Original Article
A meta-analysis of voxel-based morphometric studies on migraine

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Abstract: Purpose: To identify consistent results of voxel-based morphometry (VBM) studies in migraine. Methods: Whole-brain VBM studies comparing migraine patients with healthy controls (HC) were systematically searched in PubMed, ISI Web of Science, Embase, and Medline databases from January 1990 to Dec 2014. Coordinates were extracted from clusters with significant difference in gray matter volume (GMV) between migraine patients with healthy controls (HC). Meta-analysis was performed using activation likelihood estimation (ALE). Results: A total of 5 studies, comprising 126 migraineurs, including 23 migraine with aura, 41migraine without aura, 11 epidemic migraine and 16 chronic migraine as well as 19 Mm and 16 nmM, and 134 HC, were enrolled. The included studies report GMV reduction at 84 coordinates in migraine, as well as GMV increase at 2 coordinate in migraine. However, due to only two included studies have classified patients into these two phenotypes and one stated they included only migraine with aura patients , we were not able to perform a subgroup analysis and separate meta-analyses on each phenotype. Conclusion: There were significant reductions in Middle frontal cortex (BA6, 9) structures and the Inferior frontal cortex (BA44) in migraine. These changes of GMV may indicate the mechanisms of the associated symptoms such as cognitive dysfunction, emotion problems and autonomic dysfunction. But whether this is the characteristics of the subtypes of migraine or can distinguish the types of migraine or primary headache, further studies examining larger samples may better elucidate the changes related to the illness and highlight its pathological mechanism.

Keywords: Migraine, voxel-based morphometry (VBM), voxel, voxel-wise, voxel-based or morphometry, meta-analysis

Introduction

Migraine is a form of episodic primary neurovascular headache that is probably based fundamentally on dysfunction in the brain [1]. Migraine headaches cause significant individual and societal burden due to pain, environmental sensitivities, resulting disability, and lost productivity. Migraine costs much directly and indirectly and results in substantial pain, disability, and a decreased overall quality of life [2-6]. A better understanding of migraine mechanisms will lead to improved treatments and a reduction in the negative impact of migraine [7-10].

Advances in our understanding of the neurobiology of migraine have provided considerable insights into the problem. Neuroimaging has led to advances in the description of migraine mechanisms and to the identification of secondary structural and functional effects of migraine [11]. However, due to the episodic and generally unpredictable nature of individual migraine attacks, imaging during spontaneous migraine has proven difficult [12, 13]. New imaging techniques may have potential to identify mechanisms responsible for the transformation from infrequent to frequent headache patterns, and thus, lead to novel diagnostic and therapeutic interventions that will help to improve the lives of millions of patients with migraine [14]. Voxel-based morphometry (VBM) is a newer technique that aims to detect consistent structural differences between groups of subjects that can be related to functional correlates and thus further understanding of disease pathophysiology in the brains of patients with migraine and non-migraine controls [7, 9, 12]. In the past decade, VBM has been widely used in many types of cephalalgia, such as cluster headache [15], chronic tension type

headache [16], hypnic headache [17]. Moreover, in recent years, VBM also has been conducted in migraine. However, the results about these studies were full of contradictions. An initial VBM study of migraine found no differences in global or regional grey or white matter between patients and controls [18], but more recent studies have found differences. A separate VBM study confirmed that patients with migraine had decreased grey matter in the anterior cingulate cortex, insula, amygdala, parietal operculum, and middle and inferior frontal gyrus [19]. JH Kim and colleagues found those had regions of reduced grey matter density in the bilateral insula, motor premotor, prefrontal, cingulate cortex, as well as right posterior parietal cortex and orbitofrontal cortex [20], and increased density of the PAG and the dorsolateral pons [21].

Therefore, the present work aims to systematically and voxel wisely meta-analyze the GM changes in patients with migraine. We used Activation likelihood estimation (ALE) to do this analysis, which is a powerful voxel-based meta-analytic technique originally designed for functional neuroimaging studies [22, 23], and has been effectively applied in a number of disorders, such as idiopathic [21] Parkinson's disease [24], amyotrophic lateral sclerosis [25], and obsessive-compulsive disorder [26-28], Neuromyelitis Optica Patients [29]. Though finding the core regions of structural changes, our work may be helpful in obtaining insights for further understanding of the pathophysiology underlying migraine [7-9, 30].

