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Association between migraine frequency and neural response to emotional faces: An fMRI study

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ABSTRACT

Previous studies have demonstrated that migraine is associated with enhanced perception and altered cerebral processing of sensory stimuli. More recently, it has been suggested that this sensory hypersensitivity might reflect a more general enhanced response to aversive emotional stimuli. Using functional magnetic resonance imaging and emotional face stimuli (fearful, happy and sad faces), we compared whole-brain activation between 41 migraine patients without aura in interictal period and 49 healthy controls. Migraine patients showed increased neural activation to fearful faces compared to neutral faces in the right middle frontal gyrus and frontal pole relative to healthy controls. We also found that higher attack frequency in migraine patients was related to increased activation mainly in the right primary somatosensory cortex (corresponding to the face area) to fearful expressions and in the right dorsal striatal regions to happy faces. In both analyses, activation differences remained significant after controlling for anxiety and depressive symptoms. These findings indicate that enhanced response to emotional stimuli might explain the migraine trigger effect of psychosocial stressors that gradually leads to increased somatosensory response to emotional clues and thus contributes to the progression or chronification of migraine.

1. Introduction

Migraine headaches affect approximately 12% of the general population, with a lifetime incidence of 43% for females and 18% for males (Lipton et al., 2007; Stewart et al., 2008). Patients with migraine process and perceive sensory information differently than people without migraine (for a review, see Harriott and Schwedt, 2014; Schwedt et al., 2015). There is a large body of research supporting that during and between migraine attacks patients show enhanced perception and altered cerebral processing of somatosensory, visual, auditory, and olfactory stimuli. This hypersensitivity to sensory stimuli is specific to migraine and it has not been reported to the same extent in other headache or pain disorders. However, more recently, it has been proposed that migraine may be associated with a more general sensitivity to aversive/unpleasant stimuli (Wang et al., 2017; Wilcox et al., 2016). That is, patients with migraine display altered brain activation in response to negative emotional stimuli.

In support of this view, negative emotional events and emotional stress have been shown to play a significant role in precipitating or increasing migraine attacks (Andress-Rothrock et al., 2010; Kelman,

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2007). In these studies, patients with migraine reported emotional stress as the most common trigger for their headache. Nevertheless, only a limited number of studies examined whether migraine patients display alterations in their processing of emotional stimuli, and they have found inconsistent results, with some showing enhanced reaction to all kinds of emotional stimuli and others demonstrating this response to negative emotional stimuli only.

For instance, based on event-related brain potential (ERP) studies (Buodo et al., 2011; Steppacher et al., 2016), there is evidence that adults and children with migraine exhibit enhanced reaction (indexed by larger late positive potential, LPP) to both positive and negative emotional stimuli (i.e., pictures depicting emotionally evocative scenes) selected from the International Affective Picture System database (IAPS; Lang et al., 2008). In addition, Andreatta et al. (2012) demonstrated that migraine patients showed enhanced N170 amplitudes toward angry faces and larger LPP toward happy faces (compared to neutral ones) than controls. These results raise the question if migraine patients are generally more sensitive to the high emotional relevance of a situation instead of its unpleasantness. It can be assumed that the cortical hyperresponsivity to sensory stimuli frequently demonstrated in migraine patients (Aurora and Wilkinson, 2007; de Tommaso et al., 2014) might also lead to intensified perceptions of emotional stimuli.

In contrast, according to recent functional magnetic resonance imaging (fMRI) studies, migraine patients exhibited increased brain response to negative IAPS stimuli, and no differences were found between patients and controls in response to positive IAPS pictures (Wang et al., 2017; Wilcox et al., 2016). These studies demonstrated increased activation to negative pictures in regions involved in visual, emotional and pain processing (such as amygdala, posterior cingulate, caudate, thalamus, Wilcox et al., 2016; visual cortex, cerebellum, Wang et al., 2017).

However, to our knowledge, no previous studies have employed fMRI to examine the neural response to face stimuli in migraine patients. In addition, research about the effect of migraine severity indices (e.g., disease duration, attack frequency) on the processing of emotional stimuli is still lacking. Given that previous studies have found association between brain structural and functional alterations and indices of disease severity in migraine (Hubbard et al., 2014; Mathur et al., 2016; Schwedt and Dodick, 2009), it is reasonable to believe that sensitivity to emotional stimuli may differ across patients as a function of migraine severity. It seems that migraine patients show alterations mainly in pain-related brain regions and these alterations are positively associated with longer disease duration and higher headache frequency.

