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Relationship between the Somatosensory Cortex Morphology, Cutaneous Allodynia, and Clinical Features of Patients with Migraine

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Abstract: Recent studies have demonstrated the presence of brain alterations in patients with migraine. Functional and vascular changes in the brain are related to the presence and severity of cutaneous allodynia. However, the association between brain structural changes and cutaneous allodynia has not been yet investigated in patients with migraine. Thus, the purpose of this study was to evaluate the correlation between the severity of cutaneous allodynia, migraine features, and the thickness and volume of the somatosensory cortex. Forty-five patients with migraine, with and without aura and chronic migraine, were included. Volunteers filled out the Allodynia Symptom Questionnaire (ASC-12/Brazil) and were evaluated via magnetic resonance imaging (MRI). The images were inspected by a blinded neuroradiologist and analyzed with Freesurfer software. Correlation tests and a linear regression model were used to evaluate the relationship among the outcomes. The somatosensory cortex thickness and volume were not different among migraine subgroups ($p > 0.05$). There was no significant correlation between the somatosensory thickness and volume with the ASC-12/Brazil, migraine frequency, intensity, migraine onset or aura frequency. The ASC-12/Brazil score variability cannot be predicted by the somatosensory cortex thickness or volume. The results show that the somatosensory cortex morphology is neither associated with cutaneous allodynia nor with migraine features among migraineurs.

Keywords: migraine disorders; cutaneous allodynia; somatosensory cortex

1. Introduction

Migraine is a primary headache present in 12% of the worldwide population. It is related to a high economic and well-being impact due to its expressive disability levels caused by pain [1,2]. Patients with 15 or more days within a month during at least three months are classified as patients with chronic migraine. Furthermore, migraine attacks may be accompanied by an aura [3]. The aura can proceed or accompany the headache attack and it is defined by reversible signs and symptoms, such as visual hallucinations, paresthesia, and dizziness, among others [4]. Previous studies relate this symptom to cortical spreading depression (CSD), which consists of a wave of electrical activity and blood flow reduction that propagates in the cortex for a few minutes [4–6].

Up to 80% of migraineurs present cutaneous allodynia [7], defined by perception of pain or discomfort of an innocuous thermic and/or mechanic stimuli applied over the skin [8]. The cutaneous allodynia is considered a risk factor for migraine chronification [9,10], and it is recognized as a central sensitization marker among these patients [8]. Central sensitization is highly prevalent in patients with chronic migraine; however, it is also often observed among patients with episodic migraine [9]. Both the presence and severity of cutaneous allodynia are positively correlated with a greater activation of the somatosensory cortex, which could be related to an altered pain representation in migraineurs [11]. Furthermore, patients with migraine present alterations in sensorimotor connectivity and abnormal somatosensory modulation [12,13]. These abnormalities could indeed be affected by the sensory discrimination features of pain and disrupt the nociceptive pathways among patients with migraine [13].

Patients with migraine may exhibit morphologic alterations in the brain, such as changes in the volume and thickness of the frontal lobe, limbic system, parietal lobe, basal ganglia, brainstem, and cerebellum [14]. The morphologic alterations of volume and thickness can be related to migraine features [14,15]. Schmitz et al., (2008) assessed migraine patients and evidenced reduced grey matter volume in the frontal cortex in contrast to controls. Patients with greater disease onset (>15 years) and higher headache frequency had lower grey and white matter volume in comparison to the ones with reduced headache frequency and onset [15]. Furthermore, patients with chronic migraine had reduced volume in the anterior cingulate cortex in contrast to episodic patients [15]. It was particularly identified in patients without aura a greater thickness of the somatosensory cortex, associated with migraine onset and frequency [16]. The association of migraine features with morphologic brain changes among patients with aura is still unclear.

Despite the uncertain association between the presence of cutaneous allodynia and a morphologic alteration of the somatosensorial cortex in patients with migraine, it is known that reduced hippocampal and midbrain volumes are associated with the presence and severity of allodynia [17,18]. An understanding of the association between morphologic brain alterations and clinical features of migraine is essential to understanding the mechanisms related to the central sensitization and chronification process of migraine. Therefore, the aim of our study was to verify the association between volume and thickness of the somatosensory cortex with the presence and severity of cutaneous allodynia, migraine onset, frequency, intensity and frequency of aura.