Materials and methods

Data source

A systematic search of the Medline database (from January 1990 to Dec 2014), PubMed, ISI Web of Science and Embase was conducted. The key words used were ("Migraine"; "Migraine with aura"; "Migraine without aura"; "Magnetic resonance imaging (MRI)"; "Voxel-based morphometry (VBM)"; "Meta-analysis"; "Activation likelihood estimation (ALE)"; " voxel"; "voxel-wise"; "voxel-based" or "morphometry"). The references of the relevant articles were also searched for additional studies.

Selection of studies and extraction of data

A study was considered for inclusion: If it (1) reported a VBM (GMV or gray matter concentra-

tion) comparison between adult patients with migraine and healthy control (HC) subjects; (2) reported whole-brain results of changes in stereotactic coordinates; (3) used thresholds for significance corrected for multiple comparisons or uncorrected with special extent thresholds; (4) involved patients divided into migraine with aura and migraine without aura or episodic migraine and chronic migraine according to the Second Edition of International Classification of Headache Disorders (ICHD-III) [31]; (5) involved patients without intracranial surgery; (6) published in English with peer review. To avoid repetitive data, the study with the most complete description of data was recruited when the same name of author, similar characteristics of participants and data appeared in two or more publications. In cases where similar studies met the aforementioned inclusion criteria but had overlapping data with one author, the study with the largest sample size was selected.

A study was excluded: If (1) data were not sufficient even after contact with the authors by phone or e-mail; (2) fewer than seven subjects in any group were studied; (3) data overlapped with those of another article; (4) some results were uncorrected and the special extent threshold was not reported; (5) there was no HC group; (6) patients with other kinds of headache, such as cluster or hypnic headache, were involved. The method used in the current study was according to the Meta-analysis of observational studies in Migraine guidelines for meta-analyses of observational studies.

The coordinates in each study were independently extracted by neurologists (namely, Wenting Hu and Jian Guo) according to the ALE method [32-34].

Voxel-based meta-analysis

Voxel-based meta-analysis was performed on the selected studies using the ALE software (Ginger ALE 2.3.2, http://www.brainmap.org/) in a standard process to compare the VBM changes between the migraine group and the HC group. The listed coordinates in the Montreal Neurological Institute (MNI) space in those studies were transformed into Talairach space using icbm2tal [35] as implemented in Ginger ALE2.3.2. The listed coordinates in Talairach space in those studies were back-transformed

Table 1. Demographic and clinical characteristics of VBM studies on migraine in the meta-analysis

Study	Total migraine		HC					Disease	Mean frequency of migraine	Mean duration of migraine	Estimated
	Number (Male)	Age (years) (mean ± SD)	Number (Male)	Age (years) (mean ± SD)	Sub group	Number (Male)	Age (years) (mean ± SD)	Duration (year)	Attacks per year	Attacks (h)	Lifetime frequency
JH Kim et al. [20] (2008)	20 (3)	33.7 ± 11.3	33 (4)	33.8 ± 10.5	MA	5 (2)	NA	9.8 ± 6.0	32.7 ± 10.9	21.8 ± 13.1	347.1 ± 257.7
					MO	15 (1)	NA	NA	NA	NA	NA
Maria et al. [21] (2006)	16 (1)	42.7	15 (2)	38.6	MA	7 (1)	42.7	20.6±8.9	20.3	NA	NA
					MO	9 (1)	NA	NA	NA	NA	NA
Matharu et al. [18] (2003)	28 (2)	31	28 (2)	NA	MA	11 (1)	31	NA	NA	NA	NA
					MO	17 (1)	34	NA	NA	NA	NA
Walter et al. [19] (2007)	27 (6)	34.9 ± 8.4	27 (6)	34.9 ± 8.6	Episodic	11 (2)	32.1 ± 8.7	20.6 ± 8.9	NA	27.3 ± 15.5	141.6 ± 116.4
					Chronic	16 (4)	38.9 ± 6.4	NA	NA	NA	NA
Schmidt et al. [37] (2008)	32 (0)	32.4 ± 9.2	31 (0)	32.3 ± 12.6	mM	19 (0)	NA	NA	NA	NA	NA
					nmM	16 (0)	NA	NA	NA	NA	NA

Key: HC: healthy control. MA: migraine with aura; MO: migraine without aura; NA: not available; SD: standard deviation; VBM: voxel-based morphometry. Mm: menstrual migraine; nmM: not menstrual migraine.