The present study was therefore designed to investigate the neural response to emotional faces in episodic migraine without aura patients during the interictal period using fMRI. In this study, fearful, sad and happy faces were chosen because these expressions are unequivocal signals of negative and positive emotional states. Furthermore, we also aimed at evaluating the effects of different migraine indices (duration, frequency, pain intensity and impact of migraine headaches). In light of previous studies, we expected enhanced brain response to both negative and positive expressions in participants with migraine compared to healthy controls. Specifically, we hypothesized increased blood oxygen level-dependent (BOLD) response in regions related to emotional processing and pain (e.g., amygdala, prefrontal cortex, caudate, anterior cingulate cortex, insula; Cauda et al., 2012; Fusar-Poli et al., 2009; Lindquist et al., 2012; Peyron et al., 2000; Phan et al., 2004; Wilcox et al., 2016). We further hypothesized that these functional brain alterations in patients would be associated with migraine severity indices, and not explained by anxiety and depressive symptoms. These symptoms should be taken into account because both anxiety and depression are strongly associated with migraine (Louter et al., 2015; Peres et al., 2017), and these symptoms independently predict deficits in emotion processing, particularly in recognizing facial expressions (Bourke et al., 2010; Demenescu et al., 2010; Stuhrmann et al., 2011; Surcinelli et al., 2006). That is, both anxious and depressive symptoms are related to increased reactivity to negative stimuli, and depression is also associated with reduced reactivity to positive stimuli.

2. Materials and methods

2.1. Participants

Participants were recruited via university advertisements, newspaper articles and headache clinics. Of the 124 participants initially contacted, 94 participants (42 migraine patients, 52 healthy controls) aged 20 to 37 years met the inclusion criteria and agreed to participate in the study. Of these, two healthy controls had to be excluded for technical reasons and two participants, one from each group, for movement artifacts (criteria described below) resulting in a total of 90 participants (63 females, *M* age = 26.29, *SD* = 4.53).

The final sample consisted of 41 patients with episodic migraine without aura (33 females, 20–37 years old, *M* age = 27.00, *SD* = 4.92) and 49 healthy adult volunteers (30 females, 21–37 years old, *M* age = 25.69, *SD* = 4.13), matched for age and education. Both patients and controls were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision, and no history of chronic, neurological (except migraine) or psychiatric disorder. To rule out the presence of mental disorders, participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) by senior neurologist and psychiatrist researchers.

Diagnosis of episodic migraine without aura was made by a headache specialist using the International Classification of Headache Disorders-III criteria (ICHD-III, beta version; Headache Classification Committee of the International Headache Society (IHS), 2013). No patients reported migraine attacks 48 h prior to the scan, and 24 h after the scan. They refrained from taking any analgesics 48 h before the scan session and did not take any prophylactic medicine during the last three months. Controls had no history of migraine, or other headache condition.

In accordance with the Declaration of Helsinki, written informed consent forms were obtained from all subjects prior to participation in the study, and the study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council (Hungary).

2.2. Clinical measures

Demographic data (age, sex, and educational level) and the following clinical features were collected from all migraine patients: 1) age at migraine onset; 2) number of years with migraine; 3) migraine frequency (average number of migraine per month); 4) estimated lifetime number of migraine attacks; 5) pain intensity of migraine attacks in the last 3 months (measured by a 0–10 numerical rating scale); 6) impact of migraine over the last 3 months (assessed by the Migraine Disability Assessment Scale, MIDAS; Stewart et al., 2000). A total MIDAS score was calculated for each patient by summing the number of missed days due to headache from work/school, household work, non-work (family, social, leisure) activity, and days with (at least 50%) reduced productivity over a 3-month period.

Depressive and anxiety symptoms were assessed using the trait version of State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983) and the Zung Self-Rating Depression Scale (ZSDS; Zung, 1965). Both inventories consist of 20 items scored on a 4-point Likert scale (STAI-T: 1 = *almost never* to 4 = *almost always*; ZSDS: 1 = *a little of the time* to 4 = *most of the time*) and were completed prior to the MRI scan. STAI-T and ZSDS total scores demonstrated excellent internal consistency in the present study (Cronbach's alpha = .91 and .83, respectively).

Fig. 1. Experimental paradigm (block design).
N, Neutral blocks; H, Happy blocks; S, Sad blocks; F, Fear blocks; R, Rest blocks.

2.3. Experimental task

An implicit facial expression recognition task was used to measure emotional processing (Szabó et al., 2017). In this task, participants categorized the sex of grey-scale photographs of happy, fearful, sad, and neutral faces. Stimuli consisted of six adult faces (three males and three females) taken from a standard set of pictures of facial affect (Ekman and Friesen, 1976). All faces were centred on a black background and were cropped to remove any non-facial features (e.g., hair, ears).

