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

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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.

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 ventroposterior medial (VPM) and mediodorsal (MD) nuclei of the thalamus, and further cortical projections of the trigeminotalamic tract such as the primary somatosensory cortex (S1), the mid-cingulate cortex (MCC), and the dorso-posterior 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.
(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
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).
Abbreviations: 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.

Table 1
Summary of experimental orofacial pain studies.

| Reference              | N     | W/M | Age (mean ± SD or range in years) | Imaging Modality | Stimulation        | Body Part                  | QS (/20) |
|------------------------|-------|-----|-----------------------------------|------------------|---------------------|-----------------------------|----------|
| 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       |
| Ianniili et al., 2007  | 23    | 13/10 | 44/61*                           | 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       |

Table 2
Summary of VBM studies of COFP.

| Reference          | Patients | N     | W/M | Age (mean ± SD in years) | Healthy controls | Grey matter findings | QS (/20) |
|--------------------|----------|-------|-----|--------------------------|-----------------|----------------------|----------|
| Tsai et al., 2018  | COFP     | 36    | 20/16 | 58.0 ± 7.7              | 19 15/4 55.6 ± 6.8  | GMV 16               |
| 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 61.0 ± 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-Wölck et al., 2010 | PFP | 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, PFP 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: "((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 > Controls | S1       | Thal | Insula | Cingulate | PFC | Other | Reference |
|-----------------|----------|------|--------|-----------|-----|-------|-----------|
| BMS             | R dIPPC  | R PCL/Ti | R He  | bilat MTG | bilat | YFP/Thal | Sinding et al., 2016 |
|                 |          |      |        |           |      |       | Khan et al., 2014 |
| DYS > S1        | R L VP, R VL | R alNS | R vIPPC | R GP/ML/Pu, bilat MCP/VMN/VMSN | R SPL |       | Sinding et al., 2016 |
| TMD             |          |      |        |           |      |       | Younger et al., 2010 |
| CTN             |          |      |        |           |      |       | Wang et al., 2017a,b |
| PTN             | R pNS    |      |        |           |      |       | Gustin et al., 2011 |
| Controls > COFP | L PCC/sACC |      |        | L Cereb |      |       | Sinding et al., 2016 |
| BMS             | L mIPPC  |      |        |           |      |       | Khan et al., 2014 |
| DYS             | R sACC/MCC |      |        | L mACC |      |       | Sinding et al., 2016 |
| PFP             | L pNS    |      |        | R pre-SMA, L mOFCC | L dIPPC/FP, R PMC | R STG, bilat M1 | Schmidt-Wilcke et al., 2010 |
|                 | R aNS    |      |        | L dIPPC/FP |      |       | Gerstner et al., 2011 |
| S1              | R PCC, L pACC |      |        |       |      |       | Younger et al., 2010 |
| CTN             | R VP, L MD | R ACC/MCC | bilat SMA | L SMA |      | bilat Cereb, R NAc, L Hypo/IFG | Tsai et al., 2018 (right CTN) |
|                 |          |      |        |       |      |       | Tsai et al., 2018 (left CTN) |
|                 |          |      |        |       |      |       | Wang et al., 2017a,b |
| TN              | L S1     | R pNS | R ACC/MCC |       |      | bilat SMA | Li et al., 2017 |
|                 |          |      |        |       |      |       | Obermann et al., 2013 |
| PTN             | L S1     | R pNS | L ACC | R OFC | 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, dIPPC dorsolateral prefrontal cortex, DYS dyseusia, 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, mOFCC medial orbitofrontal cortex, mPFC medial prefrontal cortex, MTG middle temporal gyrus, NAc nucleus accumbens, OFC orbitofrontal cortex, pACC pregenual anterior cingulate cortex, Parahc para-hippocampal gyrus, PCC posterior cingulate cortex, PCL paracentral lobule, PCs precentral gyrus, PFC prefrontal cortex, pINS posterior insular cortex, PIP persistent idiopathic facial pain, PMC premotor cortex, pre-SMA pre supplementary motor area, PTV 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, vIPPC ventrolateral prefrontal cortex, VMSN trigeminal motor nucleus, VMSN trigeminal sensory nucleus, VS ventral striatum.

