Cortical thickness in migraine: a coordinate-based meta-analysis

LiQin Sheng
Kunshan Hospital of Traditional Chinese Medicine

HaiRong Ma
Kunshan Hospital of Traditional Chinese Medicine

YuanYuan Shi
Southeast University

ZhenYu Dai
Southeast University

JianGuo Zhong
Southeast University

Fei Chen
Southeast University

PingLei Pan (panpinglei@163.com)
Southeast University  https://orcid.org/0000-0002-9288-6384

Research article

Keywords: migraine, cortical thickness, coordinate-based meta-analysis, Seed-based d Mapping with Permutation of Subject Images

DOI: https://doi.org/10.21203/rs.3.rs-47470/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Cortical thickness (CTh) analysis is a popular method to characterize brain morphometry. Many studies have been performed to investigate CTh abnormalities in migraine. However, the results from these studies were not consistent and even conflicting. These divergent results hinder us from obtaining a clear picture of brain morphometry regarding CTh alterations in migraine. Coordinate-based meta-analysis (CBMA) is a promising technique to quantitatively pool individual neuroimaging studies to identify consistent brain areas involved.

Methods

Electronic databases (PubMed, Embase, Web of Science, China National Knowledge Infrastructure, WanFang, and SinoMed) and other sources (bioRxiv and reference lists of relevant articles and reviews) were systematically searched for studies that compared regional CTh differences between patients with migraine and healthy controls (HCs) up to May 15, 2020. A CBMA was performed using the Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) approach.

Results

In total, we identified 16 studies with 17 datasets reported that were eligible for the CBMA. The 17 datasets included 872 patients with migraine (average sample size 51.3, mean age 39.6 years, 721 females) and 949 HCs (average sample size 59.3, mean age 44.2 years, 680 females). The CBMA detected no statistically significant consistency of CTh alterations in patients with migraine relative to HCs. Sensitivity analysis and subgroup analysis verified this result to be robust. Meta-regression analyses revealed that this CBMA result was not confounded by age, gender, aura, attack frequency per month, and illness duration.

Conclusions

Our CBMA adds to the evidence of the replication crisis in neuroimaging research that is increasingly recognized. The current evidence suggests that CTh is not a reliable biomarker of migraine. Many potential confounders, such as underpowered sample size, heterogeneous patient selection criteria, and differences in imaging collection and methodology, may contribute to the inconsistencies of CTh alterations in migraine, which merit attention before planning future research on this topic.

Background

Migraine is a highly prevalent neurological condition that affects about one billion people worldwide at all ages and more common in women than in men [1]. Migraine ranks second in terms of year lived with disability among neurological disorders, leading to significant individual and societal burdens [2]. Migraine is multifactorial and is often comorbid with other diseases [3, 4]. The pathophysiology underlying migraine is complex and remains to be elucidated. It has been widely accepted that trigeminovascular system plays a fundamental role in migraine [5]; however, more recent studies have suggested that multiple neural networks that compromise brainstem, diencephalic, and cortical structures are involved as well [6–8].

Cortical thickness (CTh) via surface-based morphometry (SBM) analysis is one of the advanced non-invasive neuroimaging metrics that characterize brain morphometry [9]. Many studies have been performed to investigate CTh abnormalities in migraine. CTh abnormalities in migraine were found to be associated with age [10, 11], gender [12], disease duration [11, 13–15], attack frequency [13–15], pain intensity [14], aura [15–17], and photosensitivity [18]. Brain CTh combining cortical surface area and regional volumes have shown to be highly accurate in distinguishing individual people with chronic migraine from episodic migraine and healthy controls [19]. These studies have helped us better understand the pathophysiology of migraine [20, 21]. However, the results from these studies were not consistent and even conflicting. Increased CTh in patients with migraine relative to healthy controls (HCs) was observed in the left middle frontal sulcus [17], left temporoparietal incisure [17], lateral occipito-temporal cortex [22], and left occipital lobe [23]. In contrast, patients with migraine compared to HCs showed reduced CTh in the left superior frontal sulcus [17], left middle frontal gyrus [13, 15], left precentral sulcus [17], bilateral central sulcus [15], bilateral post-central gyrus [13], right occipito-temporal area [15], left primary visual cortex [15], left secondary visual cortex [15], left anterior midcingulate [14], and insula [22, 24]. While several other studies did not detect any CTh differences between patients with migraine and HCs [11, 25–28]. These divergent results hinder us from obtaining a clear picture of brain morphometry regarding CTh alterations in migraine.

Coordinate-based meta-analysis (CBMA) is a promising technique to quantitatively pool individual neuroimaging studies to find brain areas consistently involved in particular neuropsychiatric disorders across studies [29, 30]. Recently, CBMA of voxel-based morphometry (VBM) studies showed no consistency of gray matter (GM) volume/density alterations in migraine relative to HCs [26, 31, 32]. CTh is more sensitive than VBM to characterize brain morphometry. To date, no CBMA of CTh studies in migraine has ever been reported. With the development of the algorisms [33, 34], CBMA has been recently applied to quantify CTh alterations in major depressive disorder [35]. Therefore, we aimed to conduct a CBMA of studies that investigate CTh differences at the whole-brain cortical level between patients with migraine and HC subjects using the Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) approach [33, 34].
**Literature search and study selection**

This study was reported conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [36] and followed guidelines and the recent recommendations for neuroimaging meta-analysis [29, 30]. The protocol (CRD42020175789) was registered in the International Prospective Register of Systematic Reviews (PROSPERO).