Table 2. Technique details of VBM studies on migraine in the meta-analysis

Study	MRI scanner	Software	Smoothing (FWHM)	*P*-Value	Foci number	Greater GMV	Smaller GMV
JH Kim et al. (2008)	1.5 T	NA	NA	NA	19		Y
Maria et al. (2006)	3 T	SPM2	12 mm	P < 0.001 (uncorrected)	40	Y	Y
Matharu et al. (2003)	2.0 T	SPM99	10 mm	P < 0.005 (uncorrected)	0		
Walter et al. (2007)	1.5 T	SPM2	12 mm	NA	21	Y	Y
Schmidt et al. (2008)	1.5 T	SPM2	12 mm	P < 0.05	4		Y

Key: FDR: false discovery rate; FEW: family-wise error; FWHM: full width at half-maximum; MRI: magnetic resonance imaging; NA: not available; SPM: statistical parametric mapping; T: tesla; VBM: voxel-based morphometry.

to MNI space using tal2mni as implemented in Ginger ALE 2.3.2, and then retransformed into Talairach space using tal2mni as implemented in Ginger ALE 2.3.2, and then retransformed into Talairach space using icbm2tal.

The full width half maximum (FWHM) was set in accordance with a quantitative uncertainty model as described in an article []. The ALE values were permuted 5000 times to determine their significance while minimizing distributional assumptions. The statistical threshold was set by a false discovery rate (FDR) value of $P <$ 0.05 and by clusters of supra threshold voxels exceeding 100 mm³·

Results

A total of 24 VBM studies on migraine was selected, among which 5 studies [18-21, 37] met the inclusion criteria for meta-analysis (**Table 1**). Excluding an article without reporting whole-brain results of changes in a stereotactic space in three-dimensional coordinates (X, Y, Z) [38] and one reporting no change in the structure of the brain in migraine [18], a total of 4 VBM studies on migraine was selected, among which 4 studies [19-21, 37] met the inclusion criteria for meta-analysis (**Table 1**). In 4 studies [19-21, 37], migraine is lateralized according to the medical history, symptoms, and neuroimaging examinations and the Second Edition of International Classification of Headache Disorders (ICHD-III) [31]. No additional articles were found in the reference lists of the selected studies.

Finally, these studies compared the whole-brain GMV differences of 127 migraine patients including 23 migraine with aura, 41 migraine without aura, 11 episodic migraine, 16 chronic migraine, 19 menstrual migraine, 16 not menstrual migraine and 134 HCs. Some information about age and gender were not available (**Table 1**). Hence, statistical analyses in terms of age and gender between groups were not performed. However, in each individual study, no difference in age or gender between patients and HC was found. The main characteristics of the included populations were presented in **Table 1**.

Only GMV reduction was found in the patients in 2 studies [20, 37], whereas both GMV increased and reduction were found in the remaining 2 studies [19, 21]. The identified articles included 84 foci GM abnormalities among which 2 corresponded to a greater GMV and 82 corresponded to a smaller GMV in PFD patients compared with HC. The technical details of the included studies are shown in **Table 2**. Group analyses were performed between the migraine with or without aura group and HC subjects, respectively. The group analysis of GMV increase was not successfully performed because only two studies reported GMV increase and there were few coordinates reported. As shown in **Table 3** and **Figure 1**.

We found no increase of GMV in migraine patients in our study. The reduction of GMV has been validated in ALE and JACKKNIFE sensitivity analysis, and that is independent of age and disease duration.

Nine clusters were identified in the ALE analysis under FDR < 0.05 and voxels > 100. As illustrated in **Figure 1** and **Table 3**, smaller GMV in the middle frontal cortex (BA6, 9), inferior frontal cortex (BA44), pre-central cortex (BA44), sub-lobar insula (BA13), sub-gyral temporal cortex (BA20), temporal cortex (BA20), whereas, no greater GMV were identified in patients with PFD compared to healthy controls.

