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Abnormal cortical activity in patients with temporomandibular disorder evoked by cognitive and emotional tasks

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ABSTRACT

Patients with temporomandibular disorder (TMD) perform poorly in neuropsychological tests of cognitive function. These deficits might be related to dysfunction in brain networks that support pain and cognition, due to the impact of chronic pain and its related emotional processes on cognitive ability. We therefore tested whether patients with TMD perform poorly in cognitive and emotion tasks and whether they had abnormal task-evoked brain activity. Seventeen female subjects with nontraumatic TMD and 17 age-matched healthy female subjects underwent functional magnetic resonance imaging while performing counting Stroop tasks comprising neutral words, incongruent numbers, or emotional words, including TMD-specific words. Group differences in task-related brain responses were assessed. Connectivity between 2 pairs of coupled brain regions during the cognitive and emotional tasks (prefrontal-cingulate and amygdala-cingulate) was also examined. The patients had sluggish Stroop reaction times for all Stroop tasks. Furthermore, compared to controls, patients showed increased task-evoked responses in brain areas implicated in attention (eg, lateral prefrontal, inferior parietal), emotional processes (eg, amygdala, pregenual anterior cingulate), motor planning and performance (eg, supplementary and primary motor areas), and activation of the default-mode network (medial prefrontal and posterior cingulate). The patients also exhibited decoupling of the normally correlated activity between the prefrontal and cingulate cortices and between the amygdala and cingulate cortex. These findings suggest that the slow behavioral responses in idiopathic TMD may be due to attenuated, slower, and/or unsynchronized recruitment of attention/cognition processing areas. These abnormalities may be due to the salience of chronic pain, which inherently requires attention.

1. Introduction

Temporomandibular disorder (TMD) is a functional pain disorder that is more prevalent in women [51]. These patients can have reduced cognitive ability, as demonstrated by poorer performance in neuropsychological tests [42,74]. Performance on attention-demanding and divided attention tasks can predict treatment outcome, whereas peripheral clinical signs and symptoms of TMD [29] do not discriminate between treatment responders and nonresponders [43]. Furthermore, amplification of self-reported chronic pain levels [26], spatial distribution of TMD pain [30,31], increased temporal summation in remote body areas [57], and impaired central modulation of pain [39,46,69] suggest that central mechanisms may contribute to the maintenance of chronic pain in TMD as opposed to peripheral mechanisms, as thought previously.

Previous studies have shown interactions between brain networks supporting pain and cognition [18,53,71,72]. Specifically, pain can capture attention to adjust behaviour [20,35,50], mediated by a bottom-up process that engages areas implicated in pain salience detection (eg, anterior mid cingulate cortex [aMCC] and insula) [2,28,70]. Activation of the aMCC due to a salient noxious stimulus while concurrently performing a goal-directed cognitive task can also activate a top-down process driven by prefrontal and parietal cortical areas to engage attention [17,59]. Effective connectivity between the aMCC and the prefrontal areas such as the dorsolateral prefrontal cortex (DLPFC) is therefore essential for goal-directed task performance [11,45,48,49,86]. Conversely, attentional load can modulate pain with top-down processes that recruit the antinociceptive system [47,83]. During a cognitive task, regions of the default mode network (DMN), such as the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC), are usually deactivated [40], and a disturbance in this network has

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been implicated in attention deficits in pathological conditions [41,80], including chronic pain [6].

Hypervigilance to chronic pain may load the cortical attention network, which limits the amount of available resources to perform a goal-directed cognitive task [21,36,50]. This effect is suggested by slower responses to cognitive tasks during experimentally induced pain [71] and in chronic pain conditions [32–34]. Moreover, effective cognitive functioning may be aided through protective mechanisms that filter out emotional interference. This mechanism includes top-down modulation from the PFC to the pregenual anterior cingulate cortex (pgACC), which further modulates amygdala activity [9,62,79,81]. Thus, successful cognitive function also depends on functional connectivity between the pgACC and the amygdala. The valence of emotionally salient stimuli has been shown to affect task performance and neural correlates in a number of psychopathologies [85].

In this study, our aim was to examine how chronic pain in nontraumatic TMD impacts goal-directed task performance during cognitive and emotional interference tasks and to delineate the neural correlates of this interference effect. We hypothesized that TMD patients have (i) slower reaction times (RTs) in interference tasks; (ii) greater activation in frontoparietal areas underlying attention and regions involved in salience/emotional functions (aMCC, pgACC, insula, and amygdala), as well as regions of the DMN; and (iii) decoupling of the prefrontal-cingulate and amygdala-cingulate connectivities.

2. Methods

2.1. Study participants

A total of 34 participants were enrolled in this study; 17 female subjects with TMD and 17 age-matched healthy female subjects. Patients were examined and diagnosed with TMD by dentists who are TMD specialists in the Pain Unit of the Mount Sinai Hospital Dental Clinic, using the standard clinical diagnostic criteria from this institution and involvement of myofascial and/or temporomandibular joint based on clinical testing. Criteria for inclusion in the study included the following: (i) nontraumatic TMD (also known as idiopathic TMD), a sub-group of TMD with unclear peripheral aetiology of TMD [74] (in doing so, we focused our investigation on centrally mediated mechanisms that play a role in maintenance of chronic pain); (ii) musculoligamentous pain in the temporomandibular area; (iii) pain in the masticatory muscle region rated above 4 on a 0–10 numeric pain scale (NPS) for more than 3 months, or pain aggravated by mandibular function (see above); and (iv) moderate pain (grade II on a scale of 0-III) to palpation, and/or persisting pain after examination in at least 3 muscle sites, and/or moderate pain to palpation of the temporomandibular joint region, and/or limitation in the mandibular movement (opening less than 40 mm). Additional inclusion criteria for all study participants were right-handedness and primary English language use. Exclusion criteria were: (i) serious metabolic, rheumatoid, or vascular disorders; (ii) chronic pain disorders (except from the TMD-related pain); (iii) presence of previously diagnosed psychiatric disorders (depression, schizophrenia, attention deficit hyperactivity disorder); (iv) presence of abnormal neurological examination; (v) standard contraindication for magnetic resonance imaging (MRI) testing. In addition, all participants were required to be free of analgesic medication at least 24 h prior to MRI scanning. All participants in the study provided written informed consent to the study procedures approved by the Mount Sinai Hospital and University Health Network research ethics boards. All patients reported having graduated from at least high school. The control subjects were recruited from the hospital research institute and university environments and consisted of students and staff who typically had at least a high school education.

2.2. Cognitive testing

To test for attention-demanding cognitive processes, we used the number counting Stroop task (ncStroop) designed and validated for use during brain imaging [14]. To test for emotional interference associated with TMD, we developed a TMD-specific emotional counting Stroop task that contains TMD-specific emotional words (ecStroop) akin to other disease-specific emotional Stroop tasks [23,82]. The Stroop tasks were programmed with E-prime (Psychology Software Tools, Inc, Sharpsburg, PA) as a block-design functional MRI (fMRI) study. The task required the subjects to report the number of words (1 to 4) appearing on the screen, regardless of the word meaning. Words were projected to participants via an MRI-compatible goggle system (VisuaStim Digital, Resonance Technology Inc, Northridge, CA). To register a response, subjects used their right hand to press a corresponding button on a fiber optic 4-button inline response box (Current Designs, Inc.; Philadelphia, PA). Subjects were instructed to respond as quickly as possible without sacrificing accuracy for speed.

The protocol consisted of 3 Stroop tasks: (i) neutral Stroop (nStroop), which included common household items (ie, sofa, table, or window); (ii) number counting Stroop (ncStroop), that evoked cognitive interference, and consisted of number words (one, two, three, or four) whose content was incongruent with the number of times the word appeared (eg, "three" written 2 times); and (iii) emotional counting Stroop (ecStroop), that evoked emotional interference, and consisted of TMD-related emotional words (ache, tight, annoying, pain, stress, hurt, clench, anxious, throb, unpleasant, pressure, tiring). RTs and accuracy were recorded during scanning with E-Prime software.