2. Materials and Methods

2.1. Sample

We included in the sample females aged between 18 and 55 years, with at least 3 migraine attacks within the last month. They were screened in the headache outpatient clinic of the University Hospital of the Ribeirão Preto Medical School, Brazil. The migraine diagnosis was performed by specialized neurologists, according to the International Classification of Headache Disorders, 3rd edition (ICHD) [3]. Based on the migraine diagnosis, we considered a sample of participants with migraine without aura (MoA, $n = 15$), migraine with aura (MA, $n = 15$), and chronic migraine (CM, $n = 15$). For the MA and MoA patients, we included the ones with a maximum of 12 days with a headache within a month, during the last six months. Patients with CM had to have at least 15 days with a headache over the course of a month, during the last three months.

Patients were excluded if they were diagnosed with systemic diseases, such as fibromyalgia, diabetes, rheumatoid disease or uncontrolled hypertension, concomitant headache diagnosis, obesity (body mass index > 30), pregnancy, history of claustrophobia, any general MRI contraindications (e.g., pacemakers, metallic implants), any associated neurologic or psychiatric disease, or chronic pain.

An examiner collected the demographic and headache information, including age, diagnosis, headache onset, migraine frequency, headache intensity, and frequency of aura. This project was approved by the local Ethics Committee (process num. 13068/2015) and

before their enrollment, all patients signed a written consent form, formulated according to the Helsinki Declaration.

2.2. Allodynia Symptom Checklist (ASC-12/Brazil)

All participants were assessed regarding the presence and severity of cutaneous allodynia using the Allodynia Symptom Checklist (ASC-12/Brazil) [19]. This questionnaire is comprised of 12 questions related to the discomfort level caused by thermic, static, and dynamic mechanic stimuli on daily living activities during a migraine attack. These activities include taking a shower, wearing glasses, and hair brushing, among others. The questionnaire's scores range from 0 to 24, and the presence of allodynia is verified with 3 or more points. The severity of allodynia is classified as mild (3 to 5 points), moderate (6 to 8 points), and severe (greater than 9 points) [19].

2.3. MRI Acquisition

All patients underwent brain magnetic resonance imaging (MRI). The images were acquired using an Achieva Duo 3-T scanner (Philips Medical Systems, Best, The Netherlands). The protocol included an axial turbo spin-echo T2-weighted sequence; a sagittal fluid-attenuated inversion recovery (FLAIR) images with isotropic voxel and 3D reconstruction. High-resolution 3D GE sequence T1 weighted (MPRAGE) was also performed using the following parameters: TR/TE = 2500/3.2 ms, time echo spacing 7.0 ms, inversion time 900 ms, voxel size 1 mm isotropic, flip angle = 8°, FOV = 240 × 240 × 160 mm^3, 176 sagittal slices.

During the 20 min of data acquisition, the patients were instructed to stay as still as possible. All images were inspected by a specialized neuroradiologist, blinded towards the migraine diagnosis, for detection of motion artifacts or morphologic brain alterations that would exclude the participant from the study. Volume (mm^3) and cortical thickness (mm) of the somatosensory cortex were processed and analyzed by another blinded examiner towards the study hypothesis using the recon-all routine in the 6th version of the Freesurfer software (http://surfer.nmr.mgh.harvard.edu/, accessed on 5 May 2020). The Destrieux atlas was used for cortical parcellation, since it has a good anatomical specificity by dividing the cortex into gyri and sulci with 74 regions per hemisphere [20]. A visual check of the cortical estimates was performed. Further details of the above-mentioned procedure are described in previous publications [20–23].

2.4. Statistical Analysis

A sample size of 45 participants was selected based on the number of participants considered adequate to detect a Pearson's correlation of 0.4, with 80% power and a 5% alpha level [24]. For linear regression analysis, a minimum number of 25 subjects is suggested [25]. The brain and clinical outcomes were described using average, standard deviation and 95% confidence intervals. Data of frequency were analyzed using Fisher's exact test or Chi-squared tests. The Shapiro–Wilk test was used to verify the normal distribution of data ($p > 0.05$). A two-way ANOVA was used to compare all continuous variables among the three groups. A Pearson's correlation test verified the correlation between brain outcomes ASC-12/Brazil scores, migraine frequency, intensity, onset, and frequency of aura. Furthermore, a linear regression model was applied to assess the association between the variability of ASC-12/Brazil scores and the volume or thickness of the somatosensory cortex. All tests were performed using SPSS software v.21, with a significance level of 5%.