Faces were presented in blocks separated by three rest blocks where a white fixation cross appeared at the centre of the visual display for 20 s. Happy, fear and sad blocks (three blocks of each emotion) were presented in a pseudo-random order and interspersed with twelve neutral blocks (see Fig. 1). Each emotional block was 20 s long and comprised six faces. Faces were presented for 3000 ms (also in a pseudo-random order), followed by an interstimulus interval of 333 ms and 334 ms. The total duration of the task was 8 min.

E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, USA) was used for stimuli presentation and data collection. Participants lay in the MRI scanner and viewed the visual stimuli on a screen via a mirror which was fixed to the head coil. To ensure that participants were attending to the task, they were asked to indicate the sex of the faces using a two-button response device. Accuracy and reaction times were monitored and recorded. Subjects were familiarized with the task before scanning on a laptop computer. The practice stimuli consisted of four neutral faces.

2.4. Data acquisition

Functional MRI data were acquired with a 3 T MRI scanner (Achieva 3 T, Philips Medical System) using a BOLD-sensitive T2*-weighted echo-planar imaging sequence (repetition time [TR] = 2500 ms, echo time [TE] = 30 ms, field of view [FOV] = 240 × 240 mm) with 3 mm × 3 mm in-plane resolution and contiguous 3-mm slices providing whole-brain coverage. A series of high-resolution anatomical images were also acquired during the first functional imaging session using a T1-weighted 3D TFE sequence with 1 × 1 × 1 mm resolution.

2.5. Data analysis

Demographic, clinical and behavioural data were analysed with SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA). Independent *t*-tests were conducted to determine whether migraine patients and normal controls differed in age, anxiety and depressive symptoms, and accuracy rate and reaction times for each emotion. In addition, chi-square (χ^2) and Fisher's exact tests were performed on gender and education level. The significance threshold was set at $p < .05$. Cronbach's alpha coefficients were calculated to assess the internal consistency of all self-report measures.

2.6. fMRI analysis

Imaging data processing and analysis were conducted using the Statistical Parametric Mapping (SPM12) software package (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm12/) implemented in Matlab 2015b (Math Works, Natick, MA). Preprocessing steps included realignment, coregistration of the anatomical image to the mean functional volume, segmentation, normalization to the Montreal Neurological Institute (MNI) template, and spatial smoothing using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Data were monitored for motion outliers using the artifact detection toolbox (ART; http://www.nitrc.org/projects/artifact_detect/). Time points (volumes) in individuals' scans were identified as outliers if the global signal deviated more than three standard deviations from the mean or if scan-to-scan motion exceeded 1 mm deviation. Motion parameters and outliers were used as regressors of no interest in the individual-level analysis. Additionally, participants were excluded if > 15% of volumes were marked as outliers. As noted above, two participants were excluded due to motion artifacts.

First-level analyses were computed for three contrasts using the general linear model (GLM) in SPM12: fear-neutral, happy-neutral, sad-neutral. The resulting contrast maps were then entered into the second-level analyses. Initially, one sample *t*-tests were performed to confirm the task-related activations in the whole brain (these results are reported in the Supplementary Material). After that two-sample *t*-tests were used to explore whether neural activation differed between migraine patients and healthy controls in response to each emotion. In addition, in the patient group, separate multiple regression analyses were conducted to examine the associations between BOLD responses to emotional faces and indices of migraine severity (i.e., migraine duration, migraine frequency, estimated lifetime number of migraine attacks, pain intensity of migraine attacks, impact of migraine), with migraine indices serving as covariates. Mean beta values were extracted from each significant cluster using MarsBar (Brett et al., 2002), and correlated with severity migraine indices using SPSS (these are reported in the Supplementary Material).

Age and sex were controlled for in each of the models (except in the case of task-related activations in all participants), because previous studies demonstrated sex and age effects on migraine indices and on structural and functional brain changes in migraine patients. More specifically, the prevalence of migraine increases with age, and it peaks at the age of 30 to 39 years (Vetvik and MacGregor, 2017). The clinical characteristics of migraine also change with age, especially in females (Bolay et al., 2015). In female patients longer duration and greater intensity of migraine attacks (Bolay et al., 2015; Vetvik and MacGregor, 2017), more dysfunctional connections (Liu et al., 2011), more pronounced structural changes and increased neural responses to noxious stimuli (Maleki et al., 2012b) have been found compared to male patients. Second-level analyses were repeated to investigate whether results remain the same after including anxiety and depressive symptoms as covariates of no interest (these results are reported in the Supplementary Material).

