

Characterization of Visual Processing in Temporomandibular Disorders Using Functional Magnetic Resonance Imaging

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Running title (45 characters): Visual processing in TMD

Abstract:

Background & Purpose: Many patients with chronic pain report hypersensitivity not only to noxious stimuli, but also to other modalities including innocuous touch, sound, and light, possibly due to differences in the processing of these stimuli. The goal of this study was to characterize functional connectivity (FC) differences between subjects with temporomandibular disorders (TMD) and pain-free controls during a visual functional magnetic resonance imaging (fMRI) task that included an unpleasant, strobing visual stimulus. We hypothesized the TMD cohort would exhibit maladaptations in brain networks consistent with multisensory hypersensitivities observed in TMD patients.

Methods: This pilot study included 16 subjects, 10 with TMD and 6 pain-free controls. Clinical pain was characterized using self-reported questionnaires. Visual task-based fMRI data was collected on a 3T MR scanner and used to determine differences in FC via group independent component analysis.

Results: Compared to controls, subjects with TMD exhibited abnormally *increased* FC between the default mode network and lateral prefrontal areas involved in attention and executive function, and *impaired* FC between the fronto-parietal network and higher order visual processing areas.

Conclusions: The results indicate maladaptation of brain functional networks, likely due to deficits in multisensory integration, default mode network function, and visual attention, likely engendered by chronic pain mechanisms.

Introduction

Chronic pain is a major public health challenge, exacerbated to some extent by the lack of effective treatments. Research has identified peripheral and centralized, or *nociplastic*, contributions to chronic pain, including temporomandibular disorders (TMD).^{1,2} TMD has a lifetime prevalence of ~10-12%³ and is one of many chronic overlapping pain conditions including fibromyalgia and irritable bowel syndrome, however, much less is known about central pain processing in TMD compared to other conditions. Nociplastic pain mechanisms can include changes in brain structure, function, and metabolite concentrations.^{1,4,5} Additionally, demonstration of hypersensitivity to non-somatosensory stimuli in chronic pain suggests the presence of generalized, central mechanisms of sensory amplification.⁶⁻⁹

The mechanisms underlying discomfort evoked by non-somatosensory stimuli in TMD are unclear, despite reports of multisensory hypersensitivity.¹⁰⁻¹⁶ Differences in visual-evoked functional connectivity (FC) and brain activation have been observed in other pain conditions^{7,17} and may explain the multisensory sensitivity in TMD.¹⁸ Visual stimulation is not an irritant for all TMD patients, but it is likely more unpleasant in a subset of individuals with nociplastic (as opposed to peripheral nociceptive) pain. Therefore, the goal of this pilot study was to identify differences in the brain networks of TMD patients, compared to pain-free controls, during an unpleasant visual functional magnetic resonance imaging (fMRI) paradigm (i.e., a visual checkerboard stimulus) to uncover possible nociplastic pain-associated mechanisms which would not be evoked by noxious stimulation of a painful site.

Methods

Study Design and Subjects

This study was approved by the local Institutional Review Board. All subjects provided written informed consent prior to participation. Patients with painful and clinically diagnosed TMD were recruited from Oral and Maxillofacial Surgery/Hospital Dentistry. Pain-free controls were recruited from the local community and were healthy without history of chronic pain. Exclusion criteria for both cohorts were severe physical impairments (e.g., bilateral amputation); medical conditions (e.g., autoimmune diseases, cancer); severe psychiatric illnesses; opioid, tobacco, or hormone use; or pregnancy. One subject was excluded due to challenges with data acquisition and poor image quality. The final cohort consisted of 10 subjects with TMD (9 female), 18-49 years old (mean \pm standard deviation (SD) = 32 ± 10 years), and 6 female pain-free healthy controls (HC), 19-51 years old (31 ± 12 years). Subjects completed pain questionnaires followed by MRI acquired either the same or following day.

