Cerebral Iron Concentration in Episodic Migraineurs

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Abstract

Objective: To investigate cerebral iron concentrations in patients with episodic migraine and investigate correlations with clinical parameters, such as monthly migraine days or disease duration.

Methods: We included episodic migraineurs and healthy controls from 18 to 80 years; headache diaries were kept during a four-week baseline period. All participants underwent MRI scans, including a multi-echo 3D gradient recalled echo sequence that allowed calculating quantitative susceptibility maps.

We performed whole-brain analyses comparing the iron level of healthy controls and migraineurs and searched for regions in which migraineurs' iron concentrations correlated with their migraine frequency or disease duration. The significance level was set at 0.001 (uncorrected), the extent threshold at ten voxels.

Results: We included 15 patients and 18 controls. There were several brain regions such as the anterior cingulate cortex and the middle frontal gyrus, in which migraineurs stored more iron, but none in which controls had higher iron levels. Iron correlated positively with migraine frequency or disease duration in multiple brain regions. There was one region in which iron load correlated negatively with disease duration.

Conclusions: Migraine predisposes to increased iron levels. Not every brain area with an altered iron concentration is active during migraine attacks, so perhaps the increased iron might not solely be due to migraine but to a common cause, such as a metabolic or information processing disorder.

Introduction

Iron plays an essential role in electron transport, glucose metabolism, and synthesis of neurotransmitters and is indispensable for the brain's normal functioning.(Piñero and Connor, 2016) Its highest concentrations accumulate in the red nucleus, the basal ganglia, and the dentate nucleus of healthy adults.(Piñero and Connor, 2016). Iron influx and efflux are tightly regulated because free iron ions lead to oxidative stress implicated in the pathogenesis of neurodegenerative disorders.(Piñero and Connor, 2016) However, abnormal iron metabolism does not seem to be implicated only in neurodegenerative disorders.

Some studies investigated cerebral iron concentration in patients suffering from migraine. They found an increased load in the periaqueductal grey (PAG) and deep brain nuclei.(Kruit et al., 2009; Kruit et al., 2010; Dominguez et al., 2019; Chen et al., 2021) However, most of these studies focused on a limited number of interest regions and used turbo-spin-echo or T2-weighted sequences, which may be less sensitive to iron than a quantitative susceptibility mapping (QSM) analysis.(Bilgic et al., 2012) In fact, the susceptibility values obtained by the latter technique correlate well with iron concentrations in the grey matter.(de Rochefort et al., 2010; Schweser et al., 2011; Langkammer et al., 2012)

The reason for and consequences of migraineurs' increased iron load is unknown. On the one hand, the increased metabolic activity of specific brain areas during or outside migraine attacks could increase the

concentration of free radicals, which then might lead to tissue damage and iron deposition. On the other hand, increased metabolism might increase the need for iron without causing permanent deposition.

This study analyses the cerebral iron concentration of patients suffering from episodic migraine compared to healthy controls (HC). In addition, we search for brain regions in which the iron concentration correlates with monthly migraine days (MMD) or disease duration.

Method

Patients

We included patients between 18 and 80 years with the diagnosis of episodic migraine according to criteria published in the third edition of the International Classification of Headache Disorders.(Olesen, 2018) We excluded patients in case of pregnancy, a neurodegenerative disorder, or contraindications against MRI examinations. Furthermore, we also excluded patients who had less than two migraine days and patients who had ≥ 15 headache days and $\geq$ eight migraine days during the baseline period.

As controls, we included healthy volunteers between 18 and 80 years, who did not suffer from any headache disorder.

We excluded patients and controls if the registration of the multi-echo 3D gradient recalled echo (GRE) sequence was unsuccessful. The available data determined the sample size.

Study Design

During a four-week baseline period, migraineurs kept a headache diary that allowed the identification of migraine days according to published criteria.(Tassorelli et al., 2018)

Patients treated acute headache attacks as needed but did not change their prophylactic treatment during that period. The MRI examination defined the end of the baseline period.

The local ethics committee (Kantonale Ethikkommission (KEK), Zurich, Switzerland, approval number: 2016-00646) approved the study; all participants provided written informed consent. All experiments were performed in accordance with guidelines and regulations of the local ethics committee. The trial was registered at ClinicalTrials.gov (NCT03237754). Clinical data collected during the study have already been published elsewhere.(Pohl et al., 2020).