For all fMRI analyses, an initial threshold of $p < .001$ uncorrected for multiple comparison with a cluster size of ten voxels ($k \geq 10$) was applied and results survived family-wise error correction at a cluster-level threshold of $p_{FWE} < .05$ were reported. Peak activations of the significant clusters were identified anatomically using the Automated Anatomical Labelling atlas (aal; Tzourio-Mazoyer et al., 2002). All statistical maps were visualized on the MNI 152 template brain provided in MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/).

3. Results

3.1. Participants' characteristics and behavioural results

The demographic and clinical characteristics of participants are summarized in Table 1. Age and education level were not significantly

Table 1
Demographic and clinical characteristics of migraine patients and healthy controls.

	Patients (n = 41)		Controls (n = 49)		Test statistic	p value	Effect size
	Mean (*SD*)	Range	Mean (*SD*)	Range			
Women	33 (81%)		30 (61%)		3.994	0.047*	0.209
Age	27.00 (4.92)	20–37	25.69 (4.13)	21–37	1.369	0.175	0.288
Highest education					1.458	0.497	0.125
High school	15 (37%)		24 (49%)				
Graduate degree	22 (54%)		21 (43%)				
Professional qualification	4 (9%)		4 (8%)				
STAI-T	32.76 (6.33)	24–56	33.53 (9.45)	22–72	0.878	0.382	0.096
ZSDS	33.17 (5.19)	23–43	32.69 (6.15)	24–54	0.393	0.695	0.084
Migraine laterality							
Side-locked unilateral							
Right-sided	5 (12%)						
Left-sided	8 (20%)						
Side-shifting unilateral	9 (22%)						
Bilateral	19 (46%)						
Age at migraine onset	15.15 (7.01)	3–30					
Number of years with migraine	11.76 (7.56)	1–29					
Migraine frequency per month	3.09 (2.99)	1–12					
Estimated lifetime number of migraine attacks	400.68 (517.99)	13–2016					
Pain severity of migraine attacks (last three month, 0 to 10)	5.72 (1.85)	2–9					
MIDAS score (Total)	10.81(10.84)	0–45					

Note. Data are expressed as mean ± standard deviation (*SD*) or as percentage (%). The p values are based on chi-square (χ^2) or Fisher's exact tests for categorical data and independent-sample t-test for continuous data. Cramer's V and Cohen's d coefficients were used to measure effect sizes.
STAI-T, State-Trait Anxiety Inventory–Trait scale; ZSDS, Zung Self-Rating Depression Scale; MIDAS, Migraine Disability Assessment Scale. MIDAS scores were available for 37 patients.
* $p < 0.05$.

different between migraine patients and healthy controls, but there was a significant difference in sex ratio. Females predominated in the patient group (81%), which is in line with studies reporting higher prevalence of migraine in females compared to males (Buse et al., 2013; Lipton et al., 2007). In addition, there were no significant differences between groups in anxiety and depressive symptoms. Further details concerning the migraine patients are given in Table 1.

The accuracy rate was high in the sex identification task. The mean accuracy level across all conditions was 99.19% (*SD* = 1.69). There were no significant differences between migraine patients and healthy subjects in accuracy ($t(88) = 1.352$, $p = .180$) and reaction times (neutral: $t(88) = 1.545$, $p = .126$; fear: $t(88) = 1.476$, $p = .143$; happy: $t(88) = 0.992$, $p = .324$; sad: $t(88) = 0.723$, $p = .472$).

3.2. fMRI results

3.2.1. Task-related activations

Task-related activations in all participants are reported in the Supplementary Material (see Table S1, Fig. S1).

3.2.2. Group differences in neural response to emotional faces

After controlling for sex and age, whole-brain analyses revealed that, compared to controls, migraine patients displayed significantly increased neural activation to fearful faces in one cluster. This included regions of the right middle frontal gyrus, right superior frontal gyrus, and right inferior frontal gyrus (see Table 2, Fig. 2). Importantly, when anxiety and depressive symptoms were controlled for, the cluster remained significant with activations located in the right middle frontal gyrus (see Supplementary Table S2). Brain activation during processing sad and happy facial expressions did not differ significantly between patients and controls.