Clinical Pain Metrics and Visual Unpleasantness

The American College of Rheumatology's 2011 Preliminary Diagnostic Criteria for Fibromyalgia, which includes symptom severity and widespread pain index (WPI) subscales, was administered,¹⁹ with higher scores (range 0-31)¹⁹ indicating likely nociplastic pain. The current TMD symptoms questionnaire from the TMD research diagnostic criteria (RDC; 2002) was used to assess current face pain.²⁰ The short form of the brief pain inventory (BPI) was used to assess pain severity and interference. The Pennebaker Inventory of Limbic Languidness (PILL) was used to measure somatic awareness or hypervigilance.²¹ Immediately after the visual scan, participants were asked to rate the perceived unpleasantness of the visual stimulus on a scale from 0 to 100, where 0 means “not at all unpleasant” and 100 means “the most unpleasant sensation imaginable.” Mann-Whitney U

tests were used to compare age, clinical pain metrics, and perceived visual unpleasantness between groups.

MR Data Acquisition

MR data was acquired on a 3 T whole-body MR scanner (Signa Discovery MR750, GE Healthcare, Chicago, IL) with a 32-channel head coil. T1-weighted images were acquired using a spoiled gradient recalled echo sequence (repetition time (TR)=650 ms, echo time (TE)=3.7 ms, flip angle=8°, voxel size=1.0x1.0x0.8 mm³, field of view (FOV)=256x256 mm², 166 slices). fMRI data were acquired using a multiband gradient echo pulse sequence (TR=1200 ms, TE=30 ms, flip angle=70°, FOV=210x210 mm², 2.4 mm x 2.4 mm in-plane resolution, 51-2.5 mm thick slices, multiband acceleration factor=3). The visual paradigm included 6 cycles of 20 s “on” (8 Hz flashing checkerboard) and “off” (static crosshair) blocks (Figure 1). This same paradigm was used in Harte et al. (2016) to elicit unpleasantness and measure brain activity in fibromyalgia patients.⁷

MR Data Pre-processing

Functional data were pre-processed using SPM12 employing well-established pipelines.²²⁻²⁴ The fMRI voxel time-series were temporally shifted to account for differences in slice acquisition times, and 3D volumes were registered to a base volume. This data was then corrected for physiological noise (respiratory and cardiac) with the well-established RETROICOR²⁵ technique, and spatially normalized to the MNI-152 template. Outlier identification was performed by flagging acquisitions with fMRI time-series signal variation >5 SDs or frame-to-frame displacement >0.9 mm. First quartile, third quartile, and maximum motion across all subjects and scans were 0.17, 0.28, and 0.57 mm, respectively.

Group Independent Component Analysis

The preprocessed fMRI data from all subjects were spatially smoothed with an isotropic Gaussian filter (FWHM=6 mm) for independent component analysis (ICA) analysis. Group ICA (GICA) was performed on temporally concatenated data from all subjects (TMD and HC) using the well-established GIFT software.²⁶ This ICA algorithm decomposes the concatenated fMRI time-series data into group-level ICs, which are composed of maps (component strength expressed as t-scores), and their corresponding IC time-courses. The ICA decomposition maximizes the independence between the spatial maps of different ICs, while not constraining the form of the time-courses. Subject-level ICs corresponding to the group ICs were obtained through the ICA back-projection technique.²⁶ The group-level GICA spatial maps were visually examined for artifactual components representing draining veins, physiological noise, ventricular signal, or motion, using a well-established approach.^{27, 28} The non-artifactual ICs constitute different brain functional networks. Voxel-wise maps of group differences in FC to ICA-derived brain functional networks were obtained with independent-samples t-tests on corresponding spatial maps. These group t-test results were clustered, and the family-wise error rate (FWER)-controlled significance (α) was computed for the given cluster detection threshold t-score ($p < 0.05$) using Monte Carlo (MC) simulations of the process of image generation. Simulations were controlled for the estimated spatial autocorrelation function (sACF) of regression residuals, intensity thresholding, masking, and cluster identification using 3dClustSim program in AFNI.^{29, 30}

Results

Comparisons of clinical pain metrics and age are presented in Table 1. Current face pain, symptom severity, WPI, fibromyalgia-ness, PILL, and BPI were all significantly higher in the TMD cohort compared to HC ($p \leq .05$). Despite perceived visual unpleasantness being

somewhat higher in TMD patients (mean = 43.5) than in controls (mean = 26.2), this difference was not statistically significant in our sample [$Z(16) = -1.21, p = .23$].