Table 3. Regional difference of GMV between Migraine patients and HC

Cluster NO	Cluster volume (mm³)	X	Y	Z	ALE value (x10⁻³)	Location			
						Hemi-sphere	Lobe/sub-lobe	Gyrus/nucleus	Broadman Area
1	1112	-57.97	11.84	12.7	25.455	L	Frontal	Inferior frontal	44
2	768	60.28	13.32	10.33	14.761	R	Frontal	Inferior frontal	44
					8.759	R	Frontal	Pre-central	44
3	744	-24.5	16.96	52.38	16.251	L	Frontal	Middle frontal	6
4	728	42.13	-15.43	0.15	16.281	R	Sub-lobar	Insula	13
5	400	44.75	-9.12	-11.27	12.564	R	Temporal	Sub-Gyral	21
6	336	-55.71	-14.79	-33.03	12.413	L	Temporal	Inferior temporal	20
7	144	25.44	10.03	54.13	9.589	R	Frontal	Middle frontal	6
8	136	-4.26	41.64	18.8	9.749	L	Frontal	Middle frontal	9
9	128	41	28.25	30.26	8.917	R	Frontal	Middle frontal	9

Key: L: left; R: right; ALE: activation likelihood estimation; GMV: gray matter volume; HC: healthy control.

Discussion

To the best of our knowledge, this is the first study to pool VBM studies for meta-analysis of brain structural differences between migraine and healthy subjects. The present voxel-based meta-analysis using ALE mainly found patients with migraine to have consistent structural changes of smaller GMV in the Middle frontal cortex (BA6, 9), Inferior frontal cortex (BA44), Pre-central cortex (BA44), sub-lobar insula cortex (BA13), Sub-Gyral cortex, temporal cortex (BA20), temporal cortex (BA21). These results were in line with the findings of other positron emission tomography (PET) [39, 40], Magnetic Resonance Imaging (MRI) [41, 42], and VBM study (not included in this meta-analysis due to involved mixed patients group of migraine with and without aura). In the current analysis , Middle frontal cortex (BA6, 9) was found in both migraine with and without aura patients, in accordance with a study that used MRI and regions of interest (ROI) [41]. Therefore, further studies are needed to elucidate the issue. Interestingly, **Table 2** and **Figure 1** show wider GMV reduction in the migraine with aura than in the migraine without aura. This finding was supported by the results of other studies.

The current meta-analysis utilizes the latest version of the ALE software, which has been successfully used in some coordinate based meta-analyses on imaging data [43-45], to identify the consistent regional changes among studies. This modified software overcomes several drawbacks of the original implementation, such as the need to manually set the FWHM value as well as the anatomical uniformed anal-

ysis space and its fixed effects inference. Consequently, the specificity of the ensuring results is increased without losing the sensitivity of the original approach [36].

However, due to that the included studies did not further classify the patients into migraine with aura and migraine without aura groups, except 3 have classified patients into these two phenotypes [18, 20, 21] and 2 stated they included only episodic migraine an chronic migraine [19], and the other included only menstrual migraine and not menstrual migraine [37], we were not able to perform separate meta-analyses on each phenotype. Taken together, the current results suggest that the VBM approach can be a useful method in estimating GM abnormalities in migraine.