Magnetic resonance imaging and data processing

We acquired all MR images on a Philips 3-Tesla scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil. For QSM analysis, we obtained a multi-echo 3D gradient recalled echo (T1-FFE)

sequence with six echoes (TR/TE/ Δ TE = 60/9.8/7 ms, flip angle = 15°, voxel size (acquired) = 0.96 × 0.96 × 1 mm³, voxel size (reconstructed) = 1 × 1 × 1 mm³, field of view = 240 × 240 × 120, slices = 120, SENSE-factor = 2, flow-compensation = yes, duration = 380 s.).

Using the QSM Toolbox 2.9 (<http://godzilla.kennedykrieger.org/QSM/>)(Bao et al., 2016; van Bergen et al., 2016) we attained the quantitative susceptibility maps through several intermediate steps. After using Laplacian-based discrete phase unwrapping,(Li et al., 2011) (using echoes 4 to 6), we skull-stripped the GRE magnitude image with the Brain Extraction Tool (BET; Oxford Centre for Functional MRI of the Brain, Oxford, UK; fractional threshold: 0.4). Then, after division by $2\pi * TE$ (time of echo), we obtained a separate image of the frequency shift for each echo. Next, we eliminated background fields with the V-Multi Sophisticated Harmonic Artefact Reduction for Phase Data (VSHARP; variable spherical kernel size, maximum radius: 6 mm, regularisation parameter: 0.05)(Schweser et al., 2011) and averaged the resulting images of the echoes as suggested by Wu and co-workers.(Wu et al., 2012) Finally, the Structural Feature-Based Collaborative Reconstruction (SFCR) method, published by Bao et al., yielded susceptibility maps.(Bao et al., 2016)

We selected the white matter from the automated anatomical labelling atlas regions(Tzourio-Mazoyer et al., 2002) as the reference for the final susceptibility quantification. Hence, all susceptibility values reported in this article are relative to the mean susceptibility value of this region.

Lastly, the images were normalised using the SPM software version 12 (<https://www.fil.ion.ucl.ac.uk/>). For normalization, we used default settings (e.g. bias regularisation: very light regularisation; bias full-width half maximum: 60 mm cut-off).

Statistical analysis

This study aimed primarily to investigate whether the migraine diagnosis affects iron load in the brain. To that end, we compared migraineurs' brains with healthy controls. The secondary aim of this study was to investigate whether MMD correlate with the cerebral iron load. To that end, we searched for significant correlations between the MMD during the baseline period and iron concentrations. Finally, we also searched for significant correlations between disease duration and the cerebral iron load.

We performed whole-brain analyses with the SPM12, and set the extent threshold at ten voxels and the significance level at a voxel-threshold of $P < 0.001$ (uncorrected). We computed one-sided unpaired t-tests (e.g. controls > patients). All analyses were corrected for age and sex (whenever the sample comprised more than one sex). In addition, the analysis for correlations between the MMD and iron levels was corrected for disease duration, and the analysis for correlations between the disease duration and iron levels was corrected for MMD. We did not include headache days as independent variable because headache days and migraine days correlated highly (see below) and consequently cannot be regarded as independent. Inclusion of both variables into the model would potentially have resulted in an underestimation of the effect of migraine days.

The automated anatomical labelling atlas (AAL-3) allowed identifying brain regions.(Rolls et al., 2020)

Continuous variables are reported as means and standard deviations (SD) and categorical variables as frequencies. We estimated correlations between two variables calculating Spearman's rho. Except for the whole-brain analyses for which we used the SPM software, we conducted the statistical analysis in SPSS version 25.

Data Availability

The datasets presented in this article are not readily available because due to Swiss law, the researchers must assess whether the use of the data and coded datasets are within the primary scope of the informed consent. Data is only available upon request, after the researchers have reviewed the purpose of the inquiry. Requests to access the datasets should be directed to Dr. Lars Michels, lars.michels@usz.ch

Results

Clinical data. Of 23 migraineurs who met the inclusion criteria, we had to exclude eight as no multi-echo 3D GRE sequence had been acquired. Thus, the data of 15 patients and 18 controls entered the analysis. The average age of migraineurs and HC was 35 ± 13 and 34 ± 18 years, respectively. All migraineurs (15/15, 100%) and 13 HC (13/18, 72.2%) were female. Most migraineurs reported suffering from migraine with and without aura (15/18, 80%); only three had never experienced an aura. The average disease duration was 21 ± 14 years. Average migraine, headache, and medication days were 6 ± 3 , 8 ± 3 , and 5 ± 3 days during the baseline period. Migraine days and headache days correlated highly ($r = 0.562$). Migraineurs had a mean total MIDAS score of 28 ± 23 points.

