of results (Eickhoff et al., 2009). All the MA maps were united to form the unthresholded ALE map. Then, the Gaussian null distribution was used to calculate the

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, *fALFF* fractional apitude of low-frequency fluctuation, *fMRI* functional magnetic resonance imaging, *ITN* idiopathic trigeminal neuralgia, *M* men, *NP* neuropathic pain, *QS* quality score, *R* right, *ReHo* regional homogeneity, *TMD* temporomandibular disorder, *W* women.

[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 vibration imaginable").

ALE statistic, which attributes a p value to every ALE score, and forms the thresholded ALE image. The cluster analysis was then performed on the thresholded ALE image with the cluster-level inference algorithm at $p < .05$, based on 1000 permutations, with a cluster-forming threshold of $p < .005$. We also conducted the same analysis using a more conservative cluster-forming threshold of $p < .001$ for comparative purposes. The resulting cluster-corrected maps were visualized with the Mango software (v4.0.1) (rii.uthscsa.edu/mango) and the multiple axial slice images were created using MRIcron software (Rorden and Brett, 2000).

3. Results

3.1. Article search

Our functional database search resulted in 2467 articles and 20 articles were included (Fig. 1). Our structural database search resulted in 560 articles and ten structural COFP articles were selected (Fig. 2). In studies of healthy subjects, 12 functional studies report brain region activation in response to experimental noxious stimuli (Table 1). In COFP studies, ten structural studies are shown in Tables 2 and 3 and eight functional studies are shown in Tables 4 and 5.

3.2. Methodological quality

Quality scores for each study are reported in Tables 1, 2 and 4. Average quality scores for functional experimental pain, structural and functional COFP studies were 16.17 ± 0.94, 17.60 ± 1.27 and 17.63 ± 1.19 (mean ± standard deviation), respectively, from a maximum score of 20. Some studies did not report sufficient statistical calculations on demographics, which accounted for one point. In addition, none of the studies reported performing sample size calculations a priori.

3.3. Dataset results

Six separate datasets resulted from our data extraction with their respective total number of foci, subjects and experiments:

- Brain region activation during experimental pain > baseline in healthy subjects: 260 foci results from 198 total subjects in 14 experiments;
- Brain region activation during experimental pain < baseline in healthy subjects: 80 foci resulted from 86 total subjects in 6 experiments;
- GMV/GMC in COFP patients > healthy controls: 21 foci resulted from 199 total subjects in 5 experiments;
- GMV/GMC in COFP patients < healthy controls: 66 foci resulted from 504 subjects in 11 experiments.
- Brain activity in COFP patients < healthy controls: 38 foci resulted from 343 total subjects in 9 experiments;
- Brain activity in COFP patients > healthy controls: 109 foci resulted from 300 subjects in 8 experiments;

3.4. ALE Meta-analyses

3.4.1. Experimental orofacial pain stimuli in healthy subjects

Our ALE meta-analysis of healthy individuals subjected to experimental pain in the orofacial area showed consistently greater brain region activation in six regional clusters: bilateral MD extending to the posterior thalamus, bilateral posterior MCC (pMCC), bilateral secondary somatosensory cortices (S2), the right posterior parietal cortex (PPC) extending into S1 and the right insula, significant at cluster-corrected $p < .05$ and cluster-forming threshold of $p < .005$ (Fig. 3; Table 6). We also found similar results at a more conservative cluster-forming threshold of $p < .001$ with five clusters of activation, which

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.

included bilateral thalami, the right insula, the right PPC, the left S2 and the left pMCC (Supplementary Table A.3; Supplementary Fig. A.1). The right pMCC and the right S2 did not survive at the cluster-forming threshold $p < .001$. In addition, we found decreased brain activity in the hand region of the right S1 and primary motor cortex (M1) in response to nociceptive stimulation in the orofacial region at both thresholds, $p < .005$ and $p < .001$. A distinction in functional variations is observed in the region of S1; an increase is found in the orofacial region of S1 as opposed to a decrease in the hand region of S1.

3.5. COFP patients vs. healthy controls

3.5.1. Meta-analysis of structural brain imaging studies

Our ALE meta-analysis of COFP compared to healthy controls found consistently greater GMV/GMC in one cluster which included the right thalamus (ventral lateral (VL)) and posterior putamen (Fig. 4; Table 7). These findings are significant at a cluster-corrected $p < .05$ and a cluster-forming threshold of $p < .005$, but not at $p < .001$.

3.5.2. Meta-analysis of functional brain imaging studies

Our ALE meta-analysis of COFP patients in comparison with healthy controls found that COFP patients had consistently greater brain function (activity or resting-state fluctuations) in the left medial and posterior thalamus (MD, pulvinar) in COFP and less function in the left posterior insula in COFP compared to controls (Fig. 5, Table 7). Notably, the region of the thalamus overlaps with the finding in experimental orofacial nociceptive stimulation. These findings are significant at a cluster-corrected $p < .05$ and a cluster-forming threshold of $p < .005$. At a more conservative threshold of $p < .001$, only the left posterior insula cluster survives along with an additional cluster in the left cerebellum (Supplementary Fig. A.2).