3.2.3. Migraine severity and neural response to emotional faces

Associations between neural activation to emotional faces and indices of migraine severity (after controlling for sex and age) can be seen in Table 3. In the migraine patient group, migraine frequency and estimated lifetime number of migraine attacks were positively associated with two clusters of activation during processing fearful faces. There were increased activations in the right postcentral gyrus, right precentral gyrus and right inferior parietal lobule with increasing migraine frequency. Estimated lifetime number of migraine attacks were related to increased right angular gyrus and right postcentral gyrus activation. Furthermore, neural response to happy facial expressions showed significantly positive association with migraine frequency in one cluster covering areas of the right caudate nucleus and right putamen. Fig. 3 shows the significantly activated clusters. When Bonferroni correction was applied for the number of tests conducted ($p_{FWE} < .003$), the association between migraine frequency and activation to fearful faces in the right postcentral gyrus cluster remained significant. Results of the correlations between migraine severity indices and cluster beta values are reported in Supplementary Fig. S2. After controlling for anxiety and depressive symptoms, activations remained significant in the right postcentral gyrus, precentral gyrus, angular gyrus, and the right

Table 2
Brain regions showing increased activation in migraine patients, compared to healthy controls, in response to fearful faces.

Cluster Size	Cluster p (FWE)	Region	Peak Coordinates			Peak T-value
			x	y	z	
145	0.014	R Middle frontal gyrus	39	32	32	4.56
		R Superior frontal gyrus	27	59	2	4.39
		R Inferior frontal gyrus, pars triangularis	48	35	26	4.38
		R Middle frontal gyrus	45	47	11	4.34
		R Middle frontal gyrus, orbital part	39	50	-4	3.51

Note. The cluster is significant at $p_{FWE} = 0.05$, corrected for multiple comparison. Coordinates are in Montreal Neurological Institute (MNI) space.
R, right hemisphere.

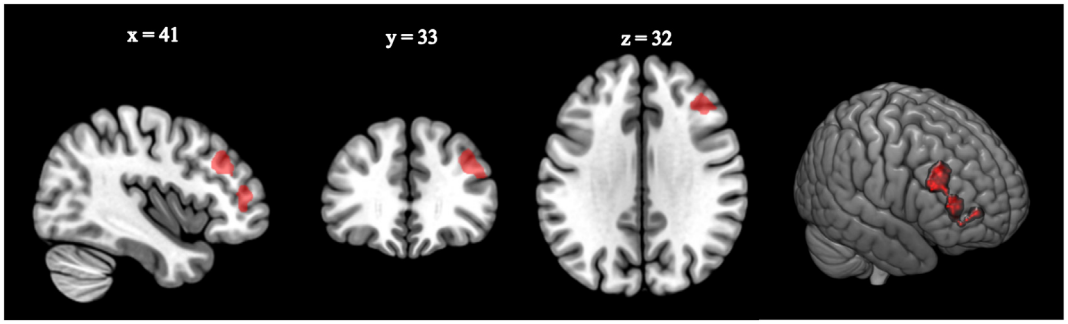

Fig. 2. Migraine patients displayed increased activation in response to fearful faces compared to healthy controls. The significant cluster is shown at $p_{FWE} = 0.05$, corrected for multiple comparison. The key areas are primarily located in the right middle frontal gyrus. Coordinates are in Montreal Neurological Institute (MNI) space.

Table 3
Associations between migraine frequency, estimated lifetime number of migraine attacks and neural response to emotional faces in migraine patients.

Cluster Size	Cluster *p* (FWE)	Region	Peak Coordinates			Peak *T*-value
			x	y	z	
Migraine frequency per month						
Fear						
276	0.000	R Postcentral gyrus	51	−16	32	5.66
		R Postcentral gyrus	57	−16	41	5.32
		R Postcentral gyrus	57	−13	29	5.24
		R Precentral gyrus	51	−1	23	4.36
		R Precentral gyrus	48	−4	29	4.35
		R Postcentral gyrus	57	−10	21	4.19
		R Postcentral gyrus	60	−13	17	3.92
59	0.043	R Postcentral gyrus	45	−25	53	4.61
		R Inferior parietal lobule	42	−37	50	4.01
Happy						
72	0.021	R Caudate nucleus	12	11	−1	4.65
		R Caudate nucleus	12	20	−4	4.32
		R Caudate nucleus	9	14	8	4.08
		R Putamen	24	5	5	3.79
		R Putamen	30	11	−1	3.48
Estimated lifetime number of migraine attacks						
Fear						
94	0.006	R Angular gyrus	42	−58	32	5.46
77	0.016	R Postcentral gyrus	45	−28	50	4.39
		R Postcentral gyrus	54	−16	44	4.21

Note. All clusters are significant at $p_{FWE} = 0.05$, corrected for multiple comparison. Coordinates are in Montreal Neurological Institute (MNI) space.
R, right hemisphere.

caudate and putamen (see Supplementary Table S3).