MRI data. First, we investigated differences in the iron concentrations of migraineurs and healthy controls (HC). There was no brain region in which HC accumulated more iron than migraine patients did. Conversely, we found several areas that contained significantly more iron in migraineurs than HC (see Fig. 1, Table 1).

Second, we investigated an association between iron content and MMD. We identified fourteen brain regions in which iron content correlated statistically significantly and positively with the number of MMD during the baseline period but no area with a negative correlation (see Table 1 and Fig. 2).

Finally, we searched for an association between iron content and disease duration. There was one brain region with a statistically significant negative correlation, and there were several regions with a positive correlation. All results are listed in Table 1 and are illustrated in Fig. 3.

Table 1

Results of the analyses of the iron levels; x, y, and z are the MNI coordinates of the maximal iron accumulation; clusters comprising multiple regions are listed one below the other and marked with an asterisk. We set the extent threshold at ten voxels.

Peak T-score	Cluster size (voxel)	x	y	z	Hemi-sphere	Brain region
Areas with a significantly <i>lower</i> iron concentration in migraineurs than in HC after correction for age and sex						
-	-	-	-	-	-	-
Areas with a significantly <i>higher</i> iron concentration in migraineurs than in HC after correction for age and sex						
5.5	214	32	30	48	right	middle frontal gyrus
5	628	-16	52	0	left	superior frontal gyrus*
4.5		-12	40	0	left	anterior cingulate cortex*
4.6	44	-10	10	54	left	supplementary motor area
4.2	85	32	-68	4	right	Calcarine*
3.4		26	-72	14	right	superior occipital gyrus*
3.2		24	-68	26	right	Cuneus*
4.2	49	-56	12	32	left	precentral gyrus
4	34	-6	-4	56	left	supplementary motor area
3.9	14	-42	-64	-26	left	cerebellum exterior
3.6	14	-50	-62	-22	left	inferior temporal gyrus
3.5	11	4	-44	44	right	Precuneus / posterior cingulate gyrus
3.5	12	36	36	-8	right	lateral orbital gyrus
Areas with a significant <i>negative</i> correlation between iron concentration and the number of monthly migraine days after correction for age, and disease duration						
-	-	-	-	-	-	-
Areas with a significant <i>positive</i> correlation between iron concentration and the number of monthly migraine days after correction for age, and disease duration						
15	8	-26	-16	60	left	precentral gyrus
10	7.8	-50	-58	6	left	middle temporal gyrus
21	7.2	-48	6	34	left	precentral gyrus
21	6.1	-52	10	-22	left	temporal pole

Peak T-score	Cluster size (voxel)	x	y	z	Hemi-sphere	Brain region
24	6.1	-54	-34	8	left	superior temporal gyrus
24	4.9	-46	-36	8	left	planum temporale
13	5.8	-6	18	68	left	superior frontal gyrus
17	5.7	-36	-84	-2	left	inferior occipital gyrus
13	5.7	32	-56	-16	right	fusiform gyrus
14	5.4	-58	14	22	left	inferior frontal gyrus
13	4.8	-52	-54	20	left	angular gyrus
10	4.8	-16	-96	4	left	occipital pole
13	4.7	-48	-36	18	left	parietal operculum
Areas with a significant <i>negative</i> correlation between iron concentration and disease duration after correction for age, and disease duration						
4.6	18	-10	-34	72	left	postcentral gyrus
Areas with a significant <i>positive</i> correlation between iron concentration and disease duration after correction for age, and disease duration						
7.9	11	-48	-24	-20	left	inferior temporal gyrus
7.1	12	28	30	60	right	superior frontal gyrus
6.8	12	-26	-16	60	left	precentral gyrus
6.5	21	-32	-66	-20	left	cerebellum exterior
6	10	4	32	20	right	anterior cingulate cortex
5.7	18	-48	-52	20	left	Angular gyrus / superior temporal gyrus
5.5	11	-42	-4	-34	left	inferior temporal gyrus
5.1	11	-48	-30	4	left	superior temporal gyrus / planum temporale
5.1	41	-8	-90	2	left	Calcarine*
5		-6	-86	20	left	Cuneus*
4.9	21	42	-16	-26	right	fusiform gyrus
4.7	17	-20	-42	38	left	precuneus
4.6	12	-30	-30	12	left	transverse temporal gyrus / parietal operculum