In our analysis, we find no definite changes in the reported reduction of GMV in pre-central gyrus [20], left amygdalae, Left Parietal Operculum [19], cingulate cortex [21]. Using VBM, JH Kim et al found that migraine patients had significant GMV reductions in the bilateral insula, motor/premotor, prefrontal, cingulate cortex, right posterior parietal cortex, and orbitofrontal cortex. The regions reported here were then recognized as being involved in general pain processing or the response to pain [46-48]. Moreover, such GM changes have also been demonstrated in other forms of chronic pain disorders, including back pain [49, 50] tension-type headache [51] and phantom limb pain [52]. We didn't find the same changes as reported in other studies. Even we set the minimum concentration value of 100 mm³, rather
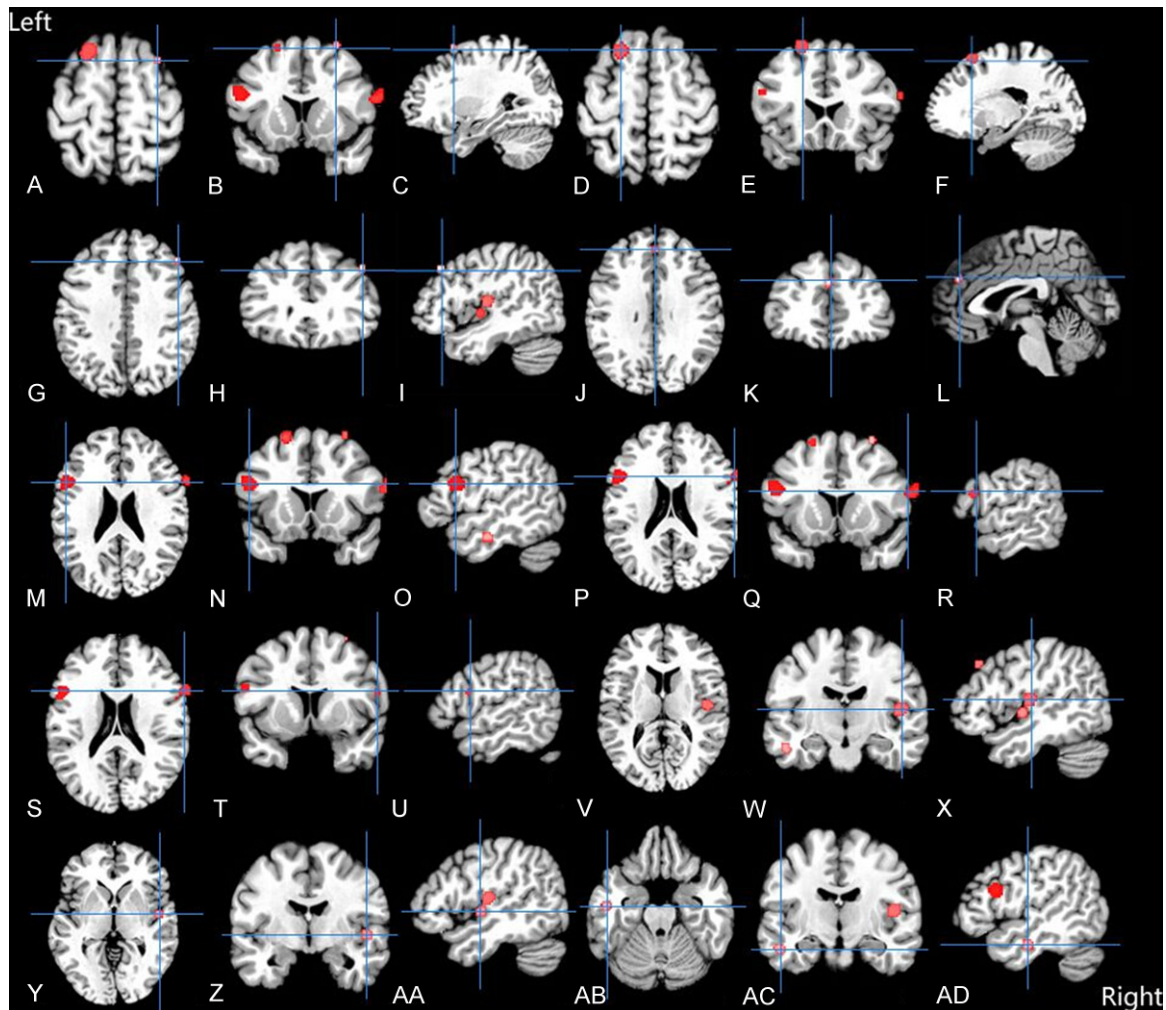
Figure 1. ALE map investigating differences in GMV between Migraine patients and HC. Key: Significant clusters were overlain onto an MRIcron template for Windows for display purposes only. GMV: gray matter volume; HC: healthy control.

than 200 mm³, it is still difficult to find a greater concentration of related brain regions.

However, up to date, the precise mechanism of the reduction of GMV and different intracranial damages in the migraine remain unclear. A few studies have shown that the brain damages maybe related to age, whereas our systematic review also did not find this correlation. A case report showed functional MRI abnormalities in brain stem regions in a subject with migraine with aura. As shown in **Table 3** and **Figure 1**, the reduction of GMV are susceptible to be in the right brain than the left, and it is supported by some studies.

Because of the deficiency of the included studies, we could not make the regression analysis

to evaluate the effects of the drugs on gray matter changes. The notion that structural abnormalities of specific CNS regions might contribute to characterizing the different headache conditions, differentiate their clinical manifestations and guide therapeutic interventions has been postulated by several authors [6, 22, 23]. We are not clear that these changes of gray mater are specific for migraine and that if it can differentiate the subtypes of migraine including migraine with aura, migraine without aura, chronic tension type headache etc. In addition, we cannot predict the development of migraine. Therefore, it needs more profound and longitudinal on a group of homogeneous patients should be conducted in the future to confirm these findings.