Each Stroop task was tested in a separate run to prevent contamination of the nStroop and ncStroop, with potentially cumulative changes in the emotional state due to the ecStroop. The nStroop was always tested in the first run as the control measure, and the 2 other Stroop tasks were randomized to runs 2 and 3 between subjects and patients. Each run (6 min, 50 s) began with an 8-s visual cue to "be ready!" and was followed by a series of 3 18-s blocks that were repeated 6 times. Each series included a fixation block during which a subject was asked to focus on a visually presented crosshair. This was followed by a tapping block (sequentially pressing each of the 4 buttons on the response box in response to a visual cue of 1, 2, 3, or 4 asterisks to control for motor performance) and ended with the Stroop task block. An additional 18-s fixation block was added at the end of each run to allow the hemodynamic response from the last Stroop block to return to baseline. Each Stroop block contained 12 sets of words (ie, trials), each presented for 1250 ms, with a task-free inter-trial interval of 250 ms.

Prior to the scanning session, participants completed a practice session that included one nStroop block followed by one ncStroop block.

2.3. Clinical assessment and questionnaires

At the beginning of the session and prior to the scanning, the patient's current medication, symptoms, and history of TMD were determined, including the type of painful and nonpainful symptoms and their pain distribution, duration, frequency, and intensity, as well as any activities that aggravate their pain and factors that relieve their pain.

Patients also rated their spontaneous pain intensity and unpleasantness using numeric pain scales (NPS: 0–10 where "0" is equivalent to no pain and "10" is equivalent to severe pain) prior to the

first Stroop task and again after each run. In addition, following the scan session, all participants were asked to rate the effect of each of the 12 words in the ecStroop on a categorical scale between 0 and 4 ("0" – not at all, "1" – slightly, "2" – moderately, "3" – strongly, "4" – severely). The specific questions posed were: "What is the effect of each word on your emotion during the scan?" and "What is the effect of each word on your pain intensity during the scan?" The number of words within each category were summed for each subject and averaged across all subjects within each group.

2.4. Imaging

Each study participant underwent a T1-weighted anatomical scan followed by T2∗-weighted functional scans obtained on a 3T GE MRI system (GE Healthcare System, Waukesha, WI) using an 8-channel phased-array head coil. A whole brain (124 axial slices, 24 × 24 cm field of view) high-resolution (256 × 256 matrix, 0.94 × 0.94 × 1.5 mm voxels) anatomical scan was obtained using a 3-dimensional fast spoiled gradient-echo pulse sequence (flip angle = 45°, echo time = 5 ms, repetition time = 25 ms). T2∗-weighted fMRI scans were acquired with an echo-planar pulse imaging sequence (28 axial slices, 20 × 20 cm field of view, 64 × 64 matrix, 3.125 × 3.125 × 4 mm voxels, echo time = 40 ms, repetition time = 2000 ms). A total of 175 functional frames were acquired for each run and the first 4 frames were removed to allow signal equilibration.

BrainVoyager software (BV QX v1.10; Brain Innovation, Maastricht, Netherlands) was used for preprocessing and statistical analysis. Datasets obtained from fMRI were interpolated to 3 × 3 × 3 mm voxels and underwent preprocessing that included: head motion correction, slice timing correction, linear trend removal, and spatial smoothing with a 6-mm full-width-at-half-maximum Gaussian kernel. The data from fMRI scans were aligned to the high-resolution anatomical image and normalized to standard Talairach space (voxels are reported as 1 × 1 × 1 mm).

2.5. Statistical analysis

2.5.1. Behavioural data

To test for differences in reaction time (RT), we ran a repeated-measures analysis of variance with conditions (ncStroop, ecStroop, and nStroop tasks) as the within-group variable, patients and healthy controls as the between-group variable, and RT (in milliseconds) as the dependent variable. The difference in RT within each group was assessed with a paired t-test corrected for multiple comparisons using the Bonferroni correction. Accuracy was calculated for each subject and each block. The average accuracy rate across blocks within each run was compared between groups with Student's t-test. Trials with zero RT were excluded from the analysis. For the emotional effect rating, we summed the number of words for each category (0–4) in the questionnaire, averaged them across all subjects within each group, and compared the sum for each category between groups using Student's t-test corrected for multiple comparisons.

2.5.2. fMRI data

The fMRI analysis consisted of 2 stages: in the first stage, a general linear model was used to delineate a general map of whole brain cognitive-related activation for each individual.

The second stage consisted of 3 analyses:

(i) Task-related brain responses for each cognitive task were delineated for patients and controls as follows. Data were concatenated from all runs done in all subjects. Task-related brain activations for each Stroop task (nStroop, ncStroop, and ecStroop) were determined from the contrast (Stroop task minus fixation) within each subject group to determine the direction of changes (activation/deactivation), and then between patients with TMD and healthy controls. Activations associated with the cognitive interference effect were determined from the between-group contrast (ncStroop minus nStroop) and for the emotional interference effect from the between-group contrast (ecStroop minus nStroop). For both analyses, we subtracted the tapping-related brain activation from each Stroop task-related brain activation in order to control for confounding motor effects. All t-maps were thresholded at a corrected $P < 0.05$ (derived from an uncorrected $P < 0.0001$ and 120-mm^3 contiguous voxels, as previously reported by Downar et al. [28] and validated using the Monte Carlo simulation implemented in the Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov/) with the AlphaSim application). Lastly, we averaged the beta weight for each group from peak activations of significant clusters.

(ii) To locate brain areas commonly activated in both the ncStroop and ecStroop, we performed conjunction analyses based on the assumption that salience/emotional brain areas are engaged during interference effects in both Stroop tasks. This was done separately for patients with TMD and controls. Conjunction maps were thresholded at $P < 0.05$ (corrected with false discovery rate).

Table 1
Clinical Characteristics.

Patient	Age	TMD duration (yrs)	TMD pain intensity	TMD pain Unpl	Pain Freq	Pain site	TMD laterality	Current medication
1	22	2	4	5	Intermittent	Joint	Bilateral	NSAID
2	20	3	3	3	Intermittent	Muscle, Joint	Bilateral	
3	24	7	4	8	Intermittent	Joint	Right	NSAID, P
4	38	20	7	6	Constant	Joint	Bilateral	NSAID
5	42	0.75	2	3	Constant	Muscle	Bilateral	
6	33	4	5	6	Constant	Muscle, Joint	Bilateral	
7	28	17	3	5	Constant	Muscle, Joint	Left	
8	34	14	2	8	Intermittent	Joint	Bilateral	
9	50	10	7	6	Constant	Muscle	Bilateral	NSAID, Ch, Di
10	59	13	7	7	Intermittent	Muscle, Joint	Bilateral	
11	18	3	6	8	Constant	Muscle, Joint	Bilateral	
12	34	15	2	3	Intermittent	Muscle	Right	
13	52	30	4	5	Constant	Muscle, Joint	Bilateral	NSAID
14	31	2	6	5	Constant	Muscle, Joint	Right	NSAID
15	33	17	5	8	Constant	Muscle, Joint	Bilateral	MR, NSAID
16	47	3	3	3	Intermittent	Muscle	Bilateral	
17	34	2	5	5	Constant	Muscle	Bilateral	NSAID

Unpl, Unpleasantness; NSAID, Non-steroidal anti-inflammatory; P, Prevacid; Ch, Champix; Di, Dixarit (Clonidine); MR, muscle relaxant.

Table 2
Stroop reaction times and accuracy.

Group	Condition	Reaction time				Accuracy
		Mean (ms)	SE	95% Confidence interval		mean (%)
				Lower bound (ms)	Upper bound (ms)	
Controls	nStroop	625	19	585	664	98
	ncStroop	670	17	635	706	96
	ecStroop	633	16	601	666	97
Patients	nStroop	661	19	622	701	98
	ncStroop	714	17	678	749	95
	ecStroop	678	16	645	710	87

nStroop, neutral Stroop; ncStroop, number counting Stroop; ecStroop, emotional counting Stroop.