Peak T-score	Cluster size (voxel)	x	y	z	Hemi-sphere	Brain region
4	14	-24	-24	12	left	thalamus

Discussion

Our analysis identified several brain regions in which episodic migraineurs' iron load exceeds that of HC or correlates positively with MMD or disease duration. Conversely, we found no brain region in which migraine patients had a lower iron concentration than HC or iron load correlated negatively with MMD and only one region in which iron levels correlated negatively with disease duration. Thus, suffering from migraine predisposes to an increased cerebral iron load.

In many brain areas in which iron levels correlated with migraine frequency or disease duration, HC did not have less iron than did migraine patients (see Table 1). This finding suggests that these areas do not generally store more iron in migraineurs than in HC. Consequently, circumstances other than episodic migraine might lead to an increased iron load there, too.

Given that migraine frequency is not stable throughout life,(Straube and Andreou, 2019) our finding of iron correlating with MMD in some areas suggests that iron accumulations might not be stable either and change with the migraine frequency. Hence, in these areas, iron deposition might not be irreversible but accessible to transcellular transport.

Some of the areas in which HC stored less iron (see Table 1) seem implicated in the pathophysiology of migraine. Of these, blood flow increases in the left cerebellum, right calcarine region, right cuneus and right middle frontal gyrus during the premonitory phase of a migraine attack.(Maniyar et al., 2014) During the pain phase, blood flow increases in the left anterior cingulate gyrus, left cerebellum, right middle frontal gyrus, right precuneus, and posterior cingulate cortex.(Weiller et al., 1995; Afridi et al., 2005; Maniyar et al., 2014) There was no overlap with areas with interictal alterations of perfusion.(Michels et al., 2019) See Table 2 for further details.

Of the areas in which iron content correlated with MMD (see Table 1), blood flow increases during the premonitory phase of migraine attacks in the left superior occipital gyrus.(Maniyar et al., 2014) Blood flow increases during the pain phase in the left angular gyrus, the left middle temporal gyrus, and the left temporal pole.(Weiller et al., 1995; Afridi et al., 2005; Maniyar et al., 2014) Again, there was no overlap with regions with altered interictal perfusion.(Michels et al., 2019)

Of the areas in which iron levels correlated with disease duration (see Table 1), blood flow increases during the premonitory phase of migraine attacks in the right anterior cingulate gyrus.(Maniyar et al., 2014) During the pain phase, blood flow increases in the left postcentral gyrus, the left angular gyrus, the left cerebellum, the right anterior cingulate cortex, and the right superior frontal gyrus.(Weiller et al., 1995;

Afridi et al., 2005; Maniyar et al., 2014) There was no overlap between these regions and interictal alterations of the perfusion.(Michels et al., 2019) Table 2 lists all identified brain areas.

Table 2

Overview of brain areas with increased iron levels and their implication in migraine pathophysiology; MMD – monthly migraine days; IL – iron levels; DD – disease duration

	Perfusion increased during the pre-ictal phase(Maniyar et al., 2014)	Perfusion increased during the pain phase(Weiller et al., 1995; Afridi et al., 2005; Maniyar et al., 2014)	Perfusion increased during the interictal phase(Michels et al., 2019)
IL lower in migraineurs than in HC	-	-	-
IL higher in migraineurs than in HC	Left Cerebellum Right Calcarine Right Cuneus Right Middle frontal gyrus	Left Ant. cingulate cortex Left Cerebellum Right Middle frontal gyrus Right Precuneus / post. cingulate cortex	-
Negative correlation between IL and MMD	-	-	-
Positive correlation between IL and MMD	Left Sup. occipital gyrus	Left angular gyrus Left middle temporal gyrus Left temporal pole	-
Negative correlation between IL and DD	-	Left Postcentral gyrus	-
Positive correlation between IL and DD	Right Anterior cingulate gyrus	Left Angular gyrus Left Cerebellum Right Ant. cingulate cortex Right Sup. frontal gyrus	-

Interestingly, we did not find altered iron levels in the insula, which holds a central place in pain processing,(Segerdahl et al., 2015) suggesting that it might not be pain *per se* that alters iron levels. Moreover, about the absence of correlation between iron load and MMD or disease duration in several areas (see Table 1), one may speculate that migraine and increased iron concentrations share a common cause instead of causing each other.