Group ICA yielded 11 artifact-free ICs including those belonging to the default mode network (DMN), left and right frontoparietal networks, fronto-striatal network, and social cognition network (Table 2). The DMN IC exhibited significant ($\alpha < 0.05$) abnormally increased FC to right ventrolateral and dorsolateral prefrontal cortices in subjects with TMD compared to HC (Figure 2, Table 3). The TMD cohort exhibited reduced DMN FC with left occipitotemporal/inferior temporal cortex (Table 3). Subjects with TMD showed reduced FC between left frontoparietal network (attention and executive function) and higher order visual processing regions, including the extrastriate body area and lateral occipital complex in the left hemisphere. Subjects with TMD also exhibited abnormally increased FC between the fronto-striatal network and cerebellum, and decreased FC between fronto-striatal network and supplementary motor area compared to HC. Additionally, the social cognition network exhibited abnormally increased FC to inferior frontal and middle frontal cortices in subjects with TMD compared to HC.

Discussion

Sensory hypersensitivity is emerging as a key feature of nociplastic pain, which may drive clinical pain in many chronic overlapping pain conditions.^{31,32} In this study, group ICA analysis of an unpleasant visual stimulus task during an fMRI paradigm revealed increased DMN FC to areas involved in attention, including dorsolateral and ventrolateral prefrontal cortices in TMD patients, possibly indicating increased attention to stimuli in TMD, consistent with prior work in chronic pain^{33,34}. Stronger activation of DMN regions associated with attention and salience were previously observed during a Stroop task in TMD

compared to controls.³⁵ The DMN is typically suppressed during attention and executive functions, supporting the hypothesis that DMN-associated dysfunction may relate to pain modulation. Indeed, DMN alterations have been associated with both chronic pain and pain-evoked activity in healthy individuals.^{36, 36} Resting-state DMN alterations have been reported following gnathological treatment in TMD, suggesting that DMN-associated changes may span rest, task-evoked activation, and treatment response.³⁷ The prefrontal cortex (PFC), in particular, is involved in executive function. Changes in grey matter, brain metabolites, and FC in the PFC have been reported in subjects with TMD as well as chronic back pain, myofascial pain, and fibromyalgia.³⁸⁻⁴¹ Furthermore, transcranial direct current stimulation and repetitive transcranial magnetic stimulation targeting the dorsolateral PFC have shown some promise.³⁸

We also observed reduced FC in TMD compared to HC between the fronto-parietal attention/executive function network and higher-order visual processing areas, and between the cognitive control network and supplementary motor area. Motor dysfunction has been observed in TMD, including increased motor cortex activation.³⁵ Alterations in executive function and attention may be the result of pain hypervigilance or rumination.^{42, 43} A recent review presents evidence for attentional bias to somatosensory stimuli in individuals with chronic pain,⁴³ and pain rumination has been positively associated with FC in the medial PFC and other DMN regions in TMD.⁴¹ While more work is warranted, a growing body of literature suggests chronic pain is associated with widespread brain changes that may affect multisensory processing, attention, and executive function.

As a pilot study, we acknowledge limitations of sample size and primarily female participants. Future studies will expand these initial results to larger cohorts, additional sensory stimuli, and structural and metabolic changes to evaluate the central mechanisms associated with multisensory hypersensitivity in TMD. Larger studies will also enable the use

of additional correlations with factors that could affect FC including clinical pain intensity and duration of TMD. We expect these and similar results from brain neuroimaging studies may be used to help differentiate pain mechanisms in TMD towards more personalized and tailored treatment.

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Data Availability

Data will be made available upon request after a data sharing agreement is executed.

Conflicts of Interest

Dr. Harte has received research support from Aptinyx and Arbor Medical Innovations, and consultation fees from Aptinyx, Memorial Slone Kettering Cancer Center, Indiana University, and University of North Carolina - Chapel Hill; not related to the present work.