4. Discussion

COFPs are heterogeneous disorders but have one chief symptom in common: chronic pain in the head and neck region. Finding convergence of brain regions of activation across COFPs would suggest overlap in the neural mechanisms of the common feature of these disorders. We performed three ALE meta-analyses to identify consistent (1) brain regions of activation in response to experimental orofacial pain in healthy subjects and (2) abnormal grey matter and (3) abnormal brain function in COFP. We found the thalamus across all meta-analyses, suggesting a key role in orofacial pain, notably in COFP pathophysiology.

4.1. Experimental orofacial stimuli

The first key set of findings in this study are related to experimental orofacial pain in healthy participants. We identified consistent activations along the ascending trigeminal pathway, including: thalamus, S1, S2, PPC, pMCC, insula, i.e. regions typically reported in pain neuroimaging (Duerden and Albanese, 2013). We also found less activation in the hand region of S1 and M1. The sensory-discriminative dimension (location, duration, and intensity) of pain is thought to be processed in somatosensory regions, including S1, S2 and the PPC (Oshiro et al., 2009). S1 and 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). The contributing foci to the right

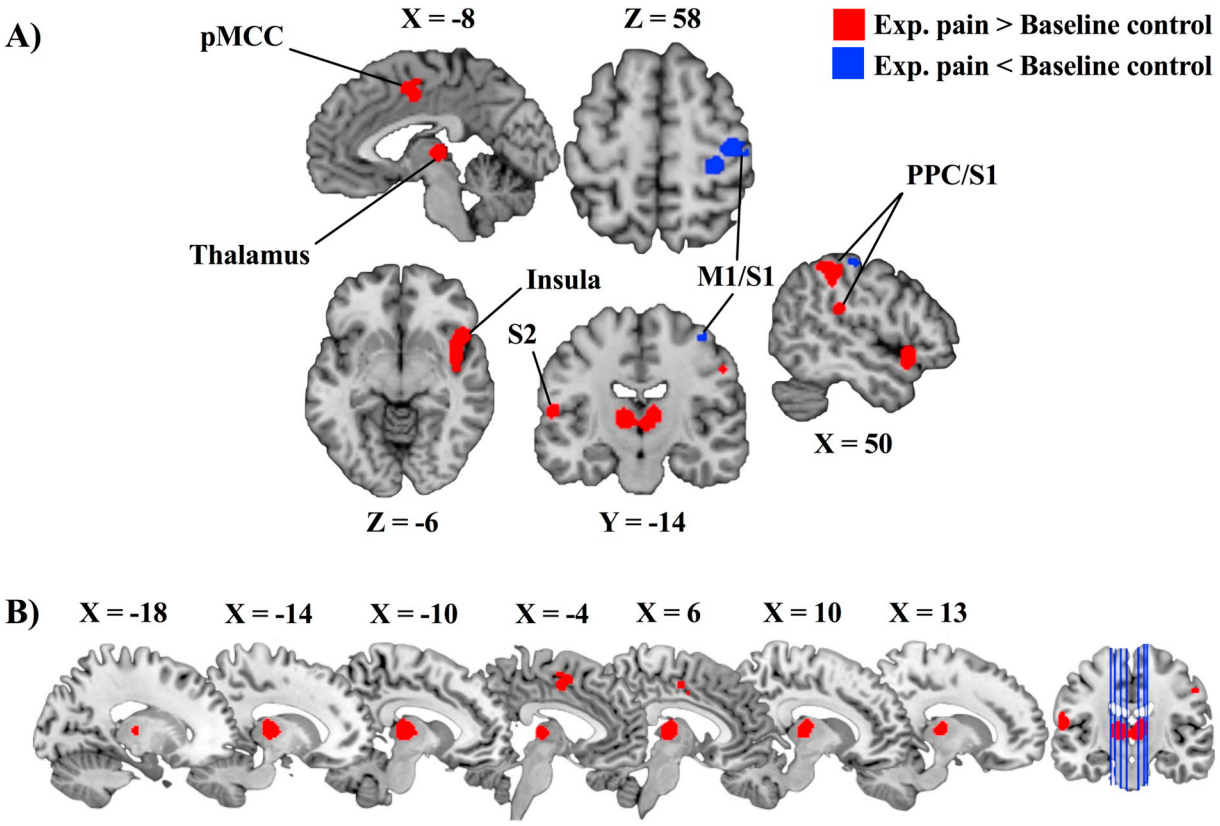

Fig. 3. (A) Significant ALE effects of functional MRI studies of healthy subjects during experimental orofacial pain. The functional MRI meta-analysis in healthy subjects identified significant ALE effects in bilateral thalami, bilateral posterior mid-cingulate cortex (pMCC) and bilateral secondary somatosensory 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 $p < .005$).

orofacial S1 cluster originate from studies which applied right facial noxious stimuli. Although we would expect bilateral S1 activation, as 20% of ascending fibers in the trigeminal tract remain ipsilateral to the innervated facial area (Roberts and Matzke, 1971; Sessle, 2000), we observed only ipsilateral activation. We also found less activation in the hand region of S1 and M1, suggesting it could be related to enhancing the spatial acuity of the stimulus. In addition, we observed activation in the PPC—a higher order somatosensory processing region, which has suggested to be a suitable target for pain intensity management (Moulton et al., 2012).

