Brain structural abnormalities in migraine patients: an observational study

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Research article

Keywords: Aura, Magnetic Resonance Imaging, Migraine, No Aura, Voxel-Based Morphometry

Posted Date: February 17th, 2020

DOI: https://doi.org/10.21203/rs.2.23773/v1

Version of Record: A version of this preprint was published at The Journal of Headache and Pain on April 25th, 2020. See the published version at https://doi.org/10.1186/s10194-020-01109-2.

Abstract

Background: Migraine is a common neurological disorder, characterized by a complex physiopathology. We analyzed brain structural differences in migraine and the possible pathogenetic mechanism underlying this disease.

Methods: We assessed brain structure in migraine patients, 14 with aura (MA) and 14 migraine without aura, (MO) compared with health subjects (HS) by using (VBM) approach.

Results: Total cerebral GMV showed a significant difference between MA and HS (p=0.03), and between MO and HS (p=0.003). In addition, there was a significative difference trend between MA and MO (p=0.05) groups. We found three clusters of regions which showed significant GMV reduction in MA compared with MO. MA subjects showed a decrease of GMV in 4 clusters if compared with HS, and MO subjects showed a decrease of GMV in 3 clusters if compared with HS. We observed that MA and MO patients had a significant reduction of GMV in the frontal and temporal lobe and the cerebellum, if compared to HS. The bilateral fusiform gyrus and the cingulate gyrus were increased in MO patients compared with HS.

Conclusion: Our findings could provide a new instrumental approach to understand possible differences in the pathogenesis of 2 type of migraine.

Introduction

Magnetic resonance imaging (MRI) is an instrumental approach which provides a non-invasive observation of brain changes. Voxel-based morphometry (VBM) is an automated technique using MRI [1] to identify changes in brain anatomy. It si characterized by high regional specificity and it do no require preventively the definition of a particular region of interest (ROI) [2]. VBM is, largely used because it is relatively easy to use [3].

A recent VBM study, in which regional volumes were compared voxel-wise between patients with migraine and controls, have detected structural differences in brain tissue composition of migraine patients [4]. Migraine is a common neurological disorder, characterized by recurrent unilateral location pain associated with nausea and other neurovegetative symptoms with moderate or severe intensity, whose physiopathology is complex [5]. Up to one third of migraineurs with aura experience visual symptoms followed by motoror somatosensory symptoms during attacks [6]. Literature data reported an association between migraine and structural brain alterations [7]. The aim of this study is to applie VBM approach in migraineurs patients with aura (MA) and without aura (MO) in order to analyze their brain structural differences and to evaluate a possible pathogenetic mechanism underlying these two types of migraine.

Methods

Subjects

Twenty-eight migraine patients (14 MA and 14 MO) and 14 sex and age matched healthy subjects (HS) were recruited. The study protocol was approved by the Local Ethics Committee of IRCCS Centro Neurolesi Bonino-Pulejo of Messina (Italy) and conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants included in the study.. All patients had had a clinical diagnosis for 10 or more years according to International Headache Society criteria (Headache Classification Committee of the International Headache, 2013). Patients with 1) other types of headache; 2) vascular disease or trauma; 3) history of major psychiatric disorders; 4) the presence of metabolic disorders were excluded.

The demographic data and clinical profiles of the patients are shown in Lo Buono et al. [6]. The patients were in treatment with analgesics (18/24), triptans (4/24)and combination of analgesics (2/24). We did not find cognitive impairment in our patients. All patient underwent a MRI examination with a scanner operating at 3.0 T (Achieva, Philips Healthcare, Best, The Netherlands), by using a 32-channel SENSE head coil. We conducted the MRI protocol as reported in Lo Buono et al. [6].

Voxel-Based Morphometry Method

We used VBM approach to examining the gray matter. The VBM is based on 3 basic preprocessing steps which are followed by the statistical analysis. These steps are reported in Kurth F [25].

The local tissue morphology was maintained by performing a modulation - correction for volume changes - on segmented brain images. The latter were also levelled off with an isotropic 12mm FWHM Gaussian kernel. Afterwards, the last step consisted of estimating the global GM and WM volumes and total intracranial volume (TIV) by using segmented images in native space.