Tables

Table 1. Group-wise comparisons of clinical pain metrics between healthy pain-free controls and subjects with temporomandibular disorders (TMD).

Parameter ^a	Healthy Controls (n = 6)	TMD Subjects (n = 10)	U ^b	p ^c
Current face pain	0.0 (0.0) ^a	2.0 (1.3)	6.0	.005
Symptom severity scale	1.6 (1.1)	5.2 (3.2)	6.5	.022

Wide-spread Pain Index (WPI)	0.5 (0.5)	5.1 (3.9)	1.5	.002
Fibromyalgia-ness	2.2 (1.5)	10.3 (6.9)	2.0	.005
Pennebaker Inventory of Limbic Languidness (PILL)	8.0 (5.2)	16.1 (7.6)	10.5	.033
Brief Pain Inventory (BPI)	0.5 (1.2)	4.8 (2.1)	2.0	.004

^aValues are reported as the mean (standard deviation). ^bNon-parametric Mann-Whitney U test-statistic. ^cp-values correspond to group-wise comparisons.

Table 2: List of Brain Functional Networks Activated

Default mode
Higher order visual processing

Right frontoparietal
Left frontoparietal
Somatosensory and pain processing
Sensorimotor
Fronto-striatal
Visuospatial attention
Anterior visual
Posterior visual
Social cognition

Table 3: Areas exhibiting significant differences in functional connectivity (family-wise error rate (FWE) corrected $\alpha < 0.05$) to specific resting state networks (group independent components) during the visual functional magnetic resonance imaging paradigm between subjects with temporomandibular disorders (TMD) and healthy controls (HC). Regions were identified using brain atlases in AFNI. Cluster-level α are obtained with the assumption the spatial autocorrelation function is Gaussian (see Methods).

TMD vs HC	Regions	Cluster peak z-statistic	Cluster size (2x2x2 mm ³ voxels)	Cluster detection threshold p-values	Cluster level FWE rate α
<i>Default mode network</i>					
TMD > HC	Right hemisphere: dorsal lateral and ventral-lateral pre-frontal cortex	3.86	4688	< 0.05	< 0.05
TMD < HC	Left occipito-temporal cortex	-3.26	4296	< 0.05	< 0.05

<i>Left fronto-parietal network</i>						
TMD > HC	Right posterior parietal cortex	4.21	6532	< 0.05	< 0.05	
TMD < HC	Left extrastriate body area and lateral occipital complex	-4.22	5048	< 0.05	< 0.05	
<i>Cognitive control network</i>						
TMD > HC	Anterior cerebellar vermis	3.83	3776	< 0.05	< 0.05	
TMD < HC	Supplementary motor area	-4.18	3928	< 0.05	< 0.05	
<i>Social cognition</i>						
TMD > HC	Right inferior frontal and middle frontal gyrus	4.458	7632	< 0.05	< 0.05	

Figure and Figure Legends

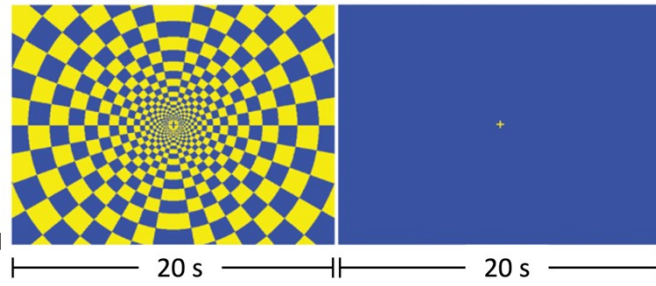


Figure 1: Visual paradigm used during fMRI. The visual task paradigm included six “on-off” cycles. The “on” block (left image) displayed an 8 Hz flashing checkered visual task for 20 seconds followed by an “off” block (right image) displaying a blue screen with a yellow crosshair in the center for 20 seconds.