We further found consistent activation salience processing regions: pMCC and insula (Seeley et al., 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 (Dum et al., 2016). Indeed, we also 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 to it (Perini et al., 2013; Shackman et al., 2011). This meta-analysis also identified activation in the insula, a region referred to as a multi-dimensional 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.

4.2. COFP disorders

Acute pain states resolve in most individuals, but in some cases, pain may persist beyond its expected healing duration, becoming chronic. Thus, we reviewed the structural and functional brain imaging literature in COFP to identify convergent patterns of brain abnormalities in these disorders. An increasing number of studies have reported structural brain abnormalities in chronic pain populations (Davis and Moayedi, 2013). Our meta-analysis found consistently greater GMV/GMC in the right VL thalamus and posterior putamen of patients compared to controls across COFP studies. These regions were identified in a previous TMD study (Younger et al., 2010), and were positively correlated with TMD duration (Moayedi et al., 2012). In contrast, one other study did not find significant GMV abnormalities in TMD (Gustin et al., 2011). Such disparities across studies may be related to statistical differences, including differences in the sample size of the studies. Our ALE finding however, weighted by a cumulative sample size, showed an increase in thalamic GMV/GMC. Evidence from a repeated experimental pain model in healthy individuals suggests that GMV increases are driven by increases in nociceptive input (Teutsch et al., 2008). In the current study, however, we could not discern whether GMV/GMC abnormalities in COFP are pre-existing or a result of persistent nociceptive drive.

We identified convergent brain function in COFP using the quantitative ALE analysis, which was only previously qualitatively established in TN and TMD studies (Lin, 2014). Our meta-analysis of functional

Table 6
ALE results of functional experimental orofacial pain.

Brain regions	BA	ALE Value	MNI coordinates			Cluster Size (mm^3)
			X	Y	Z	
Experimental pain > baseline control						
L Thalamus		0.033	−10	−20	6	4880
R Thalamus		0.022	6	−18	6	
R Insula	13	0.018	48	18	−8	3336
R mid/pINS		0.015	42	0	−6	
R aINS	13	0.012	42	10	−6	
R pINS		0.009	42	−6	−6	
R STG	38	0.009	40	2	−18	
R PPC/S1	40	0.015	50	−32	50	2240
R PPC	40	0.013	46	−38	54	
R S1	2	0.010	54	−22	44	
R S1	3	0.009	54	−14	40	
L S2	41	0.017	−58	−20	14	2176
L S2	40	0.010	−58	−26	34	
R pMCC	31	0.017	2	−8	46	2056
L pMCC	24	0.015	−2	−2	48	
pMCC	24	0.012	0	4	48	
L SMA	6	0.009	−2	−6	56	
R pMCC	24	0.009	4	−2	38	
R S2	40	0.014	54	−30	24	1696
R PPC	40	0.013	66	−34	24	
Experimental pain < baseline control						
R S1	3	0.010	28	−28	56	1792
R M1	4	0.009	40	−18	62	
R S1	3	0.009	48	−20	60	

ALE meta-analytic results of functional experimental pain studies ($n = 12$), significant at a cluster-corrected $p < .05$ and cluster-forming threshold of $p < .005$.
Abbreviations: *aINS* anterior insular cortex, *ALE* activation likelihood estimation, *BA* Brodmann area, *L* left, *M1* primary motor cortex, *MNI* Montreal Neurological Institute, *mid INS* mid insular cortex, *pINS* posterior insular cortex, *pMCC* posterior mid-cingulate cortex, *PPC* posterior parietal cortex, *R* right, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *SMA* supplementary motor area, *STG* superior temporal gyrus.

Table 7
ALE results of COFP studies.

Brain regions	ALE Value	MNI Coordinates			Cluster Size (mm^3)
		X	Y	Z	
Structural COFP studies					
COFP patients (GMV/GMC) > Controls (GMV/GMC)					
R Thalamus	0.012	16	−10	2	1640
R posterior Putamen	0.009	28	−12	10	
Functional COFP studies					
COFP patients > Controls					
L Thalamus	0.026	−6	−24	8	1080
COFP patients < Controls					
L pINS	0.013	−46	−4	10	1336
L pINS	0.010	−42	−12	6	

ALE meta-analytic results of structural COFP ($n = 10$) and functional studies ($n = 8$), significant at a cluster-corrected $p < .05$ and cluster-forming threshold of $p < .005$.
Abbreviations: *ALE* activation/anatomical likelihood estimation, *COFP* chronic orofacial pain, *GMV/GMC* grey matter volume/grey matter concentration, *MNI* Montreal Neurological Institute, *pINS* posterior insular cortex.