There was a significantly higher iron load in migraineurs' anterior and posterior cingulate cortex as well as precuneus (see Table 1). These are part of the default mode network(Buckner et al., 2008) that likely consumes the highest amount of energy of all large-scale networks in the brain.(Raichle et al., 2001) Consequently, the increased iron levels identified in this sample might be due to an underlying metabolic disorder. There is some evidence that mitochondrial dysfunction may occur in migraineurs(Gross et al., 2019) and that mitochondrial dysfunction is associated with iron accumulation.(Urrutia et al., 2014) Furthermore, a previous study suggested that the processing of sensory information might require more energy in migraineurs than in HC.(Gantenbein et al., 2013) So, in patients without mitochondrial pathology, a constantly increased energy demand might exceed mitochondria's maximum energy output.

We included many migraineurs with aura in this study (see above). Thus, a different sample might not have suggested the hypothesis of iron being linked to an underlying metabolic disorder, because previous studies indicated that – unlike in patients without aura – cerebral lactate concentrations are higher in migraineurs with aura.(Gross et al., 2019) Hence, we encourage further research with a different sample.

Changes within the default mode network occur in patients with mild cognitive impairment or at risk of Alzheimer's dementia,(Sperling et al., 2009; Mevel et al., 2011) and a recent study reported an elevated risk of dementia in patients suffering from migraine.(Islamaska et al., 2020) Considering that iron slows the formation of mature amyloid aggregates and prolongs the life span of more toxic, smaller species, (Liu et al., 2011) iron load might contribute towards the risk of neurodegeneration. Currently, however, the role of iron in the association between migraine and dementia is unclear.

Interestingly, not only does processing of sensory information require more energy in migraineurs (see above),(Gantenbein et al., 2013) previous studies also found atypical processing of sensory information. (Schwedt et al., 2015) Studies investigating brain activity changes in response to olfactory and visual stimuli, and heat pain found an increase in several areas with altered iron levels (see Table 3). (Demarquay et al., 2008; Moulton et al., 2011; Griebel et al., 2014) These findings suggest that abnormalities of information processing might be an inherent part of migraine – perhaps due to an underlying disorder of energy supply.

Given that we found a positive correlation between iron concentration and MMD in some regions reacting abnormally to sensory stimulation (see Table 3), one might wonder whether these abnormalities increase with MMD. However, given the absence of a correlation between the extent of interictal phono- or photophobia and MMD,(Ashkenazi et al., 2009; Cucchiara et al., 2015) it seems less likely that an increasing iron load is associated with a growing impairment of normal functioning.

In this regard, the increased iron load in the temporal pole (see Table 1) is an intriguing finding. This area is implicated in processing sensory stimuli (see Table 3),(Demarquay et al., 2008; Moulton et al., 2011) indicating that iron deposition in that region might also be due to a disorder of information processing. Moreover, a case series suggests that the anterior temporal lobe might induce migrainous headaches, (Yankovsky et al., 2005) and one study documented increased perfusion of this area during migraine attacks.(Afridi et al., 2005) So, the positive correlation between iron and migraine frequency (see Table 1)

might reflect the temporal pole's proneness for inducing attacks. However, the available knowledge is insufficient to verify this speculative hypothesis.