(iii) A connectivity analysis was used to interrogate the associated neural activity between the aMCC and the DLPFC (Brodmann areas [BA] 9, 46) and between the amygdala and pgACC, which are thought to be engaged during cognitive and emotional function, respectively [25]. We chose the location (x, y, z) of seeds for these 4 regions of interest (each: $5 \times 5 \times 5$ mm) based on previous studies of the counting Stroop [8,13,60]: right aMCC (7, 23, 30; BA 32); right superior frontal gyrus (43, 9, 33; BA 9); pgACC (3, 40, 4; BA 24/32); right amygdala (24, −4, −16). The mean beta weight for each subject was extracted from general linear model analysis for each region of interest (ROI). Then the association within each pair of brain areas was examined by a linear regression model, including the RT for the cognitive interference effect as an independent variable in the aMCC-DLPFC analysis and the RT for the emotional interference effect in the pgACC-amygdala analysis.

3. Results

3.1. TMD clinical characteristics

Patients' clinical characteristics are presented in Table 1. The group means ± SD were: age: 35.2 ± 11.6 years, pain duration: 9.3 ± 8.3 years, pain intensity 4.2 ± 1.6. The site of pain, based on clinical examination, was deemed to be in the masticatory muscles (5 patients), joint (4 patients), and a combination of both muscle and joint (8 patients). Also, 13 of the 17 patients reported bilateral pain. Four patients reported that they experienced intermittent

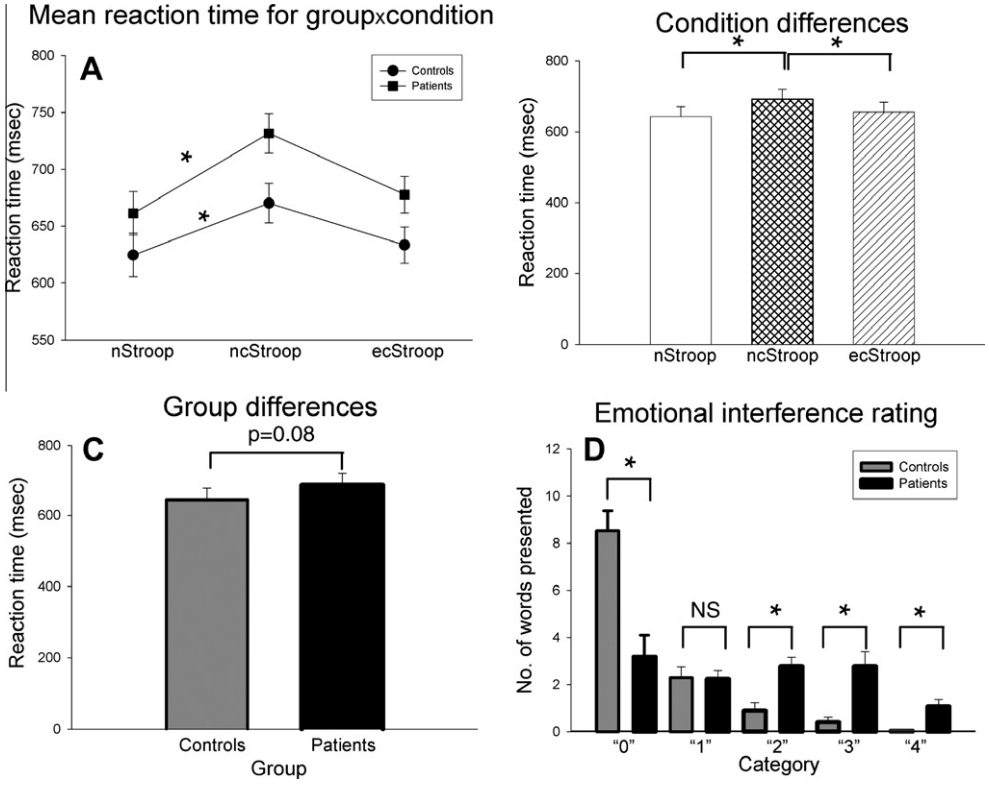

Fig. 1. Behavioural performance for Stroop tasks and the emotional impact of temporomandibular disorder (TMD)-specific emotional words. (A) There was no statistically significant interaction between group (patients vs. controls) and condition (Stroop task). Within-group analysis revealed that the reaction times (RTs) to the number counting Stroop (ncStroop) were longer for both the patients (squares) and controls (circles) compared to neutral Stroop (nStroop). (B) There was a significant condition effect. The RT for the ncStroop was longer compared to nStroop and emotional counting Stroop (ecStroop). (C) Patients showed a trend towards slower RTs in their responses to all Stroop tasks compared to controls. (D) Most of the control subjects (gray bars) were not affected by the TMD-related words of the ecStroop. However, patients (black bars) were moderately to severely affected by these words. $^{*}P < 0.05$.

headache or neck/shoulder pain, and one patient reported having intermittent nonspecific knee pain. The mean (±SD) age of the healthy control subjects (34 ± 9.9 years) was not significantly different from the patients ($P = 0.62$).

3.2. Behavioural data

A summary of RT and accuracy for each condition within each subject group is presented in Table 2. There was an overall increase in RT to the ncStroop compared to the nStroop in both the patient and control groups (patients: $P = 0.002$; controls: $P = 0.006$). There was no significant difference in the RT for the ecStroop and nStroop in either group (patients: $P = 0.39$; controls: $P = 0.73$) (Fig. 1A). There was no significant between-group difference in RT in the tapping task during the nStroop (patients: 422 ± 71 ms, controls: 416 ± 95 ms; $P = 0.86$).

Repeated-measures analysis of variance showed that there was no significant interaction between group and condition for the RT ($P = 0.88$). There was a main effect of condition ($P = 0.016$), with slower RTs for ncStroop compared to the nStroop RTs ($P = 0.0001$) (Fig. 1B). However, for the main effect of group, the patients showed only a trend towards slower RTs in their responses to each Stroop task compared to controls ($P = 0.08$) (Fig. 1C). The lack of significant group-condition interaction precluded post-hoc testing of group differences for each Stroop task, although t-tests did show a trend of slower RTs in the patients compared to controls for the ncStroop ($P = 0.087$) and ecStroop ($P = 0.058$).

Mean ± SD spontaneous pain intensity at the beginning of the scan session was: 3 ± 2 on the NPS. During the ecStroop, some patients reported an increase in their pain intensity. Using the NPS it was shown that the mean pain intensity increased to 4 ± 2 (corrected $P = 0.021$). The TMD-specific emotional words affected the patients, but only had a modest effect on the healthy controls (Fig. 1D). When subjects were asked how much the words affected them, the controls reported that most of the words (mean = 8.5) did not affect them at all (rating = 0). In contrast, patients reported that most of the emotional words (mean = 8.8) affected them in some way (ranging from slightly up to severely; Fig. 1D).

3.3. Imaging data

3.3.1. Group differences in Stroop and interference effects

Whole brain analysis revealed that each Stroop task, for both the patients and controls, activated brain areas implicated in attention, cognition, and motor planning. Activated regions included the middle (GFm) and inferior (GFi) frontal gyrus (BA 9, 46), inferior parietal lobe (LPi) (BA 40), superior parietal lobe (LPs) (BA 7), premotor areas including the supplementary motor area (SMA) (BA 6), and frontal eye fields (FEF) (BA 8), as well as middle (GTm) and inferior (GTi) temporal gyrus (BA 21, 37). In addition, during all Stroop tasks, so-called "deactivations" (ie, reduced blood oxygen level dependent (BOLD)) were apparent in areas implicated in affective processing (pgACC and subgenual anterior cingulate cortex [sgACC]) and areas considered to be part of the "default-mode network" such as the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus (PCu). However, the magnitude of activations and deactivations varied between groups and across tasks (see below for details).

3.3.1.1. The nStroop. Brain responses to the nStroop were more pronounced in patients with TMD compared to the healthy controls, particularly in the frontal cortex (Fig. 2, Table 3). Specifically, greater deactivation in the mPFC was found for the TMD group compared to controls. Moreover, in the TMD group there was prominent deactivation bilaterally in the orbitofrontal cortex (OFC) and FEF, as well as in the right GTm. In contrast, the healthy controls showed only modest activations or deactivations within these brain areas.