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 in line 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 (Alshelh et al., 2016; Ji et al., 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-aminobutyric acid (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 (Ushida et al., 2010). We also report that COFP patients have less function in the posterior insula, a region typically observed in experimental pain studies, and in line with previous evidence of insular abnormality in TN (Yuan et al., 2018) and TMD (Nebel et al., 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.

4.3. Study limitations

There are several limitations to our study. First, we limited our search to orofacial pain, and have excluded headache and migraine disorders to focus on COFPs. As a result, our study may not be representative of the field as a whole.

The experimental orofacial pain meta-analysis did not analyze

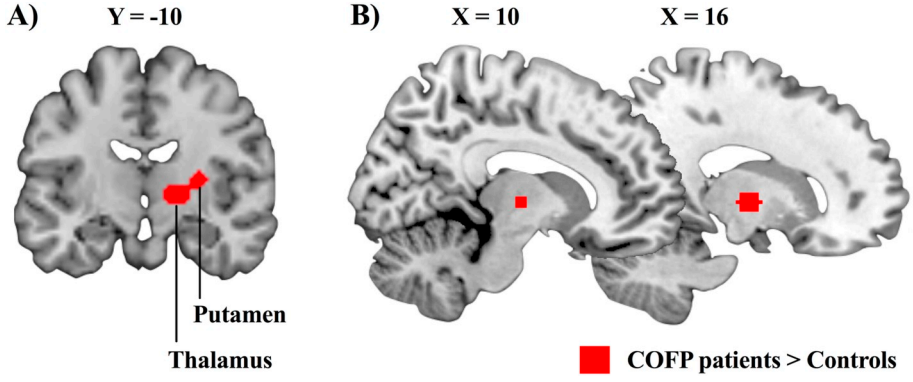

Fig. 4. (A) Significant ALE effects of structural COFP studies. The structural MRI (grey matter) COFP meta-analysis identifies structural GMV/GMC increase in the right thalamus and putamen in COFP patients compared to healthy subjects, significant at $p < .05$ (cluster-corrected, cluster-forming threshold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

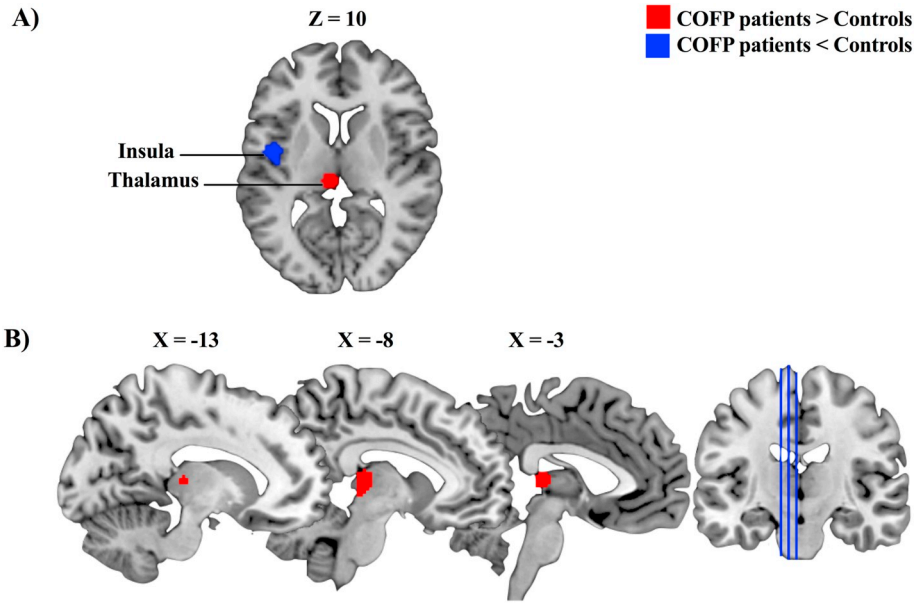

Fig. 5. (A) Significant ALE effects of functional COFP studies. The functional MRI COFP meta-analysis identified significant ALE effects in the left posterior thalamus and left posterior insula of COFP patients compared to healthy controls, significant at $p < .05$ (cluster-corrected, cluster-forming 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 $p < .005$).

studies according to stimulation laterality or noxious stimulus modality. Recent studies have led us to hypothesize bilateral activation of regions associated with orofacial nociceptive processing (Mazzola et al., 2009; Nash et al., 2010a; Nash et al., 2010b). In addition, a study reported that different stimulus modalities have both overlapping and unique patterns of brain activations (Iannilli et al., 2008). Our study could not further investigate these unique patterns, given the paucity of experimental orofacial pain studies.