3. Results

Initially, 47 patients were included in the study, but two were excluded due to morphologic brain alterations detected by the neuroradiologist. Therefore 45 patientswere included in the analyses. The demographic characteristics and headache features can be found in Table 1. No differences between the three groups were observed regarding age, body mass

index, headache onset, headache intensity, presence or allodynia severity, thickness, or volume of the somatosensory cortex. The frequency of migraine differed between the chronic migraine group and the remaining groups ($p = 0.04$).

Table 1. Average (SD) and distribution (%, *n*) of demographic characteristics, headache features, scores of the allodynia symptom checklist (ASC-12/Brazil), somatosensory cortex volume and thickness of the migraine groups without aura (MoA), with aura (MA) and chronic migraine (CM).

	MoA (*n* = 15)	MA (*n* = 15)	CM (*n* = 15)	*p*
Age (years)	32.73 (9.70)	32.73 (8.14)	33.06 (10.30)	0.46
BMI (kg/cm^2) [1]	24.26 (3.60)	24.55 (4.47)	23.15 (2.91)	0.64
Migraine onset (years)	15.40 (7.27)	16.20 (8.25)	14.13 (10.10)	0.46
Migraine intensity (NVS) [2]	7.53 (0.83)	7.67 (1.63)	7.67 (1.95)	0.26
Migraine frequency (days)	6.80 (2.89)	8.13 (2.95)	23.07 (5.82)	0.04
Aura frequency (days)	-	4.10 (2.54)	1.87 (4.07)	0.06
Thickness (mm)	2.51 (0.09)	2.50 (0.09)	2.49 (0.08)	0.93
Volume (mm^3)	3016.93 (370.87)	3129.26 (445.36)	2967.13 (399.74)	0.98
ASC-12/Brazil	% (*n*)	% (*n*)	% (*n*)	
Without allodynia	13.3 (2)	0 (0)	6.7 (1)	0.34
With allodynia	86.6 (13)	100 (15)	93.3 (14)	
Mild allodynia	15.4 (2)	13.3 (2)	28.6 (4)	
Moderate allodynia	46.2 (6)	33.3 (5)	28.6 (4)	0.73
Severe allodynia	38.5 (5)	53.3 (8)	42.9 (6)	

[1] BMI: body mass index, [2] NVS: numeric visual scale.

There was no significant correlation between the thickness and volume of the somatosensory cortex with migraine features, such as migraine and aura frequency, migraine intensity, and migraine onset. The brain features also do not correlate with the scores of the ASC-12/Brazil (Table 2). The linear regression model showed that the morphology of the somatosensory cortex is not able to explain the variability of the ASC-12/Brazil scores (Table 3).

Table 2. Correlation between migraine and aura frequency, headache onset, allodynia symptom checklist (ASC-12/Brazil) scores with the thickness and volume of the somatosensory cortex.

	Volume (mm^3)		Thickness (mm)	
	r [1]	95% CI [2]	r [1]	95% CI [2]
ASC-12/Brazil	0.22	−0.47 to 0.01	−0.16	−0.40 to 0.11
Migraine frequency	−0.14	−0.36 to 0.10	−0.10	−0.34 to 0.15
Migraine onset	−0.12	−0.35 to 0.11	−0.06	−0.29 to 0.20
Migraine intensity	−0.11	−0.33 to 0.12	−0.10	−0.39 to 0.19
Aura frequency	−0.02	−0.27 to 0.28	−0.20	−0.37 to 0.03

[1] r: Pearson's correlation, [2] 95% CI: 95% confidence intervals.

Table 3. Linear regression model with the scores of the allodynia symptom checklist (ASC-12/Brazil) as dependent variables and the somatosensory cortex thickness and volume as independent variables.