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

| Reference                  | Patients  | Healthy controls | fMRI analysis method | Stimulation | Pain intensity (/10) | N  | W/M | Age (mean ± SD or S.E.M. in years) | QS (20) |
|----------------------------|-----------|------------------|----------------------|-------------|----------------------|----|-----|-----------------------------------|---------|
| Wang et al., 2017a         | CTN 17    | 10/7             | 62.53 ± 7.41         | fALFF       | Rest                 | 16 | R   | 6.12 ± 1.50                       | 19       |
| Yuan et al., 2018          | ITN 23    | 9/14             | 59.6 ± 12.5          | ReHo and fALFF | Rest                 | 16 | R   | 8.1 ± 1.6                         | 19       |
| Alshelh et al., 2016       | NP 17     | 14/3             | 50.6 ± 2.8           | Task Chemical | Healthy: 5          | 44 | R   | 4.12 ± 2.61                       | 45.9 ± 2.0|
| Wang et al., 2015          | ITN 17    | 10/7             | 63.41 ± 7.25         | fALFF       | Rest                 | 19 | R   | 6.12 ± 1.50                       | 19       |
| He et al., 2014            | TMD 23    | 14/9             | 22.4 ± 3.6           | ReHo        | Rest                 | 17 | R   | 47.3 ± 21.4                       | 23.1 ± 2.4|
| Weissman-Fogel et al., 2011| TMD 17    | 17/0             | 35.2 ± 11.6          | fALFF       | Rest                 | 18 | R   | 4.41 ± 1.77                       | 34.0 ± 9.9|
| Nebel et al., 2010         | TMD 13    | 13/0             | 28.7 ± 7.6           | ReHo        | Rest                 | 18 | R   | 28.4 ± 7.9                        | 28.8 ± 7.9|
| Albuquerque et al., 2006   | BMS 8     | 8/0              | 49.1 ± 10.1          | fALFF       | Rest                 | 8  | R   | 5.8 ± 1.8                         | 59.3 ± 12.3|

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, MM neuropathic pain, QS quality score, R right, ReHo regional homogeneity, TMD temporomandibular disorder, W women.

A Grade Chronic Pain Scale of 52% of patients.

Graded Chronic Pain Scale of 5% of patients.

Graded Chronic Pain Scale of 10% of patients.

Graded Chronic Pain Scale of 100 being “most intense vibration imaginable.”

Table 6). We also found similar results at a more conservative cluster-forming threshold of p < .001 with five clusters of activation, which

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            |
|------|----------|------|---------------|--------------------|-----------|-------------------------|----------------------|
| BMS  | controls | R aMCC | L pINS        | L dIPFC/InsP       | R PCu     | L dIPFC                 | Wang et al., 2017   |
| CTN  |          | R Thal | L Thal        | R ACC              | R Cereb/PCu | R Fus/TPJ, L TP/SPL/MTG | Wang et al., 2017   |
| ITN  |          | R Thal | L dpINS/pINS  | R ACC              | R Cereb/PCu | R Fus/TPJ, L TP/SPL/MTG | Wang et al., 2017   |
| PTN  | L S1     |       |               | R ACC              | R Cereb/PCu | R Fus/TPJ, L TP/SPL/MTG | Wang et al., 2017   |
| TMD  | L S1     |       |               | R ACC              | R Cereb/PCu | R Fus/TPJ, L TP/SPL/MTG | Wang et al., 2017   |

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, dIPFC dorsolateral prefrontal cortex, dIPFC dorsolateral pons, dINS dorsal posterior insular cortex, fALFF fractional amplitude 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 mediiodorsal thalamus, mFP medial frontal pole, mid INS mid insular cortex, MOG middle occipital gyrus, MTG middle temporal gyrus, OFC orbitofrontal cortex, pACC pregenual anterior cingulate cortex, ParaHc parahippocampal gyrus, PPC posterior cingulate cortex, PCu precuneus, PFC prefrontal cortex, pINS posterior insular cortex, PMCs 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, SPG superior frontal gyrus, SPL superior pariotal lobe, STn spinal trigeminal nucleus, STN subthalamic nucleus, SUL superior parietal lobule, TPJ temporoparietal joint, Thal Thalamus, TMD temporomandibular disorder, TP temporal pole, VP ventral visual cortex, VP ventral thalamus, VL ventral lateral thalamus.

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 < .005 and a cluster-forming threshold of p < .005, but not at p < .001.

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 Albanez, 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 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
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 nocicensive 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
consistent thalamic hyperactivity may result from persistent pain trigeminal neuralgia (Moisset et al., 2011). Previous studies show painful trigeminal neuralgia (PTN) (Becerra et al., 2006) and qualitative meta-analysis of trigeminal disorders which reported greater activation in contrast BOLD studies, and abnormal BOLD variability in COFP studies found consistently greater function – defined as greater 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.

(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 Table 7

| Brain regions | ALE Value | MNI Coordinates | Cluster Size (mm³) |
|---------------|-----------|-----------------|-------------------|
| 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 |
| L pINS | 0.013 | −46 | −4 | 10 | 1336 |
| L pINS | 0.010 | −42 | −12 | 6 | |

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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).
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 assumes 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.
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