The complexity of COFP disorders lies not only in the plurality of their etiologies, but the heterogeneity of the patient population, comorbidities and medication usage. These factors were taken into consideration within their specific studies. The disorders included in COFP meta-analyses were heterogeneous in nature; which is both a strength and limitation of our meta-analysis. We did not separate studies based on disease etiology (neuropathic vs. non-neuropathic), study condition (task vs. rest) or grey matter metric (GMV vs. GMC). Our analysis is not aimed at drawing out these differences as there are not sufficient studies to draw such inferences. Rather, by combining these COFPs in our meta-analysis we can identify transdiagnostic abnormalities in COFPs, which provide both mechanistically relevant information, and potential therapeutic targets.

The outcomes of the functional COFP meta-analysis will be affected by the heterogeneity of the experimental designs of the studies included. Indeed, this is precisely the aim of a meta-analysis—to identify common activation despite experimental heterogeneity. Here, the functional COFP studies did not all employ matched stimulus intensities between the two groups, although one did. The unmatched stimulus intensities could bias brain activation differences observed.

Furthermore, our systematic search selectively included whole-brain analyses to prevent false negative or positive results, as the null-hypothesis of the ALE method presumes a uniform distribution of foci activation throughout the whole brain. Also, the ALE method does not include in its algorithm the heterogeneity in statistical thresholding methods among studies. Rather, studies are weighted by sample size. Therefore, studies with varying levels of evidence are not weighted differently. Our systematic search did not discriminate between uncorrected and stringent statistical thresholding approaches. Among the studies selected, ten did not account for multiple comparison analyses, and reported findings at an uncorrected *p*-value (de Leeuw et al., 2006; Gerstner et al., 2011; He et al., 2014; Iannilli et al., 2007; Lin et al., 2013a; Lin et al., 2013b; Obermann et al., 2009; Schmidt-Wilcke et al., 2010; Sinding et al., 2016; Wang et al., 2017a). We have, however, presented a quality score that accounts for the correction method. Nonetheless, these studies may bias our final ALE results.

Finally, our COFP findings were only significant at $p < .005$, likely due to the paucity of imaging data (with the exception of the functional analysis findings of the insula and cerebellum, which were significant at $p < .001$). As such, our study allowed us to determine which brain regions are abnormal across conditions as conducted in a previous ALE analysis (Dehghan et al., 2016). Accordingly, ALE meta-analyses require an approximate 8–15 experiments per contrast for robust statistical power (Simons et al., 2014; Wagner et al., 2014), suggesting that our contrasts of 6 and 5 experiments should be interpreted with caution.

5. Conclusion

In conclusion, our coordinate-based meta-analysis of experimental acute pain in healthy subjects is convergent with previous studies that show sensory, affective and cognitive systems are implicated in acute orofacial pain. In addition, we present the first coordinate-based meta-analysis in COFP disorders, excluding headache/migraine, to show directionality in functional and structural abnormalities across COFPs.

Acknowledgements

DAS is supported by a grant from NIH/NIDCR under Grant 1R21DE023964. MM is supported by an NSERC Discovery Grant. M Moayedi acknowledges support from the Bertha Rosenstadt Endowment. We would also like to thank Mr. Erick Patrician and Mr. Steven Lee for their help in reviewing coordinates for the meta-analysis.

Conflict of interest

The authors have no conflicts to report.

Author contributions

LA: analysis of data; LA, MM: drafting of manuscript; DAS, MM: conception and design of study, revising the manuscript. All authors have approved the final version and agree to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.09.018.

References

Albuquerque, R.J.C., De Leeuw, R., Carlson, C.R., Okeson, J.P., Miller, C.S., Andersen, A.H., 2006. Cerebral activation during thermal stimulation of patients who have burning mouth disorder: an fMRI study. Pain 122, 223–234.

Alshelh, Z., Di Pietro, F., Youssef, A.M., Reeves, J.M., Macey, P.M., Vickers, E.R., Peck, C.C., Murray, G.M., Henderson, L.A., 2016. Chronic Neuropathic Pain: It's about the Rhythm. J. Neurosci. 36, 1008–1018.

Apkarian, A.V., Hashmi, J.A., Baliki, M.N., 2011. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 152, S49–S64.

Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Brain Res. Rev. 22, 229–244.

Becerra, L., Morris, S., Bazes, S., Gostic, R., Sherman, S., Gostic, J., Pendse, G., Moulton, E., Scrivani, S., Keith, D., Chizh, B., Borsook, D., 2006. Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. J. Neurosci. 26, 10646–10657.

Benoliel, R., Sharav, Y., 2008. Masticatory myofacial pain, and tension-type and chronic daily headache. In: Sharav, Y., Benoliel, R. (Eds.), Orofacial Pain & Headache. Elsevier, Philadelphia, pp. 109–148.

Benoliel, R., Sharav, Y., 2010. Chronic orofacial pain. Curr. Pain Headache Rep. 14, 33–40.

Bogdanov, V.B., Vigano, A., Noirhomme, Q., Bogdanova, O.V., Guy, N., Laureys, S., Renshaw, P.F., Dallel, R., Phillips, C., Schoenen, J., 2015. Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: an fMRI study in healthy subjects. Behav. Brain Res. 281, 187–198.

Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. Nat. Rev. Neurosci. 3, 243–249.