Data processing and analysis

Image data processing was performed with SPM12 (www.fil.ion.ucl.ac.uk). We considered GM tissue to calculate the GM tissue volume (GMV) and TIV in the native space. Subsequently, we used the affine registration algorithm to record all the native-space tissue segments to the standard Montreal Neurological Institute template (included in SPM12). The use of the exponentiated lie algebra toolbox (DARTEL) to all participants' GM and WM was necessary to refine the inter-subject registration via the application of the diffeomorphic anatomical registration. In the last step of DARTEL, we used a non-linear approach to modulate the GM tissues, in order to compare the relative GMV tailored to individual brain size. In addition, we performed the spatial normalization [8] to estimate the Jacobian determinant which was used to modulate the voxel values in the tissue maps. In addition, an assessment of the homogeneity of the GM tissues was needed. For this reason, we performed a quality check with a CAT12 toolbox after preprocessing pipeline. Finally, a Gaussian filter with 8mm of FWHM was used to fit each participants' modulated and normalized GM tissue segments.

Statistical analysis

The VBM analysis was carried out using the CAT12 toolbox in MatLab (www.mathworks.com). The first step consisted of performing a 2-sample t-test – with age, sex and TIV as covariates- to compare the GMV between patients and HCs. Statistical parametric maps were generated after family-wise error (FWE) correction for multiple voxel-wise comparison. Such maps were created using an initial threshold $p<0.001$ and estimated at peak statistical significance level for $p<0.05$.

Results

All participants completed the study. The total cerebral GMV showed a significant difference between MA and HS ($p=0.03$), and between MO and HS ($p=0.003$). In addition, there was a significative difference trend between MA and MO ($p=0.05$) groups. (Table 1). We corrected the analysis for multiple comparisons ($p<0.05$ family-wise error corrected), and we detected regions with significant GM changes between MA and MO groups. At $p < 0.05$, we found 3 clusters of regions which showed significant GMV reductions in MA if compared with MOand an increase of GMV in the right frontal lobe (Fig. 1 and Table 2). MA group showed a decrease of GMV in 4 clusters(right cerebellum, left postcentral and precentral gyrus, right inferior frontal gyrus, left Broadman area 20-22 and left lingual gyrus), and an increase of GMV in right superior parietal gyrus and left thalamus (Fig. 1 and Table 2) if compared to HS. Finally, MO subjects showed a decrease of GMV in 3 cluster(bilateral cerebellum, left cerebellum crus I, left superior/medial and right inferior/middle frontal gyrus, right superior frontal gyrus, left fusiform gyrus, left Broadman area 20, right parahippocampal gyrus and insula) and an increase of GMV in right thalamus (Fig. 1 and Table 2) if compared to HS.

Discussion

MRI plays an important role in the identification of migraine cerebral networks. Several fMRI studies revealed abnormalities of resting state functional connectivity in pain network involved in the migraine pathophysiology [6, 9, 10]. Migraine patients showed significant GM abnormalities of several brain regions involved in central pain processing [11–12]. In particular, VBM data established that the GMV was decreased in the anterior cingulate cortex, insula, amygdala, parietal operculum, middle and inferior frontal gyrus [13]. In addition, regions with reduced grey matter density are located in bilateral insula, motor premotor, prefrontal, cingulate cortex, right posterior parietal cortex and orbitofrontal cortex [14].

In this study, we applied the VBM approach to MA and MO patients and HS. We observed that MA and MO subjects had a significant reduction of GMV compared to HS in cerebellum, and frontal and temporal lobe. Our previous study [6] analyzed the resting state findings in the same patient simple and we found an increased hyperactivity in bilateral fusiform and cingulate gyrus of MO subjects compared with controls. In this study, the VBM approach showed a decrease in the volumes of same cerebral areas. Although the volume of bilateral fusiform and cingulate gyrus is descreased, the increase of their hyperactivity could be ascribed to the fact that the fusiform gyrus seems to be hyperactive in migraineurs, in ligh of its involvment in the treatment of cognitive pain, while the cingulate gyrus is involved in the process of transformation of migraine from “an episodic” to “a chronic brain disorder” [26].

In addition, the cerebellum of migraineurs and controls differs structurally. In a study of Mehnert [15] the GMV and the neuronal activity in response to trigeminal pain were increased in posterior part of the cerebellum (crus). Migraine patients had also a decreased connectivity in the thalamus and higher cortical areas, suggesting a decreased inhibitory involvement of migraine cerebellum on trigeminal nociception. The frontal cortex is an area associated with cerebral abnormalities in migraine patients [16–17]. Previous studies have suggested that the medial prefrontal cortex could be involved in mediating the attenuation of pain perception by a cognitive control mechanisms [18–19], which is associated with pain modulation [20–21]. Schmitz et al. [22] reported that migraine patients had decreased gray matter density in the medial prefrontal cortex which correlated significantly with a slower response time to the set-shifting task.