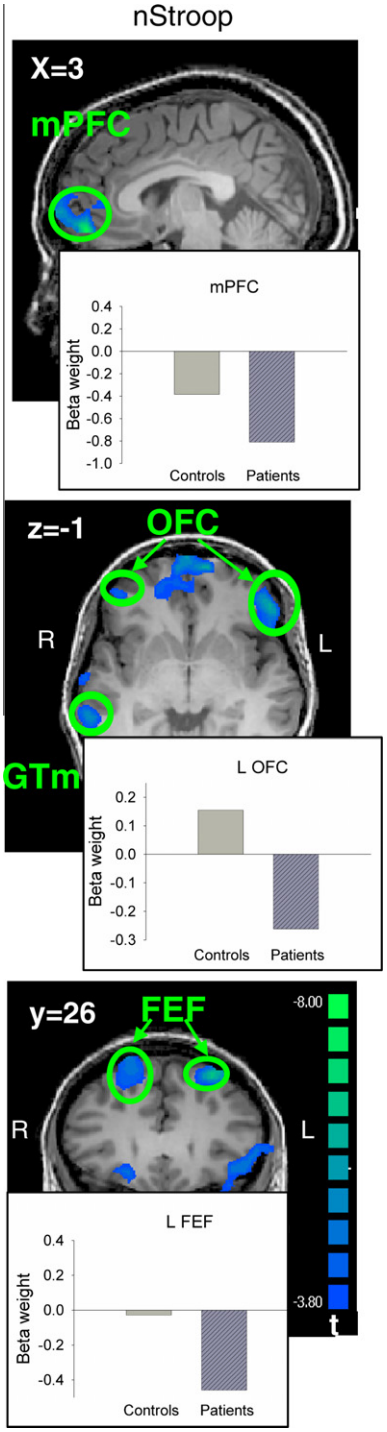

Fig. 2. Temporomandibular disorder (TMD) patients have greater neutral Stroop-evoked deactivation in the mPFC, orbitofrontal cortex, and frontal eye fields. Each brain map represents the group differences in activation to the neutral Stroop for patients minus controls in a whole brain analysis. To control for motor performance, for each of the patient and control groups, the tapping-related brain activation was subtracted from all maps. All maps were thresholded at a corrected $P < 0.05$. The color flare represents t-value for significant group differences. The bar graphs show the mean beta weight from controls (light gray) and TMD patients (dark gray with diagonals) extracted from significant clusters. mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; FEF, frontal eye field.

Table 3
Group differences for the nStroop, ncStroop and ecStroop tasks.

Region		Coordinates	BA	TMD beta weight	Controls beta weight	TMD-controls t-value
nStroop task						
Frontal	GFm	8, 55, −6	10, 32	−0.811	−0.384	−6.67
	GFs	17, 24, 58	8	−0.447	−0.103	−5.23
		−26, 27, 51	8	−0.459	−0.029	−6.50
	GFi	40, 46, −1	10, 47	−0.081	0.210	−4.43
		−46, 39, −1	10, 47	−0.262	0.155	5.92
Temporal	GTm	56, −33, −3	21	−0.198	0.175	−5.86
ncStroop task						
Frontal	sgACC	−5, 17, −6	25	0.030	−0.289	4.88
	pgACC	−2, 32, 5	24, 32	−0.211	−0.648	6.54
	GFm	47, 34, 25	9/46	0.529	0.158	4.82
		40, 40, 8	10	0.454	−0.012	5.67
		49, 0, 38	6, 4	0.538	0.161	6.36
		−58, 4, 11	6, 4	−0.299	0.243	7.05
Parietal	LPs	17, −72, 47	7	0.829	0.312	8.53
		−21, −67, 54	7	0.898	0.401	8.03
	LPi	47, −47, 43	40	0.611	0.167	6.56
Temporal	GTm	−50, −59, 2	21	0.766	−0.568	5.43
Anterior and middle insula		37, −3, 0		0.100	−0.242	5.33
Subcortical	Amygdala	−17, −8, −13		−0.002	−0.307	4.68
ecStroop task						
Frontal	sgACC	−8, 33, −6	32, 10	−0.211	−0.538	4.59
	GFm	37, 49, 25	9, 10	0.485	−0.056	6.86
	GFs	5, −2, 65	6	0.382	0.052	6.98
	aMCC	3, 2, 44	24	0.246	−0.017	4.86
Parietal	LPi	46, −44, 44	40, 7	0.334	−0.053	5.98
		−42, −48, 35	40, 7	0.290	−0.089	5.84
	PCC	−4, −35, 30	23, 30, 31	0.223	−0.230	7.27
	RSC	−4, −45, 8	29	0.141	−0.192	5.28
Anterior insula		32, 17, 7		0.499	0.175	5.44
Posterior insula		36, −7, −1		−0.054	−0.356	4.84
Subcortical	NC	4, 7, −2		0.053	−0.243	4.45

Anatomical locations and peak activation coordinates (in Talaraich space) extracted from brain areas that were found to be significantly different between patients and controls at image wide of $p < 0.05$, for each Stroop test. GFs, superior frontal gyrus; GFm, middle frontal gyrus; GFi, inferior frontal gyrus; LPs, superior parietal gyrus; LPi, inferior parietal gyrus; GTm, middle temporal gyrus; sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; aMCC, anterior mid cingulate cortex; PCC, posterior cingulate cortex; RSC, rostral splenial cortex; NC, caudate nucleus.

3.3.1.2. The ncStroop. Compared to the healthy control group, the TMD group had (i) stronger activation in brain areas involved in attention and motor planning (Fig. 3, Table 3): bilateral LPs/precuneus, right GFm, right LPi, and (ii) activation in the bilateral SMA (BA 6), whereas in controls the left SMA was deactivated. In addition, patients showed less deactivation and even activation in emotional brain areas that are normally deactivated in controls: pgACC, sgACC, right anterior insula, and left amygdala.

3.3.1.3. The ecStroop. The ecStroop strongly activated attention-cognitive and motor planning brain areas such as the right GFm, bilateral LPi, and SMA in the TMD group. However, the control group showed little or no response to the ecStroop in these areas. Furthermore, in the TMD group, the emotion/salience areas showed either greater activation (right anterior insula), became activated (aMCC, rostral splenial cortex [RSC] and PCC), or were less deactivated (sgACC) (Fig. 4, Table 3).

3.3.1.4. Brain areas commonly activated with ncStroop and ecStroop testing. Several brain areas associated with cognitive and motor preparation were commonly activated (or deactivated) during the ncStroop and ecStroop in both the patients and controls (Fig. 5). These areas included bilateral GFi, left LPs/LPi, left SMA/premotor cortex, left fusiform gyrus, and mPFC. However, areas implicated in salience detection were activated in patients with TMD (but not controls) during both interference tasks; these areas were the aMCC ($t = 3.512$, $P = 0.002$) and right anterior insula ($t = 5.98$, $P = 0.00001$). In addition, the central SMA/premotor cortex ($t = 5.906$, $P = 0.00002$) were also activated in TMD but not in controls during both interference tasks.

3.3.1.5. Group response differences evoked by cognitive interference and emotional interference. There were 2 main types of differences between groups in the brain responses associated with the cognitive interference effect (ie, ncStroop minus nStroop) (Fig. 6, Table 4). One type of group difference was prominent in areas associated with emotional processing such as the pgACC/mPFC region and the right amygdala. In the control group these areas were deactivated during cognitive interference, but in the TMD group these areas were activated. Another type of group difference occurred in motor areas, such as the right subthalamic nucleus, the left premotor and sensorimotor cortex, and the LPi, where the patients showed greater activation than the controls.