Brooks, J.C., Tracey, I., 2007. The insula: a multidimensional integration site for pain. Pain 128, 1–2.

Brooks, J.C., Zambreanu, L., Godinez, A., Craig, A.D., Tracey, I., 2005. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. NeuroImage 27, 201–209.

Brugger, M., Ettlin, D.A., Meier, M., Keller, T., Luechinger, R., Barlow, A., Palla, S., Jancke, L., Lutz, K., 2011. Taking sides with pain - lateralization aspects related to cerebral processing of dental pain. Front. Hum. Neurosci. 5, 12.

Burns, E., Chipchase, L.S., Schabrun, S.M., 2016. Primary sensory and motor cortex function in response to acute muscle pain: a systematic review and meta-analysis. Eur. J. Pain 20, 1203–1213.

Bushnell, M.C., Ceko, M., Low, L.A., 2013. Cognitive and emotional control of pain and its disruption in chronic pain. Nat. Rev. Neurosci. 14, 502–511.

Colloca, L., Horin, A.P., Finniss, D., 2016. Placebo effects in pain. In: Battaglia, A.A. (Ed.), An Introduction to Pain and its Relation to Nervous System Disorders. John Wiley & Sons, Ltd, West Sussex (UK), pp. 249–265.

Craig, A.D., 2003. Pain mechanisms: labeled lines versus convergence in central processing. Annu. Rev. Neurosci. 26, 1–30.

Davis, K.D., Moayedi, M., 2013. Central mechanisms of pain revealed through functional and structural MRI. J. NeuroImmune Pharmacol. 8, 518–534.

de Leeuw, R., Davis, C.E., Albuquerque, R., Carlson, C.R., Andersen, A.H., 2006. Brain activity during stimulation of the trigeminal nerve with noxious heat. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102, 750–757.

Dehghan, M., Schmidt-Wilcke, T., Pfleiderer, B., Eickhoff, S.B., Petzke, F., Harris, R.E., Montoya, P., Burgmer, M., 2016. Coordinate-based (ALE) meta-analysis of brain activation in patients with fibromyalgia. Hum. Brain Mapp. 37, 1749–1758.

Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 52, 377–384.

Duerden, E.G., Albanese, M.C., 2013. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Hum. Brain Mapp. 34, 109–149.

Dum, R.P., Levinthal, D.J., Strick, P.L., 2016. Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. Proc. Natl. Acad. Sci. U. S. A. 113, 9922–9927.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum. Brain Mapp. 30, 2907–2926.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Peter, T., 2012. Activation Likelihood Estimation meta-analysis revisited. NeuroImage 59, 2349–2361.

Gerstner, G., Ichesco, E., Quintero, A., Schmidt-Wilcke, T., 2011. Changes in regional gray and white matter volume in patients with myofascial-type temporomandibular disorders: a voxel-based morphometry study. J. Orofac. Pain 25, 99–106.

Gustin, S.M., Peck, C.C., Wilcox, S.L., Nash, P.G., Murray, G.M., Henderson, L.A., 2011. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. J. Neurosci. 31, 5956–5964.

Gustin, S.M., Wrigley, P.J., Youssef, A.M., McIndoe, L., Wilcox, S.L., Rae, C.D., Edden, R.A., Siddall, P.J., Henderson, L.A., 2014. Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. Pain 155, 1027–1036.

He, S.S., Li, F., Song, F., Wu, S., Chen, J.Y., He, N., Zou, S.J., Huang, X.Q., Lui, S., Gong, Q.Y., Chen, S., 2014. Spontaneous neural activity alterations in temporomandibular disorders: a cross-sectional and longitudinal resting-state functional magnetic resonance imaging study. Neuroscience 278, 1–10.

Henderson, L.A., Peck, C.C., Petersen, E.T., Rae, C.D., Youssef, A.M., Reeves, J.M., Wilcox, S.L., Akhter, R., Murray, G.M., Gustin, S.M., 2013. Chronic pain: lost inhibition? J. Neurosci. 33, 7574–7582.

Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., Dostrovsky, J.O., 1999. Pain-related neurons in the human cingulate cortex. Nat. Neurosci. 2, 403–405.

Iannilli, E., Gerber, J., Frasnelli, J., Hummel, T., 2007. Intranasal trigeminal function in subjects with and without an intact sense of smell. Brain Res. 1139, 235–244.

Iannilli, E., Del Gratta, C., Gerber, J.C., Romani, G.L., Hummel, T., 2008. Trigeminal activation using chemical, electrical, and mechanical stimuli. Pain 139, 376–388.

Ji, X.T., Qian, N.S., Zhang, T., Li, J.M., Li, X.K., Wang, P., Zhao, D.S., Huang, G., Zhang, L., Fei, Z., Jia, D., Niu, L., 2013. Spinal astrocytic activation contributes to mechanical allodynia in a rat chemotherapy-induced neuropathic pain model. PLoS One 8, e60733.