In coherence with previous VBM findings, in migraine patients [11–12, 17], our results corroborate with the study of Kim et al. [4], that found a decrease of volume of insula bilaterally, motor/premotor, prefrontal and cingulate cortex, right posterior parietal cortex, and orbitofrontal cortex. Moreover, Jin et al. [9] showed a decreased GMV in several brain regions involved in pain processing, such as left medial prefrontal cortex, cingulate, right occipital lobe, cerebellum, and brainstem. From the results obtained we can affirm that patients with migraine have a decreased GMV in the precentral gyrus as well as in the post-central gyrus and temporal lobe.

The possible mechanisms underlying the reduction of grey matter in migraine are currently unknown. The observed decrease in grey matter may reflect tissue shrinkage (changes in extracellular space and microvascular volume) as well as more complex processes such as neurodegeneration. Therefore, there are several possible explanations for the observed abnormalities in our patients. Variations in gray matter may result from repeated ischaemia caused by blood flow to the brain abnormalities observed both during migraine attacks and in the interictal phase. In contrast, the reduction of gray matter may be a consequence of migraine specific neurotoxic mechanisms. It has been hypothesized that migraine is associated with a state of neuronal hyperexcitability, involving over-activity of the amino acid exciters glutamate and aspartate. VBM analysis has shown that migraineurs present a significant reduction in the gray matter of different brain areas belonging to the pain activation network [6].

Conclusion

The VBM approach is an important and useful tool to assess brain structural changes in neurological disorders, such as migraine. The different results reported by aforementioned studies could be attributed, in part, to the use of different MRI scanners (3T vs. 1.5T) [23–24]. In fact, different scanners may led to the different approaches for segmentation of GM and to detect structural abnormalities of a different type. In addition, migraine is a heterogeneous disorder, whereby it is difficult to obtain a phenotypically homogeneous group.

Although we investigated a small sample of patients, our results could provide a new instrumental approach useful to understand the pathogenesis of MA and MO migraine.

Declarations

Ethics approval and consent to participate

Participants provided written informed consent. The study protocol was approved by the Local Ethics Committee according to Declaration of Helsinki.

Consent for publication

Partecipant have give the consent for to be published in the journal of headache and pain.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the Local Ethics Committee but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

Not applicable

Authors' contributions

LB: a substantial contribution to the concept and design of the work; analysis and interpretation of data; drafted the article. VLB: acquisition and interpretation of data and drafted the article. FC: acquisition and interpretation and revised it critically for important intellectual content. EP: acquisition of data. CR: acquisition of data. VT: acquisition of data. PB: revised it critically for important intellectual content. SM: revised it critically for important intellectual content and approved the version to the published.

Acknowledgments

None

Abbreviations

MA
migraine with aura
MO
migraine without aura
HS
health subjects
MRI

Magnetic Resonance Imaging
GMV
gray matter volume
NBV
normalized brain volume
ROI
region of interest
TIV
intracranial volume
FEW
family-wise error

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Tables

Table 1. Grey matter volume (GMV) results in MA and MO groups.

	MA	MO	P-value (T-Student)
GM	814.73±29.10	793.83±47.10	0.05
HS-GM	850.98±46.11	850.98±46.11	-
P-value (T-Student)	0.03	0.003	

Legend: MA= Migraine with Aura; MO= Migraine without Aura; HS= Heath Subjects; GM=Gray Matter.

Table 2. Regions of significant decrease or increase in grey matter volume in migraine patients compared with controls.

	Location	Coordinates (mm)			Peak Z	Corrected p
		x	y	z		
MA vs MO	L Inferior Temporal	-52	-34	-27	-3.76	0.04
	R Frontal lobe	33	18	40	3.83	0.04
	R Cerebellum	16	-82	-20	-3.51	0.04
MA vs HS	R Cerebellum	2	-64	-57	-5.14	0.01
	L Postcentral gyrus	-26	30	74	-4.87	0.03
	R inferior frontal gyrus	39	34	9	-3.51	0.01
	L Brodmann area 22	-58	8	-2	-4.30	0.04
	L lingual gyrus	-15	-46	-4	-3.52	0.03
	R superior parietal gyrus	15	-45	63	4.12	0.02
	L Thalamus	-14	-15	10	3.67	0.01
MO vs HS	Cerebellum	9	-60	-54	-7.03	0.03
	L Cerebellum crus 1	-45	-64	-24	-4.27	0.02
	L superior/medial frontal gyrus	-10	38	39	-4.54	0.004
	R Inferior/middle frontal gyrus	40	30	-6	-4.74	0.01
	R superior frontal gyrus	32	57	26	-4.29	0.001
	L fusiform gyrus	-22	-62	-15	-4.31	0.001
	L Brodmann area 20	-34	-20	-33	-5.25	0.02
	R parahippocampal gyrus	24	-52	-3	-5.14	0.04
	R Insula	40	30	-6	-4.74	0.03
	R Thalamus	15	-18	3	4.33	0.04

Legend: MA= Migraine with Aura; MO= Migraine without Aura; HS= Heath Subjects; R=Right; L= Left; BA= Brodmann’s area.