Other indices of migraine severity (i.e., duration, pain intensity and impact of migraine headaches) were not associated with significant brain activations (neither positively, nor negatively) in response to emotional faces.

4. Discussion

In this study, we explored the neural processing of emotional faces in migraine without aura patients (during the interictal period) using functional MRI. Our results indicated that patients with episodic migraine exhibited increased neural activation to fearful faces in the right middle frontal gyrus and frontal pole compared to healthy controls. We further observed that depending on attack frequency, both fearful and happy facial expressions were related to enhanced brain activation in migraine patients.

The main finding in the present study was the significant neural activation in the right middle frontal gyrus in migraine patients relative to controls (which remained significant even after anxiety and depressive symptoms were controlled for). This brain region has been recognized as involved in the attentional network. More specifically, the right middle fontal gyrus has been proposed to contribute to both dorsal (top-down) and ventral (bottom-up) attention networks (Corbetta et al., 2008; Fox et al., 2006; He et al., 2007; Vossel et al., 2014). Considering the high priority of fearful expressions in capturing attentional resources (e.g., Ikeda et al., 2013; Phelps et al., 2006), it can be assumed that the activation of this region might be associated with the attention being paid to fearful faces in migraine patients. Several studies have demonstrated that fearful expressions, even though their emotional content is task-irrelevant, capture attention and interfere with the relevant task (Williams, 2006). In support of this view, previous studies have found that the right middle frontal gyrus and the right inferior frontal gyrus are involved in the detection of salient, behaviourally relevant but task-irrelevant stimuli (Doricchi et al., 2010; Shulman et al., 2009; Vossel et al., 2014).

Notably, the dorsolateral prefrontal cortex (dlPFC) spans over the middle and the superior frontal gyrus, and has been found to be involved in attentional processing of emotional stimuli, and appears to have a regulatory role in emotional responses (Jacob et al., 2014; Lindquist et al., 2012; Mondino et al., 2015; Phillips et al., 2003). In our study, increased activation was found in the posterior-dorsal subregion of the dlPFC which has been implicated in cognitive control related to stimulus processing and the selection of behaviourally relevant information (Cieslik et al., 2013). It is worth noting that the dlPFC has also been found to have increased pain-related activation in patients with migraine or chronic knee pain (Hiramatsu et al., 2014; Schwedt et al., 2014). The dlPFC is implicated in pain modulation, possibly due to its involvement in cognitive and attentional processes (Peyron et al., 2000; Seminowicz and Moayedi, 2017).

Of interest, our results revealed increased activation in migraine patients for the facial expression of fear. This sensitivity might be related to the perception of potential danger (threat detection) which is prioritized automatically (Turano et al., 2017; Williams, 2006; Williams et al., 2006). However, reaction times to fearful stimuli in migraine patients were comparable to those showed by healthy controls. This suggests that, although behavioural reaction to emotional stimuli can be similar in participants with and without migraine, neurological measures implicate different processing of emotional information.

In addition, we found significant association between neural response to fearful and happy faces and migraine severity indices (which remained significant even when the potential effect of anxiety and depressive symptoms was controlled for). Migraine attack frequency and estimated lifetime number of migraine attacks were related to increased activations mainly in the right postcentral gyrus to fearful faces. This region corresponds to the primary somatosensory (S1) cortex, and it is worth mentioning that activations were found in the face area of the S1 cortex (Kuehn et al., 2017; Moulton et al., 2009). In previous