The group differences in responses associated with the emotional interference effect (ie, ecStroop minus nStroop) are shown in Fig. 7 and Table 4. Areas considered part of the DMN, such as the mPFC and PCC, and brain areas within the limbic lobe such as the pgACC, RSC, and parahippocampal gyrus, were deactivated in the controls, whereas these areas were activated in the patients during emotional interference. In addition, cognitive areas in the GFm, LPi, and motor preparation brain areas (SMA), which show little activation or deactivation in controls, showed greater activation in TMD patients.

3.3.1.6. Behavioural performance and connectivity within cognitive and emotional networks. We examined the connectivity between 2 pairs of brain areas thought to have network connectivity, the aMCC-DLPFC and the amygdala-pgACC. Fig. 8 shows the correlations for each pair for the control and patient groups based on beta weights for each brain area within each subject. These correlations

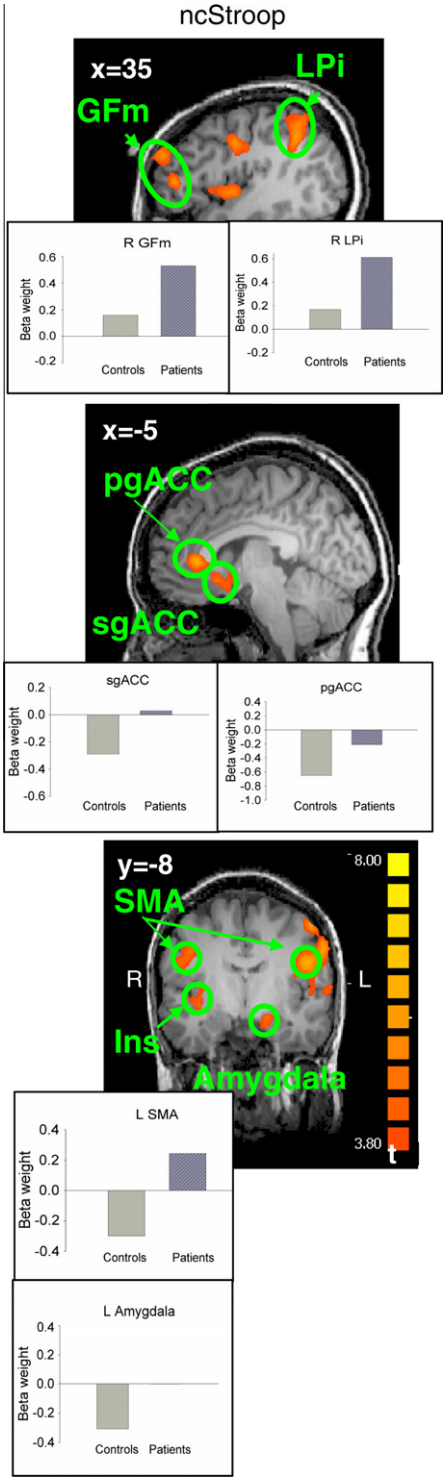

Fig. 3. Temporomandibular disorder (TMD) patients have greater number counting Stroop-evoked activation areas in the middle frontal and inferior parietal and less deactivation/activation in task-evoked deactivation areas (subgenual anterior cingulate cortex [ACC], pregenual ACC, and amygdala). Each brain map represents the whole brain activation to the number counting Stroop task (ncStroop) in the contrast of patients minus controls, with the tapping-related brain activation subtracted from all maps to control for motor performance. All maps were thresholded at a corrected $P < 0.05$. The color flare represents t-value for significant group differences. The bar graphs show the mean beta weight from controls (light gray) and TMD patients (dark gray with diagonals) extracted from significant clusters. GFm, middle frontal gyrus; LPi, inferior parietal gyrus; sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; SMA, supplementary motor area; Ins, insula.

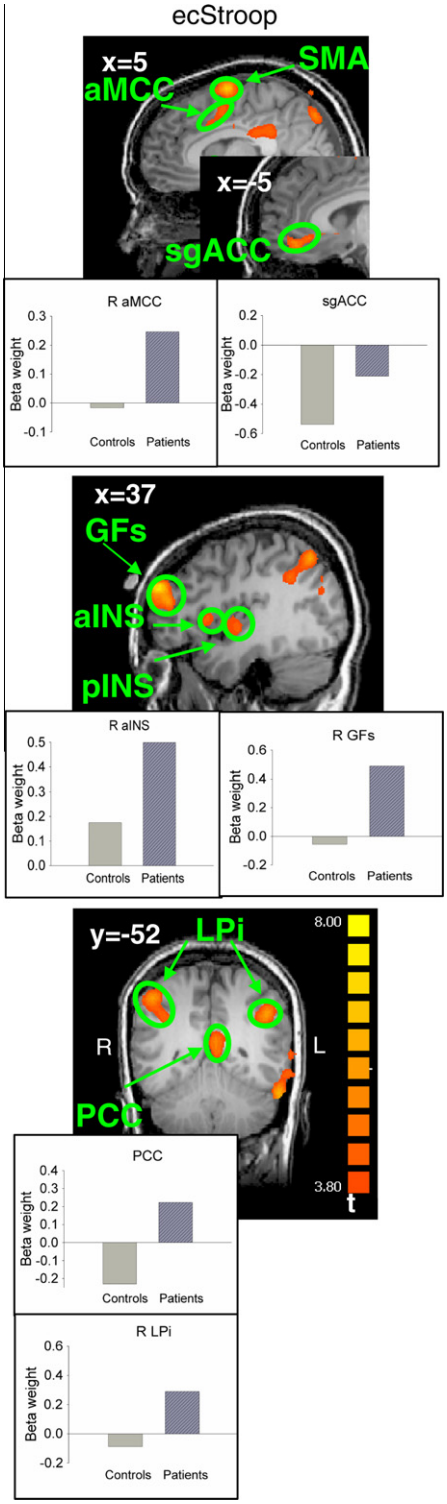

Fig. 4. Temporomandibular disorder (TMD) patients have greater emotional counting Stroop (ecStroop)-evoked activation in the anterior insula, activation in the anterior MCC, PCC, superior frontal and inferior parietal cortices, and less deactivation in the subgenual ACC. Each brain map represents the whole brain activation to the ecStroop in the contrast of patients minus controls, with the tapping-related brain activation subtracted from all maps to control for motor performance. All maps were thresholded at a corrected $P < 0.05$. The color flare represents t-value for significant group differences. The bar graphs show the mean beta weight from controls (light gray) and TMD patients (dark gray with diagonals) extracted from significant clusters. aMCC, anterior mid cingulate cortex; sgACC, subgenual anterior cingulated cortex; GFs, superior frontal gyrus; aINS, anterior insula; pINS, posterior insula; LPi, inferior parietal gyrus; PCC, posterior cingulate cortex.