Figures

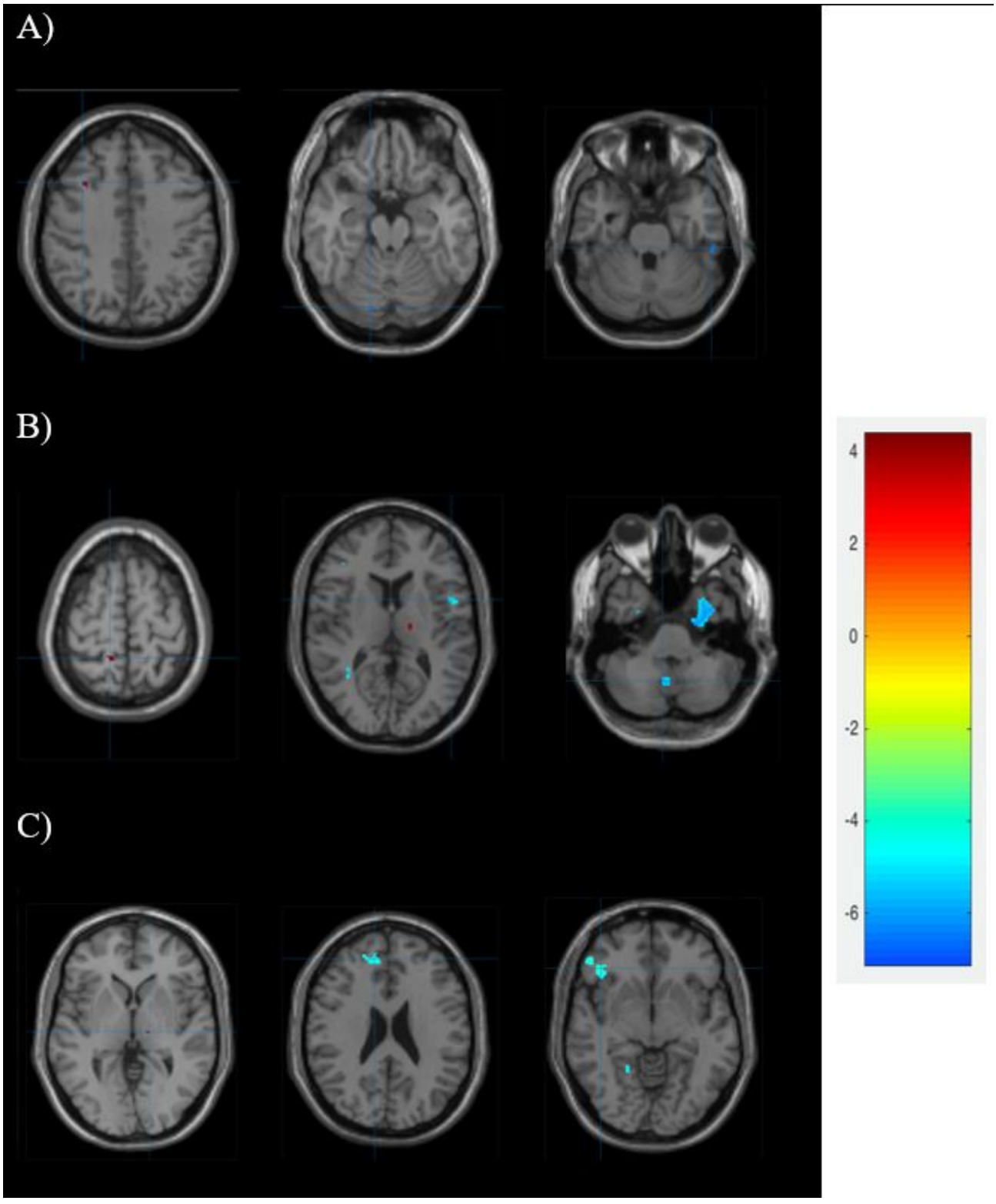

Figure 1

Gray matter volume (GMV) changes. A) GMV of migraine with aura compared with migraine without aura. B) GMV of migraine with aura compared with health control. C) GMV of migraine without aura compared with health control. Statistical parametric maps show gray matter volume alterations with a threshold of $P < 0.001$ uncorrected superimposed on a standard T1 image. The color bar reflects t values (red/yellow = increased volume, blue = decreased volume).