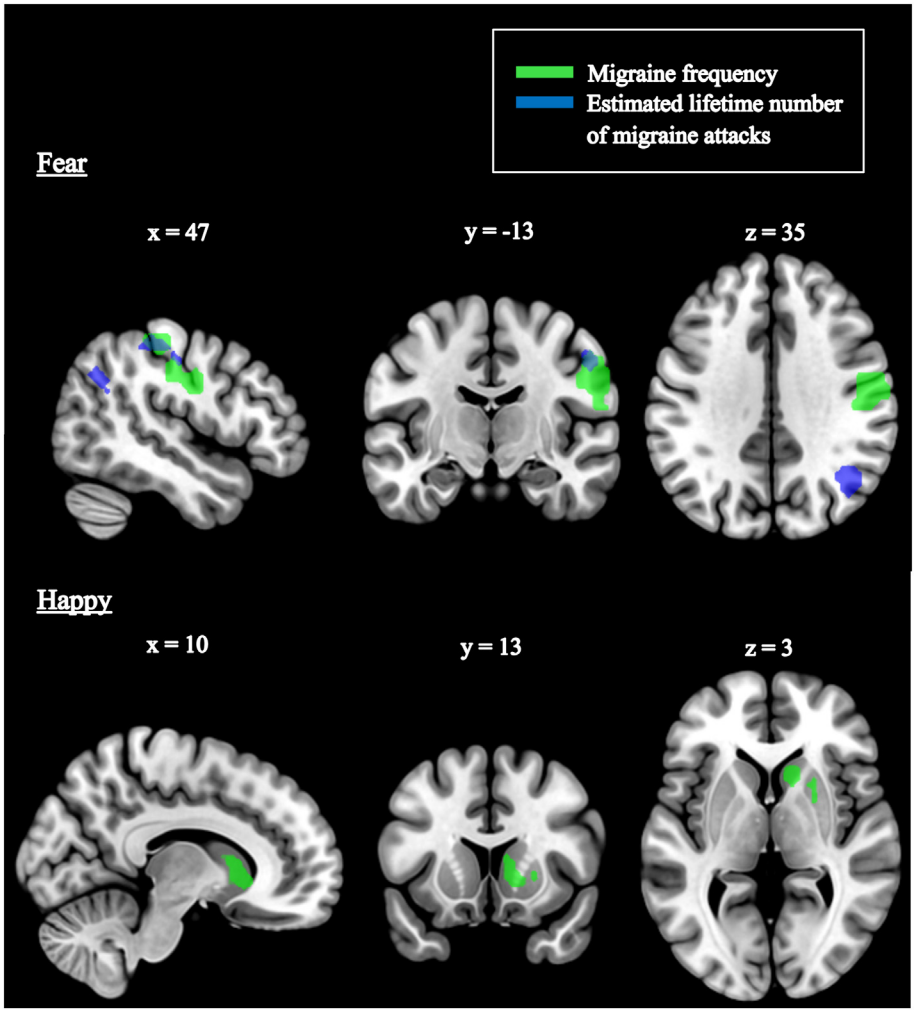

Fig. 3. During exposure to fearful faces migraine frequency was associated with increased activation in the right postcentral gyrus and right inferior parietal lobule, and estimated lifetime number of migraine attacks were related to increased right postcentral gyrus and right angular gyrus activation. Increased neural response related to happy faces showed significant association with migraine frequency in the right caudate nucleus and right putamen. Significantly activated clusters are shown at $p_{FWE} = 0.05$, corrected for multiple comparison. Coordinates are in Montreal Neurological Institute (MNI) space.

migraine studies, S1 has been associated with hyperresponsivity in the interictal state of migraine (Lang et al., 2004; Maleki et al., 2012a; Schwedt et al., 2014). Similar to our results, these studies also found that increased activation in the S1 cortex was linked to the frequency of migraine attacks. This is in line with the notion that the S1 is part of the 'pain matrix' regions and the functional/structural plasticity of the S1 cortex is closely related to pain chronification (Kim et al., 2017). Along this line, several studies have reported correlations between the extent of functional brain changes and indices of migraine severity (headache frequency or disease duration) (for a review, see Maniyar and Goadsby, 2013; Schwedt et al., 2015). This raises the possibility that migraine has a cumulative effect on brain function or the extent of underlying dysfunctions is connected to the risk of more debilitating migraine.

Finally, we provided evidence that higher attack frequency in migraine patients was associated with increased activation in dorsal striatal regions to happy faces. The processing of positive facial expressions evoked greater activation in two striatal subnuclei with increasing migraine frequency: the right putamen and the right caudate (predominantly the caudate head). The involvement of striatum in positive affect has been consistently reported in the literature. The best explored area in this field is probably the association of caudate nucleus and putamen with reward-related processing (Balleine et al., 2007; Delgado, 2007; Gerdes et al., 2010; Knutson and Cooper, 2005; Robinson et al., 2012). That is, increases in the activation of these nuclei, especially the head of the caudate nucleus, have been observed when participants are presented with rewarding and pleasant stimuli, such as social reward or monetary gain. Interestingly, these regions are frequently activated during studies of pain as well (Borsook et al., 2010). It seems that the putamen shows somatotopic activation to pain and contributes to the sensory aspects of pain-related processes (Bingel et al., 2004; Starr et al., 2011), while the caudate is part of the pain modulatory system (Freund et al., 2009, Freund et al.,2007). Notably, studies of migraine patients revealed abnormal caudate and putamen activation to painful stimuli, and altered resting state functional connectivity of the caudate with increasing migraine frequency (Maleki et al., 2011; Yuan et al., 2013).