Table 3

Brain areas with altered iron levels implicated in sensory processing; MMD – monthly migraine days; IL – iron levels; DD – disease duration; * reduced activation compared to HC; **the increased activity was noted in the temporal pole contralateral to the heat stimulus

	Olfactory stimuli(Demarquay et al., 2008)	Visual stimuli(Griebe et al., 2014)	Heat pain(Moulton et al., 2011)
IL higher in migraineurs than in HC	Right middle frontal gyrus* Posterior cingulate gyrus*	Right middle frontal gyrus Right sup. occipital gyrus Right precuneus	
Positive correlation between IL and MMD	Left temporal pole Left inferior frontal gyrus* Left angular gyrus*	-	Left temporal pole**
Negative correlation between IL and DD	-	-	
Positive correlation between IL and DD	Left angular gyrus* Left superior temporal gyrus*	Left cuneus	

We failed to confirm increased iron loads in the red nucleus or the periaqueductal grey (PAG) that previous studies had discovered.(Kruit et al., 2009; Kruit et al., 2010; Dominguez et al., 2019) The reason for this might be the extent threshold of 10 voxels in this study. Moreover, iron levels in that region might only be increased in chronic migraineurs. A recent study by Chen et al., (2021) used QSM imaging, and found cortical alterations in some of the brain regions reported in our study, such as the cuneus, precuneus, superior frontal gyrus, indicating that iron levels share some overlap between episodic and chronic migraineurs (Chen et al., 2021). Yet, it was not examined whether chronic migraineurs show alterations in the brainstem (e.g. PAG).

We consider it unlikely that altered iron levels in our cohort are the result of a particular diet, as none of the patients reported being on a special diet during the study period. In addition, Domínguez and colleagues (2019) demonstrated that patients with chronic migraine have larger iron deposits in the PAG that were related to levels of biomarkers of inflammation (higher plasma levels of soluble tumour necrosis factor) and blood-brain barrier disruption (higher levels of cellular fibronectin) but not diet. Parallel mechanisms have been proposed to explain iron deposition in other neuroinflammatory conditions, such as multiple sclerosis, independent of dietary iron intake.

Strengths and Limitations

The strength of this study is that it is the first to perform a whole-brain analysis and to use QSM sequences to analyse the iron concentrations in migraineurs' brains. Consequently, these analyses provide novel insights.

Some limitations need to be addressed. First, we only included episodic migraine patients with at least two monthly migraine days. If we had included participants with higher and lower migraine frequencies, we might have discovered additional brain areas in which iron levels correlate with migraine frequencies. Given this limitation, we might only identify brain regions as correlating with MMD if iron concentration rises very steeply with an increasing number of monthly migraine days.

Second, our sample includes only female migraineurs. Thus, we do not know whether the results can be generalised to male patients.

Finally, even though the ideal sample size for studies analysing cerebral iron content is unknown, a larger sample might have yielded different or more reliable results. Hence, we encourage further research on that topic.

Conclusion

In this study, we showed that migraine attacks predispose to an increased cerebral iron load. In some brain areas, iron levels correlated with MMD but were comparable to HC, implying that circumstances other than episodic migraine might lead to an increased iron load there, too. This finding suggests that, in these regions, iron is not deposited irreversibly but accessible to transcellular transport in these areas.

Not every brain area with an altered iron concentration is active during migraine attacks suggesting that the consequences of the headache disorder reverberate widely – even in areas not directly implicated in the attacks.

Concerning the absence of any correlation between iron load and MMD in many areas, one may speculate whether the increased iron identified in this study might not solely be due to migraine but to a common cause such as an underlying metabolic disorder or a disorder of information processing.

Abbreviations

AAL	automated anatomical labelling
BA	Brodmann area
BET	brain extraction tool
GRE	gradient recalled echo

HC	healthy controls
MMD	monthly migraine days
MRI	magnetic resonance imaging
PAG	periaqueductal grey
QSM	quantitative susceptibility mapping
SHARP	Sophisticated Harmonic Artefact Reduction for Phase Data
SFCR	Structural Feature-Based Collaborative Reconstruction
TE	time of echo
TR	time of repetition
V5	middle temporal visual area

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Figures

Figure 1

Illustration of iron concentrations differences between migraineurs and healthy HC. For example, patients showed higher iron concentrations at prefrontal regions but also in the visual cortex. The full list of group differences is listed in Table 1.

Figure 2

Illustration of significant ($p < 0.001$ uncorrected, $k \geq 10$ voxels) positive correlations between monthly migraine days and iron load in patients with episodic migraine. The full list of group differences is listed in Table 1.

Figure 3

Illustration of significant ($p < 0.001$ uncorrected, $k \geq 10$ voxels) positive correlations between disease duration and iron load in patients with episodic migraine. The full list of group differences is listed in Table 1.

Supplementary Files

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