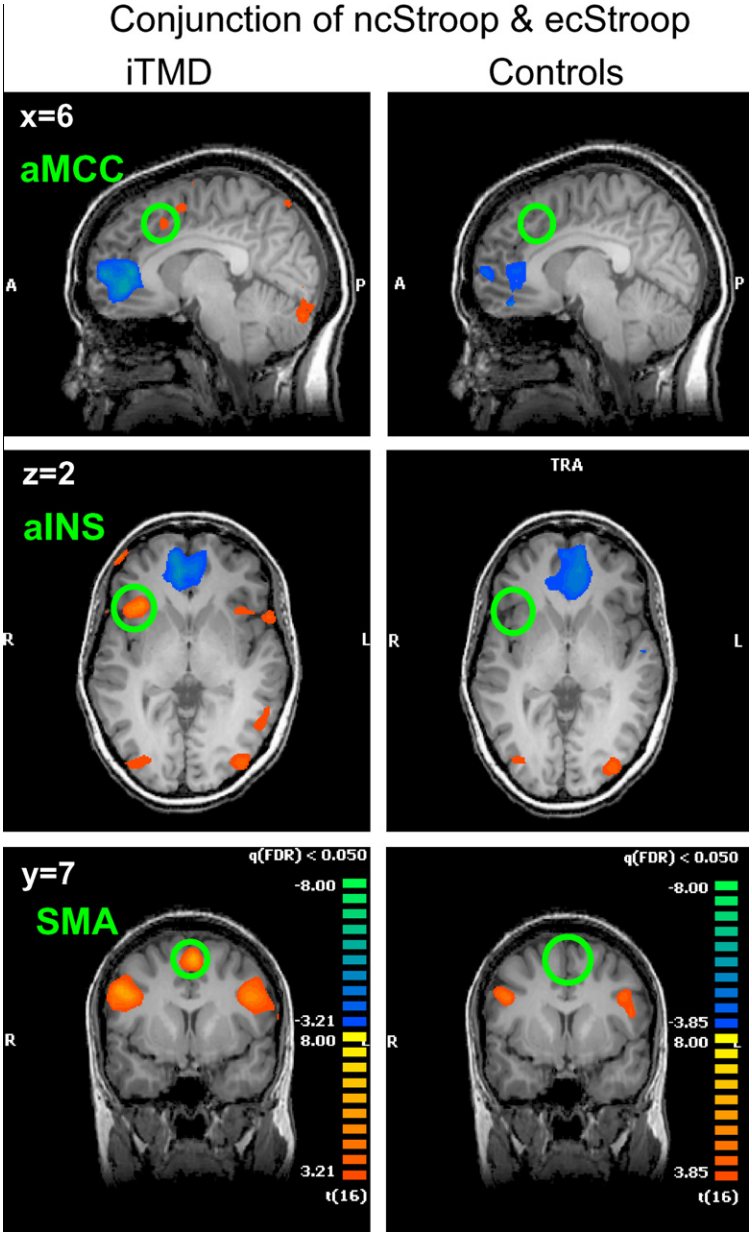

Fig. 5. Whole brain group conjunction analysis of number and emotional counting Stroop tasks showing that temporomandibular disorder (TMD) patients but not controls activated the anterior MCC, anterior insula, and SMA in both tasks (circled in green). All maps were thresholded at $P < 0.05$ corrected with false discovery rate. The color flare represents t-value for areas where activation (red colour) or deactivation (blue colour) was common across all subjects in both tasks. aMCC, mid cingulate cortex; aINS, anterior insula; SMA, supplementary motor area.

indicate that the patients have a different neural association for these pairs compared to the controls.

In the controls, during the cognitive interference task, there was a strong correlation between the DLPFC and the aMCC ($r = 0.77$, $P < 0.0001$) as well as between the pgACC and the amygdala ($r = 0.65$, $P = 0.0004$) (Fig. 8A). Moreover, the behavioural interference effect (RT for ncStroop minus RT for nStroop) was associated with enhanced activity in the DLPFC during cognitive interference processing ($r = 0.6$, $P = 0.011$). However, for the TMD patients there were no significant correlations between either of the 2 pairs of brain areas: aMCC-DLPFC ($r = 0.2$, $P = 0.44$) and amygdala-pgACC ($r = 0.29$, $P = 0.27$). Also, there was no correlation between the increase in the DLPFC activation during the cognitive interference processing and behavioural performance (RT) ($r = 0.31$, $P = 0.22$).

There were also group differences in the coupling of these pairs of brain regions during the emotional interference task (Fig. 8B). In controls, there was no significant coupling of the aMCC-DLPFC pair ($r = 0.27$, $P = 0.29$) or between the RT and the change in DLPFC activation during the interference processing ($r = 0.32$, $P = 0.21$). Also, controls showed only a modest association for the amygdala-pgACC pair ($r = 0.52$, $P = 0.032$) and for the relation between RT and the increased activation in the amygdala during the emotional interference processing ($r = 0.53$, $P = 0.028$). In contrast, the patients showed a significant coupling for the amygdala-pgACC pair ($r = 0.57$, $P = 0.017$) and for the aMCC-DLPFC pair ($r = 0.59$, $P = 0.013$). However, no correlation was found between RT and the activity in the amygdala ($r = 0.07$, $P = 0.798$), aMCC ($r = 0.06$, $P = 0.824$), and the DLPFC ($r = 0.027$, $P = 0.92$) during the emotional interference processing.

Table 4
Group differences in cognitive and emotional interference effects.

Region		Coordinates	BA	TMD beta weight	controls beta weight	TMD-controls t-value
Number Stroop interference						
Frontal	GFs	3, 50, −10	10	0.178	−0.413	6.76
	pgACC	0, 36, 6	24/32	0.294	−0.254	5.92
	GPrC	−55, 3, 38	4, 6	0.269	−0.352	4.70
Parietal	GPoC	−58, −11, 38	3	0.264	−0.323	6.18
	LPi	−48, −33, 50	40	0.281	0.091	4.81
Temporal	GTi	−50, −55, −3	37	0.446	0.009	4.80
Subcortical	Amygdala	28, −2, −22		0.242	−0.252	5.30
	STN	15, −14, −6		0.239	−0.164	4.34
Emotional Stroop interference						
Frontal	GFm	−46, 3, 30	6,8,9	0.365	−0.002	4.29
	pgACC&GFs	−6, 61, 0	32,10	0.401	−0.195	5.85
Parietal	LPi	−41, −69, 29	39	0.462	−0.100	6.06
	PCC	−2, −37, 32	23,31	0.389	−0.090	5.26
	RSC	−4, −46, 10	29	0.355	−0.090	5.08
Temporal	GTm	−56, −38, −9	21, 37	0.513	−0.030	5.78
	PHG	−25, −19, −7		0.243	−0.253	5.33

Anatomical locations and peak activation coordinates (in Talaraich space) extracted from brain areas that were found to be significantly different between patients and controls at image wide of $p < 0.05$, for interference effect. GFs, superior frontal gyrus; GFm, middle frontal gyrus; GPrC, precentral gyrus; GpoC, postcentral gyrus; LPi, inferior parietal gyrus; GTm, middle temporal gyrus; GTi, inferior temporal gyrus; pgACC, pregenual anterior cingulate cortex; PCC, posterior cingulate cortex; RSC, rostral splenial cortex; PHG, parahippocampal gyrus; STN, Subthalamic nucleus.

4. Discussion

This is the first study to demonstrate that patients with TMD have abnormal brain responses to attention-demanding Stroop tasks that involve cognitive or emotional interference. The most prominent abnormalities in these patients were: (i) slower task RTs, (ii) more pronounced task-evoked fMRI responses in brain areas implicated in attention/cognition and emotional/salience processes, (iii) task-evoked activation rather than the normal task-related deactivation in the DMN, (iv) reduced connectivity within the prefrontal-cingulate and amygdala-cingulate pairs of brain regions that are normally coupled during cognitive interference, and (v) increased connectivity of these pairs of brain areas during emotional interference. Thus, sluggish behavioural responses in TMD may arise from attenuated, slower, and/or unsynchronized neural recruitment because of the salience of chronic pain, which inherently requires attention. Patients with TMD might also use different brain processes to balance attention, salient, and emotional needs.

One explanation for the reciprocal interaction between pain and attention is that pain can lead to negative feelings, fear, and anxiety and therefore can impair attention and decision-making processes. Conversely, cognitive processes and emotional state can modulate pain through the descending pathways [61,75,76,84]. In chronic pains, the interaction between pain and cognition may have even greater functional impact because the source of pain cannot be removed. Thus, chronic pain could compromise the ability to effectively attend to and properly balance cognitive needs, potentially more so in a negative emotional context [3,34,35,61,64,84].

During the cognitive interference task there was no difference in the interference effect between patients and controls despite different brain activations in the interconnected prefrontal regions (aMCC, DLPFC, premotor, and SMA) that play a role in attention and executive cognitive control [59]. In controls, the aMCC, which is involved in conflict monitoring and behavioural adjustment [15,54], was highly correlated with the activity in the DLPFC, which exerts attentional control to reduce conflict [8,15,45,54]. Moreover, task-related activity in the DLPFC correlated with the degree of behavioural interference. As expected, the pgACC and the amygdala showed nonspecific deactivation during a cognitive interference task [13,14,81]. Alternatively, in TMD, these 2 networks became decoupled and dissociated with the behavioural output due to a disruption of their functional connectivity. Furthermore, the TMD group activated the mPFC/pgACC and amygdala, which are normally engaged by emotional stimuli [13,25,81] and are known to become active during evoked/spontaneous pain [4,7,66]. This suggests that in patients with TMD, attentional and emotional networks are engaged by their chronic pain and therefore are improperly recruited for goal-directed cognitive tasks. Therefore, if patients were compensating for this deficiency through different strategies and brain processes, they would not show a net behavioural difference [16,52].