	B	SE B	β	*p*	R^2	Adjusted R^2
Model	-	-	-		0.08	0.04
Constant	31.58	17.40	-	0.08	-	-
Volume (mm^3)	−0.00	0.00	−0.21	0.17	-	-
Thickness (mm)	−6.61	7.23	−0.14	0.36	-	-

4. Discussion

Our study refuted the initial hypothesis that the morphology of the somatosensory cortex would be related to the presence and severity of cutaneous allodynia among patients with different migraine diagnosis. Our study found no association between the thickness and volume of the somatosensory cortex with the allodynia scores and headache clinical

features. Furthermore, no differences were verified among migraine subtypes for all assessed outcomes.

These results do not agree with previous reports that found a greater thickness of the somatosensory cortex among migraineurs, which correlated to migraine onset and frequency [16]. The authors suggest that the prolonged and repeated attacks would lead to morphologic changes in the areas related to pain processing, including the somatosensory cortex [16]. For this reason, we expected to find an association between morphologic changes and cutaneous allodynia, in addition to the evidence that patients with migraine often develop cutaneous allodynia over the years and once the pain frequency is increased [9].

Migraineurs can indeed exhibit maladaptive alterations in the somatosensory cortex, which can be compensatory or dysfunctional [13]. The cutaneous allodynia can be understood as a dysfunctional analgesic mechanism related to the abnormal representation of pain perception [11] and lowered pain thresholds during migraine attacks [26]. The increased pain perception can be explained by a hypofunction of the pain descendent inhibitory system, which modulates the nociceptive transmission, or by a facilitation of the ascendent pain system [27]. Chong et al., (2017) verified that migraineurs with severe allodynia had reduced midbrain volumes and concluded that the brainstem is related to altered sensory processing in migraine, reflecting the severity of allodynia and pain hypersensitivity [18]. It was also evidenced that migraineurs without allodynia have decreased activation of the somatosensory cortices in contrast to migraineurs without allodynia and controls, which was correlated with allodynia severity [11]. The presence of allodynia was also associated with greater brain activation of the anterior cingulate cortex and the middle frontal gyrus [11]. Future studies should further explore this association between the morphology of other brain regions and cutaneous allodynia, considering different subgroups of migraine and different types of aura.

We failed to demonstrate differences on cutaneous allodynia levels among the migraine subgroups. These results do not agree with previous studies that found a greater prevalence of cutaneous allodynia in patients with migraine with aura in contrast to the ones without aura [28,29]. The authors hypothesize that the brain hyperexcitability triggered by the aura would be related to the augmented perception of tactile, visual, and auditory stimuli. However, to the best of our knowledge, there is no evidence of greater levels of photophobia or phonophobia among the subtype of patients who experience aura [28,29].

Previous imaging studies also found morphological differences among patients with aura in contrast to the ones without aura. The presence of aura was related to reduced volume in the inferior and superior temporal gyrus, frontal and pre-central gyrus, and these changes do not correlate with clinical features [30–32]. We also did not find correlation with clinical features, and possibly due to sample homogeneity and absence of a control group, our imaging results do not corroborate with these findings. According to Hougaard et al., imaging differences may reflect general bias between patients and healthy controls [30]. Furthermore, negative findings are not often published, introducing bias into meta-analysis and research misinformation [33].

One strength of our study is the inclusion of different migraine subtypes and thus a migraine representative sample. Furthermore, all patients belong to a tertiary headache clinic and therefore were diagnosed by headache specialists. For the first time, a reliable and valid questionnaire to assess self-reported cutaneous allodynia was used [19]. However, since the ASC-12/Brazil assesses allodynia retrospectively, a recall-bias could have influenced our results. Future studies associating the use of questionnaires with thermic and mechanic quantitative measurements are recommended. In addition, psychosocial aspects such as depression, catastrophism and self-reported disability were not considered in this study, and the lack of a control group limited further comparisons. Despite these limitations, our study suggests that the presence of cutaneous allodynia is not related to morphological changes of the somatosensory cortex, headache features, or different migraine subtypes.

5. Conclusions

The volume and thickness of the somatosensory cortex are not associated with the presence and severity of cutaneous allodynia, migraine onset, pain intensity, frequency of headache and frequency of aura. Differences in the somatosensory cortex morphology or allodynia levels were not observed among different subgroups of migraine.

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