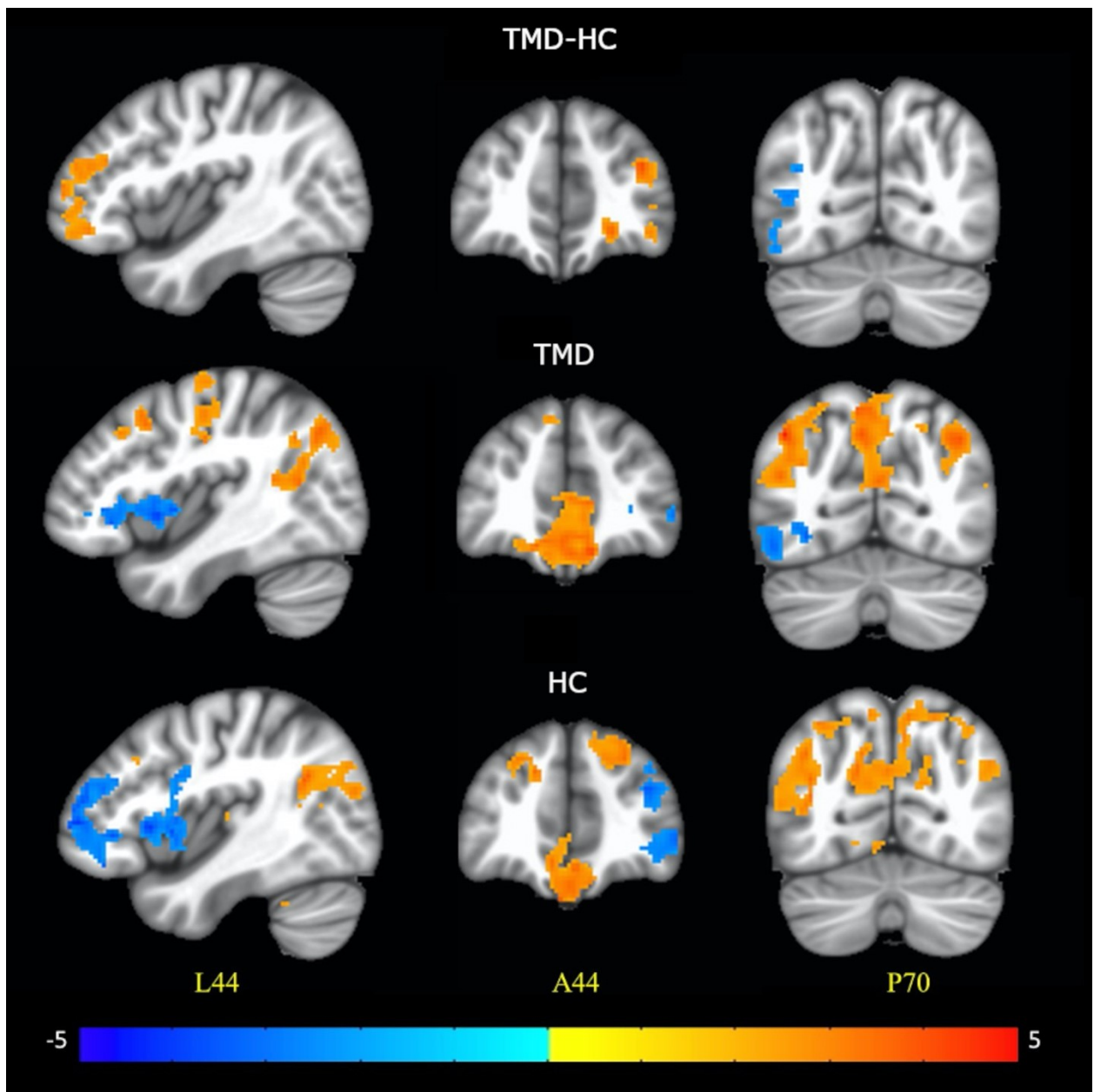


Figure 2. (top) Significant (cluster-level family-wise error rate $\alpha < .05$) differences in functional connectivity to the default mode network during the entire visual fMRI paradigm between subjects with temporomandibular disorders (TMD) and healthy control (HC) groups. 1-sample t-test results for (middle) TMD and (bottom) HC groups. The color bar represents t-test z-scores. Slice locations are in MNI coordinates (L = left; A = anterior; P = posterior).

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