Interestingly, we found that some motor areas were more strongly activated in patients compared to controls during the cognitive interference task. Painful stimuli normally evoke withdrawal reflexes, whereas persistent pain can inhibit movement to protect an affected area [38]. Boudreau et al. [12] suggested that nociceptive input impairs motor performance and the ability to learn new motor tasks due to impaired plasticity in the motor cortex. Based on this concept, we suggest that patients with TMD may recruit these motor areas during Stroop tasks as a compensatory mechanism to meet increased demands for motor planning and performance.

The amygdala is an important area, implicated in the experience and expression of emotion [1,65], and its activity is regulated by the PFC [62,63]. The pgACC, which is anatomically and functionally connected to the amygdala, is typically recruited during presentation of emotionally salient stimuli to modulate the reactivity of the amygdala [25,37,63,81,82]. Therefore, the pgACC plays an important function in tasks that require cognitive control in the presence of task-irrelevant emotional stimuli [79,81]. In our study, patients with nontraumatic TMD were affected emotionally by the TMD-related emotional words, and they activated brain areas implicated in emotional processing (mPFC, pgACC, parahippocampus/amygdala). Although the pgACC activation was correlated with amygdala activity, it did not show downregulation of parahippocampal/amygdala activity. This finding is suggestive of a weak or inefficient functional connectivity between the pgACC and amygdala. Another mechanism that can modulate the pgACC-amygdala connectivity is top-down regulation by the DLPFC. This region utilizes frontoparietal regions to control attention and minimize

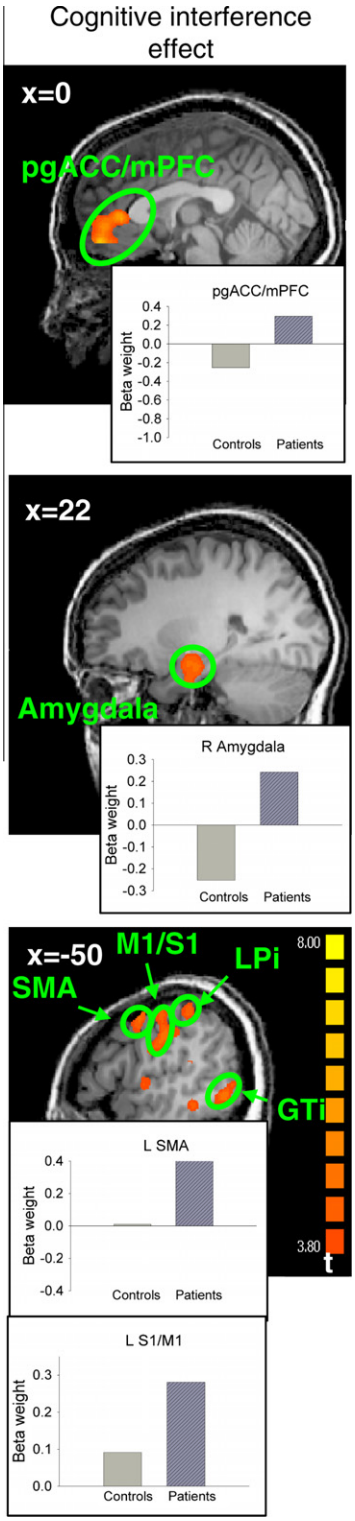

Fig. 6. Temporomandibular disorder (TMD) patients have greater cognitive interference-evoked activation in the SMA, M1, and S1, and activation in task-evoked deactivation areas (subgenual anterior cingulated cortex [ACC], medial PFC, and amygdala). Each brain map represents the whole brain activation to the number counting Stroop minus neutral Stroop in the contrast of patients minus controls, with the tapping-related brain activation subtracted from all maps to control for motor performance. All maps were thresholded at a corrected $P < 0.05$. The color flare represents t-value for significant group differences. The bar graphs show the mean beta weight from controls (light gray) and TMD patients (dark gray with diagonals) extracted from significant clusters. pgACC, pregenual anterior cingulated cortex; mPFC, medial prefrontal cortex (anatomically located in the superior frontal gyrus, BA 10); SMA, supplementary motor area; M1/S1, somatosensory cortex; LPi, inferior parietal gyrus; GTi, inferior temporal gyrus.

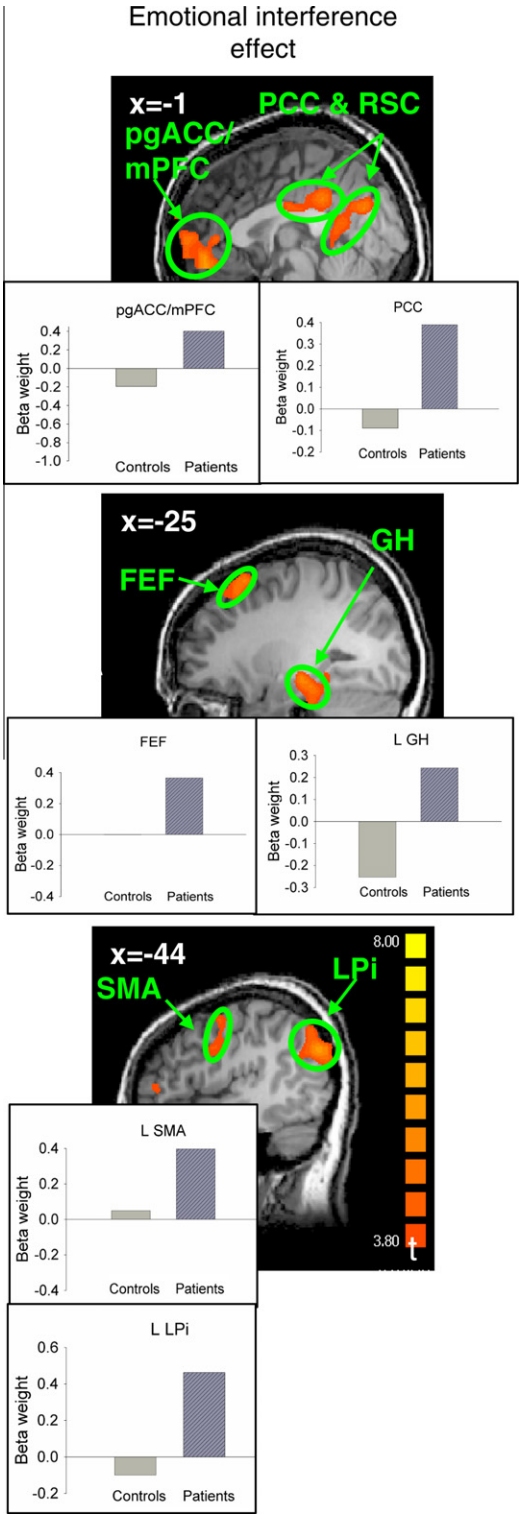

Fig. 7. Temporomandibular disorder (TMD) patients have greater emotional interference-evoked activation in the SMA and FEF and activation in task-evoked deactivation areas (subgenual ACC, mPFC, PCC, RSC, gyrus parahippocampal, and inferior parietal lobe). Each brain map represents the whole brain activation to the emotional counting Stroop (ecStroop) minus neutral Stroop in the contrast of patients minus controls, with the tapping-related brain activation subtracted from all maps to control for motor performance. All maps were thresholded at a corrected $P < 0.05$. The color flare represents t-value for significant group differences. The bar graphs show the mean beta weight from controls (light gray) and TMD patients (dark gray with diagonals) extracted from significant clusters. pgACC, pregenual anterior cingulated cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; RSC, rostral splenial cortex; FEF; frontal eye field; GH, gyrus parahippocampal; SMA, supplementary motor area; LPi, inferior parietal gyrus.