To summarize our results, patients with migraine showed enhanced processing of fearful facial stimuli compared to controls. Wang et al. (2017) and Wilcox et al. (2016) also reported increased activation to negative pictures in migraine patients in regions involved in visual, emotional and pain processing, however, emotional processing was measured by IAPS pictures (Lang et al., 2008), and these studied did not investigate the effects of migraine severity. Our findings extend previous fMRI research by demonstrating that migraine headache frequency is associated with enhanced processing of aversive and positive emotional stimuli (fearful and happy facial expressions), with increased activation within the primary somatosensory and striatal regions. Importantly, activations occurred in the right hemisphere in migraine

patients which is generally thought to be the dominant hemisphere for processing emotions (Borod et al., 1998; Killgore and Yurgelun-Todd, 2007), and based on the patients' characteristics (they had unilateral or bilateral headache episodes) this cannot be explained by the laterality of headache pain. Finally, these neural responses to the facial stimuli were not accounted for by depression and anxiety symptoms.

5. Limitations

There are certain limitations in the present study that should be acknowledged. First, our cross-sectional design precludes the examination of changes in migraine frequency over time which can have a potential sensitisation effect. Second, although groups were matched on age and education, there were more female participants in the patient than in the control group. However, given previous findings of sex-related structural and functional differences in migraine, sex was controlled for as a covariate of no interest across the analyses. It should be also emphasized that the indices of migraine severity were based on retrospective patient reports. While prior research suggests that patient estimations of headache frequency and duration are reasonably accurate, headache intensity appears more difficult to report, possibly due to the multidimensional nature of pain (Niere and Jerak, 2004).

Regarding our emotional faces task, comparing emotional stimuli to neutral ones is a widely used method to remove simple effect of visual perception (Sabatinelli et al., 2011), and the main effects of the task were in line with those reported in former studies (Fusar-Poli et al., 2009; Lindquist et al., 2012; Phan et al., 2004). However, it should be noted that because of the format of our facial expression recognition task, the rest condition could not be used as a baseline condition. Furthermore, this experimental paradigm was not able to differentiate between specific attentional processes (i.e., attentional engagement with and disengagement from emotional stimuli), and repeated stimuli presentation might have led to attenuation in neural responses. The possible differences in levels of arousal between fearful and sad facial stimuli should be also noted. It seems that fearful and sad faces are the same in terms of valence, but fearful faces are more arousing than sad faces, which can influence attention or perception (Johnsen et al., 1995; Mather and Sutherland, 2011). Thus, it is possible that fearful faces evoked higher levels of arousal in migraine patients which resulted in the differences in neural activation. Although previous studies measuring arousal (and valence) ratings of emotional pictures did not find differences between migraine patients and healthy controls (Andreatta et al., 2012; Buodo et al., 2011; Steppacher et al., 2016; Wilcox et al., 2016), obtaining subjective ratings of face stimuli during and after the task would have provided further insight into whether migraine patients experienced increased emotions. This could be tested by using angry facial expressions as well, which are also high arousing, and represent unpleasant and threatening social stimuli (Andreatta et al., 2012). Enhanced neural activations to happy faces were also observed in relation to migraine frequency. It seems that happy faces are processed more rapidly and accurately due to their unique facial features and positive valence (Calvo and Beltrán, 2013; Calvo and Lundqvist, 2008), and they might be more salient or arousing with increasing attack frequency.

Although hypersensitivity to sensory stimuli during and between headache attacks is specific to migraine, future imaging studies focusing on tension-type headache might be useful. There are some indications that patients with tension-type headache are more sensitive to negative affective states (anger, anxiety) while patients with migraine report both positive and negative emotional states as precipitants of their migraine attacks (Donias et al., 1991), which is in line with our results. Prospective studies are also needed to examine the possible link between changes in migraine frequency and corresponding changes in neural response patterns to emotional stimuli. Given that our study focused on episodic migraine, it would be also relevant to investigate patients with chronic migraine.

6. Conclusion

Based on the present and previous findings, it seems that migraine patients show enhanced response to emotional stimuli. Emotional cues encountered in everyday life can be considered as stressors, and it is well-known that stressors are potential triggers for migraine attacks. Our results suggest that the emotionally arousing stimuli, rather than unpleasantness only, might represent a possible trigger or precipitant of migraine headaches. These findings support the idea that with increasing frequency of attacks, migraine might become a more severe disease with greater central sensitivity.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101790.

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