Khan, S.A., Keaser, M.L., Meiller, T.F., Seminowicz, D.A., 2014. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain 155, 1472–1480.

Kuner, R., Flor, H., 2016. Structural plasticity and reorganisation in chronic pain. Nat. Rev. Neurosci. 18, 20–30.

Kupers, R.C., Svensson, P., Jensen, T.S., 2004. Central representation of muscle pain and mechanical hyperesthesia in the orofacial region: a positron emission tomography study. Pain 108, 284–293.

Li, M., Yan, J., Li, S., Wang, T., Zhan, W., Wen, H., Ma, X., Zhang, Y., Tian, J., Jiang, G., 2017. Reduced volume of gray matter in patients with trigeminal neuralgia. Brain Imaging Behav 11, 486–492.

Lin, C.S., 2014. 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 9, e94300.

Lin, C.S., Hsieh, J.C., Yeh, T.C., Lee, S.Y., Niddam, D.M., 2013a. Functional dissociation within insular cortex: the effect of pre-stimulus anxiety on pain. Brain Res. 1493, 40–47.

Lin, C.S., Niddam, D.M., Hsu, M.L., Hsieh, J.C., 2013b. Pain catastrophizing is associated with dental pain in a stressful context. J. Dent. Res. 92, 130–135.

Lin, C.S., Niddam, D.M., Hsu, M.L., 2014. Meta-analysis on brain representation of experimental dental pain. J. Dent. Res. 93, 126–133.

Mazzola, L., Isnard, J., Peyron, R., Guenot, M., Mauguiere, F., 2009. Somatotopic organization of pain responses to direct electrical stimulation of the human insular cortex. Pain 146, 99–104.

Mills, E.P., Di Pietro, F., Alshelh, Z., Peck, C.C., Murray, G.M., Vickers, E.R., Henderson, L.A., 2018. Brainstem pain-control circuitry connectivity in chronic neuropathic pain. J. Neurosci. 38, 465–473.

Moayedi, M., 2014. All roads lead to the insula. Pain 155, 1920–1921.

Moayedi, M., Weissman-Fogel, I., Salomons, T.V., Crawley, A.P., Goldberg, M.B., Freeman, B.V., Tenenbaum, H.C., Davis, K.D., 2012. Abnormal gray matter aging in chronic pain patients. Brain Res. 1456, 82–93.

Moayedi, M., Liang, M., Sim, A.L., Hu, L., Haggard, P., Iannetti, G.D., 2015. Laser-evoked vertex potentials predict defensive motor actions. Cereb. Cortex 25, 4789–4798.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., Group P-P, 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4 (1).

Moisset, X., Villain, N., Ducreux, D., Serrie, A., Cunin, G., Valade, D., Calvino, B., Bouhassira, D., 2011. Functional brain imaging of trigeminal neuralgia. Eur. J. Pain 15, 124–131.

Montavont, A., Mauguiere, F., Mazzola, L., Garcia-Larrea, L., Catenoix, H., Ryvlin, P., Isnard, J., 2015. On the origin of painful somatosensory seizures. Neurology 84, 594–601.

Moulton, E.A., Pendse, G., Morris, S., Strassman, A., Aiello-Lammens, M., Becerra, L.R., Borsook, D., 2007. Capsaicin-induced thermal hyperalgesia and sensitization in the human trigeminal nociceptive pathway: an fMRI study. NeuroImage 35, 1586–1600.

Moulton, E.A., Pendse, G., Becerra, L.R., Borsook, D., 2012. Bold responses in somatosensory cortices better reflect heat sensation than pain. J. Neurosci. 32, 6024–6031.

Nash, P.G., Macefield, V.G., Klineberg, I.J., Gustin, S.M., Murray, G.M., Henderson, L.A., 2010a. Bilateral activation of the trigeminothalamic tract by acute orofacial cutaneous and muscle pain in humans. Pain 151, 384–393.

Nash, P.G., Macefield, V.G., Klineberg, I.J., Gustin, S.M., Murray, G.M., Henderson, L.A., 2010b. Changes in human primary motor cortex activity during acute cutaneous and muscle orofacial pain. J. Orofac. Pain 24, 379–390.

Nebel, M.B., Folger, S., Tommerdahl, M., Hollins, M., McGlone, F., Essick, G., 2010. Temporomandibular disorder modifies cortical response to tactile stimulation. J. Pain 11, 1083–1094.

Obermann, M., Pleger, B., De Greiff, A., Stude, P., Kaube, H., Diener, H.C., Katsarava, Z., 2009. Temporal summation of trigeminal pain in human anterior cingulate cortex. NeuroImage 46, 193–200.

Obermann, M., Rodriguez-Raecke, R., Naegel, S., Holle, D., Mueller, D., Yoon, M.S., Theysohn, N., Blex, S., Diener, H.C., Katsarava, Z., 2013. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. NeuroImage 74, 352–358.

Oshiro, Y., Quevedo, A.S., McHaffie, J.G., Kraft, R.A., Coghill, R.C., 2009. Brain mechanisms supporting discrimination of sensory features of pain: a new model. J. Neurosci. 29, 14924–14931.