Nevertheless, in the present study, there were several limitations that could have affected the accuracy of the results. Firstly, the meta-analysis is subject to publication bias because unpublished international studies were not included and the studies were limited to those published in English, and the number of included studies was small. Second, the heterogeneity of the methodologies in the VBM studies, such as the different preprocessing protocols (traditional or optimized), smoothing kernels, and statistical thresholding methods, could not be entirely ruled out. Third, the voxel-wise meta-analysis was based on the pooling stereotactic coordinates with significant difference, rather than on raw data from the included studies, which may have led to less accurate results. Fourth, although this new version of the ALE accommodates the sample size of each includes study, it fails to take into account the different statistical parameters of each cluster (e.g., z scores and cluster size) in each study. Fifth, clinical variables, such as symptom dimensions, medication status and co-morbidity status, were not considered in this analysis. Sixth, a correlation analysis between GMV reduction and disease duration failed because the relative data were not available in some studies. Seventh and last, the analysis of GMV increase in migraine patients was not successfully performed because only two studies detected it. However, the fact that almost all of the studies contributed to the results argues in favor of the robustness of our findings despite the clinical heterogeneity of the study populations.

Conclusion

Whole-brain VBM studies identified consistent widespread GMV reduction in migraine, specifically in the Middle frontal cortex (BA6, 9), Inferior frontal cortex (BA44). These changes of GMV may indicate the mechanisms of the associated symptoms such as cognitive dysfunction, emotion problems and autonomic dysfunction. But whether this is the characteristics of the subtypes of migraine or can distinguish the types of migraine or primary headache, further studies examining larger samples may better elucidate the changes related to the illness and highlight its pathological mechanism.

Disclosure of conflict of interest

None.

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References

[1] Aurora SK, Welch KM. Migraine: imaging the aura. Curr Opin Neurol 2000; 13: 273-6.

[2] Manzoni GC, Stovner LJ. Epidemiology of headache. Handb Clin Neurol 2010; 97: 3-22.

[3] Brundtland GH. From the World Health Organization. Mental health: new understanding, new hope. JAMA 2001; 286: 2391.

[4] Schurks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: a systematic review and meta-analysis. Cephalalgia 2011; 31: 1301-14.

[5] Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007.

[6] Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache 2013; 53: 427-36.

[7] Cutrer FM, O'Donnell A, Sanchez del Rio M. Functional neuroimaging: enhanced understanding of migraine pathophysiology. Neurology 2000; 55 Suppl 2: S36-45.

[8] Shibata K. [Neurophysiology of visual aura in migraine]. Brain Nerve 2007; 59: 961-70.

[9] Cutrer FM. Pathophysiology of migraine. Semin Neurol 2006; 26: 171-80.

[10] Lovell BV, Marmura MJ. New therapeutic developments in chronic migraine. Curr Opin Neurol 2010; 23: 254-8.

[11] Cohen AS, Goadsby PJ. Functional neuroimaging of primary headache disorders. Expert Rev Neurother 2006; 6: 1159-1171.

[12] Borsook D, Hargreaves R. Brain imaging in migraine research. Headache 2010; 50: 1523-7.

[13] Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. Headache 1996; 36: 616-21.

[14] De Vries P, Villalón CM, Saxena PR. Pharmacological aspects of experimental headache models in relation to acute antimigraine therapy. Eur J Pharmacol 1999; 375: 61-74.

[15] Absinta M, Rocca MA, Colombo B, Falini A, Comi G, Filippi M. Selective decreased grey matter volume of the pain-matrix network in cluster headache. Cephalalgia 2012; 32: 109-115.

[16] May A. Morphing voxels: the hype around structural imaging of headache patients. Brain 2009; 132: 1419-1425.

[17] Holle D, Naegel S, Krebs S, Gaul C, Gizewski E, Diener HC, Hypothalamic gray matter volume loss in hypnic headache. Ann Neurol 2011; 69: 533-9.

[18] Matharu MS, Good CD, May A, Bahra A, Goadsby PJ. No change in the structure of the brain in migraine: a voxel-based morphometric study. Eur J Neurol 2003; 10: 53-7.

[19] Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache 2008; 48: 109-17.

[20] Kim JH, Suh SI, Seol HY, Oh K, Seo WK, Yu SW. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia 2008; 28: 598-604.

[21] Rocca MA, Ceccarelli A, Falini A, Colombo B, Tortorella P, Bernasconi L. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. Stroke 2006; 37: 1765-70

[22] Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biol Psychiatry 2008; 64: 774-81.

[23] Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 2005; 25: 155-64.