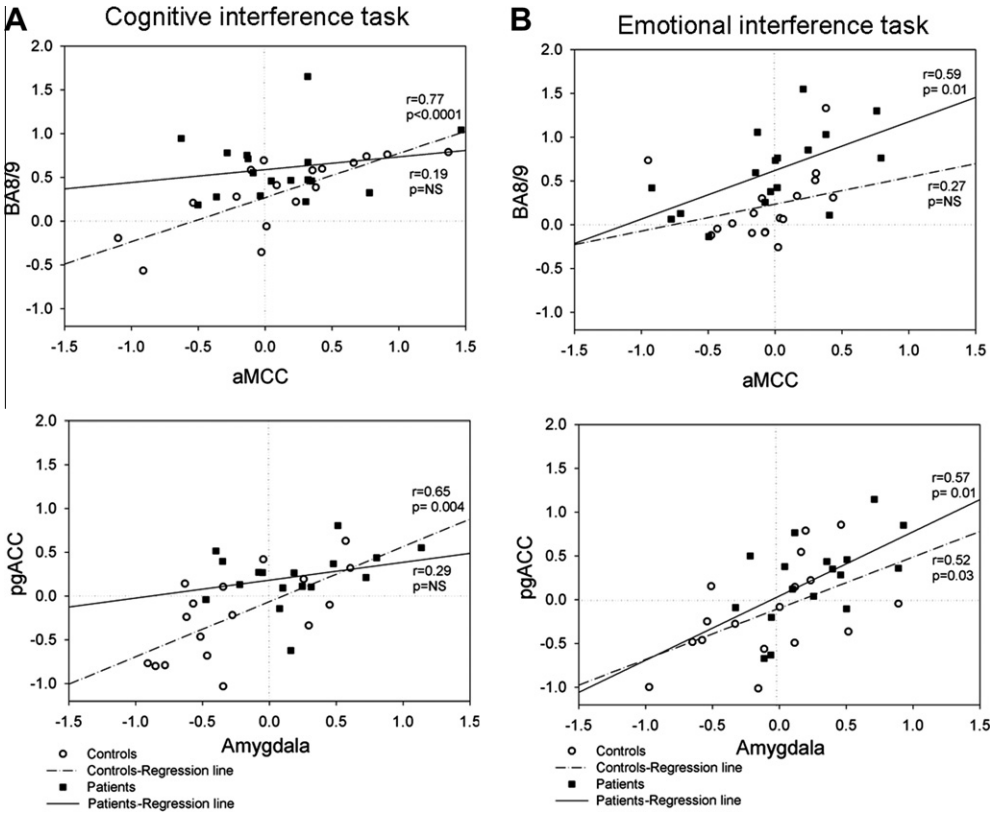

Fig. 8. Beta weight correlation between cingulate-prefrontal and amygala-cingulate during cognitive and emotional interference tasks. (A) During the cognitive interference task, controls (open circles) showed coupling between the amygdala and the pregenual cingulate cortex (pgACC) as well as between the anterior mid-cingulate (aMCC) and the dorsolateral prefrontal cortex (DLPFC; BA). In temporomandibular disorder (TMD) patients (filled squares), these 2 couples were decoupled in their neural brain activity. (B) During the emotional interference task, controls and TMD patients showed coupling between the amygdala and the aMCC. For the aMCC-DLPFC couple, no association was found between these 2 brain areas in controls, whereas patients demonstrated significant correlation.

emotional salience evoked by the ecStroop, and this is further suggested by aMCC activity in TMD patients being correlated to the DLPFC activity. Thus, the concerted function of the aMCC and DLPFC may normally facilitate task performance by inhibiting emotion-related behaviours. Because psychological distress level was not measured in our TMD patients, we cannot rule out the possibility of comorbidity with depression or anxiety disorders that might affect our results. Nevertheless, by subtracting the nStroop from the ecStroop, we can relate changes in brain activation to the interference effect of the TMD-related emotional words, but cannot control for potential interactions between chronic pain and these confounding factors.

During the emotional interference task, the PCC was also more activated in patients than in controls. This region mediates interactions of emotional and memory-related processes and is activated by emotionally salient stimuli [55,56]. The PCC may also play a role in contextualizing painful stimuli. Evidence for this concept comes from studies that show the dorsal PCC to be involved in visuospatial orientation towards innocuous and noxious somatosensory stimuli [77]. Therefore, the increased activation in patients may relate to the increase in spontaneous pain during the ecStroop, given that the emotional words had a greater emotional effect in the patients than in the controls. This could be related to activation of the ventral PCC, a region involved in assessing the self-relevance of emotional events by a cognitively mediated mechanism [77]. Accordingly, the RSC, which has a function in memory access [55,77], also showed abnormal activation in patients.

The PCC and the mPFC are functionally connected elements in the DMN. It has been suggested that they are involved in self-referential processing of both the internal and external environments [40]. During a cognitive task, these regions are usually deactivated. We identified this network in healthy subjects [72] and showed greater DMN deactivation when subjects received painful stimuli while performing a cognitive task, indicating a cumulative effect of these 2 attentional loads. The present findings are in line with previous findings that chronic back pain patients did not deactivate the mPFC and had disrupted connectivity within the DMN while performing an attention task [6]. This pattern of neural activity might be due to an overload of attentional resources due to prolonged pain, potentially affecting brain function and the ability to attend to multiple stimuli at once. Moreover, we suggest that coping with chronic pain requires internally focused processing of internal and external environments as a nocifensive mechanism that activates the DMN. Further, Baliki et al. [4] suggest that spontaneous pain, in addition to pain chronicity, can disrupt brain activity by increasing mPFC function. Accordingly, the spontaneous pain in the TMD patients during MRI scanning could recruit the mPFC and trigger antinociceptive processes via the descending pathways, in addition to increases of internally focused processing to regulate the affective valence of their pain or the TMD-related emotional words. In sum, our findings, in concert with Baliki et al. [6], suggest that changes in the DMN contribute to cognitive impairments in chronic pain patients. Neither our nontraumatic TMD patients nor the back pain patients [6] had poor performance in goal-directed tasks, suggesting that a more robust interference effect (cognitive or emotional) is required to cause behavioural deficits.

Unexpectedly, our patients showed abnormal brain responses during the nStroop, a low-conflict task that usually serves as a control condition for the high-conflict cognitive interference Stroop.

The patients had deactivations in the OFC and greater deactivation in the mPFC, indicative of abnormal activity under task-free conditions. In line with the above explanation, chronic pain may result in a hyperactive mPFC under task-free conditions and therefore more task-related deactivation.

The TMD patients showed cognitive and emotional task activation in 2 regions involved in salience detection: the aMCC and the anterior insula. The aMCC is a complex region implicated in many functions, including cognitive processes (salience, attention tasks, and conflict monitoring [10,13,22–24]), pain perception, and modulation [44,77]. The anterior insula, another multimodal region, is involved in the affective dimension of pain [68], emotion [67], salience detection [27,28], magnitude estimation [5], and interoception [19], amongst other functions. The aMCC and anterior insula areas are structurally (in nonhuman primates) [58,78] and functionally connected [73] and are components of a general multimodal salience system [27,28] that responds to the perceived salience [70]. However, the relationships between these regions in the context of pain-cognition interactions are not clear.

Our findings suggest the presence of brain mechanisms related to cognitive deficits in patients suffering from nontraumatic TMD as previously found in psychometric tests [42]. Abnormal regional brain activity, as well as disrupted connectivity between brain regions that are integral to cognitive, emotional, and default-mode networks, impacts complex cognitive functions required for activities of daily living. Moreover, cognitive deficits may be meaningful from a clinical perspective and treatment efficacy. Therefore, we speculate that the efficacy of cognitive behavioural therapy in relation to the modification of abnormal brain activity and baseline neural activity of these networks might predict successful treatment.

Conflict of interest statement

The authors have no conflict of interest.

Acknowledgments

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