Perini, I., Bergstrand, S., Morrison, I., 2013. Where pain meets action in the human brain. J. Neurosci. 33, 15930–15939.

Price, D.D., 2000. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–1772.

Roberts, P.A., Matzke, H.A., 1971. Projections of the subnucleus caudalis of the trigeminal nucleus in the sheep. J. Comp. Neurol. 141, 273–282.

Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. Behav. Neurol. 12,

191–200.
Schmidt-Wilcke, T., Hierlmeier, S., Leinisch, E., 2010. Altered regional brain morphology in patients with chronic facial pain. Headache 50, 1278–1285.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.
Sessle, B.J., 2000. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit. Rev. Oral Biol. Med. 11, 57–91.
Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12, 154–167.
Sharav, Y., Benoliel, R., 2015. Orofacial Pain and Headache. Quintessence Publishing Co, Inc, Chicago (x, 654 pages).
Simons, L.E., Moulton, E.A., Linnman, C., Carpino, E., Becerra, L., Borsook, D., 2014. The human amygdala and pain: evidence from neuroimaging. Hum. Brain Mapp. 35, 527–538.
Sinding, C., Gransjoen, A.M., Schlumberger, G., Grushka, M., Frasnelli, J., Singh, P.B., 2016. Grey matter changes of the pain matrix in patients with burning mouth syndrome. Eur. J. Neurosci. 43, 997–1005.
Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, New York.
Teutsch, S., Herken, W., Bingel, U., Schoell, E., May, A., 2008. Changes in brain gray matter due to repetitive painful stimulation. NeuroImage 42, 845–849.
Tracey, I., Bushnell, M.C., 2009. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J. Pain 10, 1113–1120.
Tsai, Y.H., Yuan, R., Patel, D., Chandrasekaran, S., Weng, H.H., Yang, J.T., Lin, C.P., Biswal, B.B., 2018. Altered structure and functional connection in patients with classical trigeminal neuralgia. Hum. Brain Mapp. 39, 609–621.
Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P., 2012. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum. Brain Mapp. 33, 1–13.
Ushida, T., Fukumoto, M., Binti, C., Ikemoto, T., Taniguchi, S., Ikeuchi, M., Nishihara, M., Tani, T., 2010. Alterations of contralateral thalamic perfusion in neuropathic pain. Open Neuroimaging J. 4, 182–186.
Vadivelu, N., Huang, Y., Mancini, P., Gruenbaum, S., Vadivelu, A., Dabu-Bondoc, S., 2014. The neurobiology of orofacial pain. In: Vadivelu, N., Vadivelu, A., Kaye, A.D. (Eds.), Orofacial Pain: A clinician's Guide. Cham. Springer International Publishing, pp. 1–8.
Wagner, S., Sebastian, A., Lieb, K., Tuscher, O., Tadic, A., 2014. A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci. 15, 19.
Wang, Y., Zhang, X., Guan, Q., Wan, L., Yi, Y., Liu, C.F., 2015. Altered reginal homogeneity of spontaneous brain activity in idiopathic trigeminal neuralgia. Neuropsychiatr. Dis. Treat. 11, 2659–2666.
Wang, Y., Cao, D.Y., Remeniuk, B., Krimmel, S., Seminowicz, D.A., Zhang, M., 2017a. Altered brain structure and function associated with sensory and affective components of classic trigeminal neuralgia. Pain 158, 1561–1570.
Wang, Y., Xu, C., Zhai, L., Lu, X., Wu, X., Yi, Y., Liu, Z., Guan, Q., Zhang, X., 2017b. Spatial-temporal signature of resting-state BOLD signals in classic trigeminal neuralgia. J. Pain Res. 10, 2741–2750.
Weissman-Fogel, I., Moayedi, M., Tenenbaum, H.C., Goldberg, M.B., Freeman, B.V., Davis, K.D., 2011. Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks. Pain 152, 384–396.
Willis, W.D., Westlund, K.N., 1997. Neuroanatomy of the pain system and of the pathways that modulate pain. J. Clin. Neurophysiol. 14, 2–31.
Younger, J.W., Shen, Y.F., Goddard, G., Mackey, S.C., 2010. Chronic myofascial temporomandibular pain is associated with neural abnormalities in the trigeminal and limbic systems. Pain 149, 222–228.
Youssef, A.M., Macefield, V.G., Henderson, L.A., 2016. Pain inhibits pain; human brainstem mechanisms. NeuroImage 124, 54–62.
Yuan, J., Cao, S., Huang, Y., Zhang, Y., Xie, P., Zhang, Y., Fu, B., Zhang, T., Song, G., Yu, T., Zhang, M., 2018. Altered spontaneous brain activity in patients with idiopathic trigeminal neuralgia: a resting-state functional mri study. Clin. J. Pain 34, 600–609.
Zakrzewska, J.M., 2013. Multi-dimensionality of chronic pain of the oral cavity and face. J Headache Pain 14, 37.