[24] Pan PL, Shi HC, Zhong JG, Xiao PR, Shen Y, Wu LJ. Gray matter atrophy in Parkinson's disease with dementia: evidence from meta-analysis of voxel-based morphometry studies. Neurol Sci 2013; 34: 613-9.

[25] Chen Z, Ma L. Grey matter volume changes over the whole brain in amyotrophic lateral sclerosis: A voxel-wise meta-analysis of voxel based morphometry studies. Amyotroph Lateral Scler 2010; 11: 549-54.

[26] Radua J, van den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry 2010; 67: 701-11.

[27] Matsumoto R, Ito H, Takahashi H, Ando T, Fujimura Y, Nakayama K. Reduced gray matter volume of dorsal cingulate cortex in patients with obsessive-compulsive disorder: a voxel-based morphometric study. Psychiatry Clin Neurosci 2010; 64: 541-7.

[28] Rotge JY, Langbour N, Guehl D, Bioulac B, Jaafari N, Allard M, et al. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. Neuropsychopharmacology 2010; 64: 541-7.

[29] Cong C, Bo H, Hui Y, Yue-Lei L, Yan X, Feng F. A voxel-based morphometry study of grey matter volume changes in neuromyelitis optica patients. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2014; 36: 432-8.

[30] Schoenen J. Neurophysiological features of the migrainous brain. Neurol Sci 2006; 27 Suppl 2: S77-81.

[31] Sharma N, Mishra D. International Classification of Headache Disorders, 3rd edition: what the pediatrician needs to know. Indian Pediatr 2014; 51: 123-4.

[32] Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 2005; 25: 155-64.

[33] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12.

[34] Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum Brain Mapp 2012; 33: 1-13.

[35] Lancaster JL, Tordesillas-Gutiérrez D, Martinez M, Salinas F, Evans A, Zilles K. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum Brain Mapp 2007; 28: 1194-205.

[36] Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 2009; 30: 2907-26.

[37] Schmidt-Wilcke T, Gänssbauer S, Neuner T, Bogdahn U, May A. Subtle grey matter changes between migraine patients and healthy controls. Cephalalgia 2008; 28: 1-4.

[38] Jin C, Yuan K, Zhao L, Zhao L, Yu D, von Deneen KM. Structural and functional abnormalities in migraine patients without aura. NMR Biomed 2013; 26: 58-64.

[39] Denuelle M, Boulloche N, Payoux P, Fabre N, Trotter Y, Géraud G. A PET study of photophobia during spontaneous migraine attacks. Neurology 2011; 76: 213-8.

[40] Kim JH, Kim S, Suh SI, Koh SB, Park KW, Oh K. Interictal metabolic changes in episodic migraine: a voxel-based FDG-PET study. Cephalalgia 2010; 30: 53-61.

[41] Ruchalla E. [Migraine: Structural brain changes in MRI]. Rofo 2013; 185: 1130.

[42] Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structural brain MRI abnormalities in pediatric patients with migraine. J Neurol 2014; 261: 350-7.

[43] Cauda F, Geda E, Sacco K, D'Agata F, Duca S, Geminiani G. Grey matter abnormality in au-

tism spectrum disorder: an activation likelihood estimation meta-analysis study. J Neurol Neurosurg Psychiatry 2011; 82: 1304-13.

[44] Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of Alzheimer's disease: a meta-analysis of VBM studies. Neurobiol Aging 2011; 32: 1733-41.

[45] Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neurosci Biobehav Rev 2012; 36: 341-9.

[46] Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000; 30: 263-88.

[47] May A. A review of diagnostic and functional imaging in headache. J Headache Pain 2006; 7: 174-84.

[48] Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 2000; 30: 263-88.

[49] Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD,. Migraine as a risk factor for subclinical brain lesions. JAMA 2004; 291: 427-34.

[50] Schmidt-Wilcke T, Leinisch E, Ganssbauer S, Draganski B, Bogdahn U, Altmeppen J. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. Pain 2006; 125: 89-97.

[51] Schmidt-Wilcke T, Leinisch E, Straube A, Kampfe N, Draganski B, Diener HC. Gray matter decrease in patients with chronic tension type headache. Neurology 2005; 65: 1483-6.

[52] Draganski B, Moser T, Lummel N, Ganssbauer S, Bogdahn U, Haas F. Decrease of thalamic gray matter following limb amputation. Neuroimage 2006; 31: 951-7.