We systematically and comprehensively searched the online electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), and Web of Science (http://apps.webofknowledge.com/) on March 16, 2020 for records published in English, using the following keywords: “migraine” and (“cortical thickness” or “cortical thinning” or “surface-based morphometry”). The searches were updated on May 15, 2020. We also searched China National Knowledge Infrastructure (CNKI, https://www.cnki.net/), WanFang (www.wanfangdata.com.cn), and SinoMed (http://www.sinomed.ac.cn/) for studies published in Chinese. No restrictions were incorporated in the search itself. Additionally, the reference lists of the included articles and any relevant review articles were manually reviewed other potentially qualified studies. We also searched bioRxiv (https://www.biorxiv.org/about-biorxiv) for unpublished preprints that were qualified for the meta-analysis.

To be included, the study needed to satisfy the following inclusion criteria: (1) enrollment of adult patients with migraine according to the accepted criteria; (2) case-control studies that employed a whole-brain cortical analysis to compare regional CTh differences between patients with migraine and healthy controls (HCs); (3) studies with significant CTh results that reported three-dimensional peak coordinates in standard Montreal Neurological Institute (MNI) or Talairach space and studies with non-significant CTh results. Exclusion criteria were as follows: (1) there were seven or fewer participants in either the migraine group or the HC group [29]; (2) the study did not list three-dimensional coordinates of significant results regarding regional CTh differences between patients with migraine and HCs; (3) the study only performed region of interest analysis or global CTh analysis; (4) the study lacked a direct migraine-HC group comparison of regional CTh difference; (5) the patient sample was duplicated or overlapped with another study with a larger sample size; (6) no baseline comparison results were reported in case of a longitudinal study; (7) the publications were reviews, study protocols, conference abstracts, correspondence, and editorials.

**Data extraction**

The following information was extracted from the retrieved studies: the first author’s name, year of publication, sample size, age, sex distribution, patient type (episodic/chronic migraine), the number of patients with and without aura, illness duration, attack frequency per month, MRI scanner manufacturer and platform, field strength, head coil, MRI sequence, repetition time (TR)/echo time (TE), voxel size, imaging processing software package, smooth kernel, statistical model, covariate, statistical threshold, peak coordinates, the height of the peaks (t-values, z-values, or p-values. The latter two values could be converted to t-values via the web utilities: https://www.sdmproject.com/utilities/?show=Statistics), and their stereotactic reference space (MNI or Talairach).

**Quality assessment**

Currently, no official tools have been established to assess the quality of CTh studies. A 12-point checklist (Table S1), which was based on a previous CTh meta-analysis [35], was utilized for the quality assessment of the included studies. This checklist constitutes a 4-point scale for evaluation of sample characteristics (0–4 points), a 5-point scale for assessment of methods for image acquisition and analysis (0-5 points), and a 3-point (0-3 points) scale for assessment of results and conclusions. Studies recording an overall score of ≥ 10 were considered as good quality, studies with an overall score between 7 and 9 as moderate quality, and an overall ≤ 7 as poor quality.

**Data analysis**

**Main CBMA by pooling all included studies**

Main CBMA of all included studies was performed using SDM-PSI (version 6.21, www.sdmproject.com) as described in detail previously [33, 34]. The standard SDM-PSI pipeline was followed for the CBMA. Preprocessing was first conducted to calculate an image of the lower bound and an image of the upper bound of possible effect sizes for each study separately using a specific GM freesurfer mask, a 20 mm full width half maximum (FWHM) anisotropic Gaussian kernel, and a 2 mm voxel size. Mean analysis was then performed to estimate the Hedge-corrected effect sizes in a standard random-effects model using MetaNSUE algorithms [37, 38], multiple imputations of maximum likelihood estimation (MLE), and Rubin’s rules. Finally, voxel-wise results are determined using threshold-free cluster enhancement family-wise error rate (TFCE FWER) p < 0.05 corrected for multiple comparisons and extent threshold of ≥ 10 voxels. This statistical thresholding has been suggested to be neither too conservative nor too liberal in the simulation work [33, 34].

**Sensitivity analysis**

To assess the stability of the results identified in the main CBMA, a sensitivity analysis was performed by repeating the same analyses by consecutively removing one study at a time.

**Heterogeneity analysis**

Heterogeneity of significant brain clusters identified in the main CBMA was estimated using the I² statistic and I² > 50% was defined as high heterogeneity across studies.

**Publication bias analysis**

The risk of publication bias was evaluated using the Egger’s test [39] by extraction of the values from the significant peaks in the main CBMA. A threshold at p < 0.05 was set of significance.
Subgroup meta-analysis

Subgroup meta-analyses were performed to investigate the possible effects of the results on the overall conclusions if at least 10 datasets were available based on (1) migraine patients with aura/without aura, (2) patients with episodic migraine/chronic migraine, (3) use of 3.0 T/1.5 T MRI scanners.

Meta-regression analysis

We conducted random-effects meta-regression analyses, exploring if regional CTh alterations across studies might be moderated by main study characteristics, including age, gender, aura, attack frequency per month, and illness duration if relevant information was available from at least 10 datasets. A statistical threshold was set at p < 0.05 (TFCE FWER) and a cluster extent of 10 voxels.

Results

Study selection and characteristics

After deleting the repetitive publications from the electronic database and manual searches, 250 records were screened. Based on the eligibility criteria, a total of 16 studies that reported 17 datasets were finally included in the CBMA [10-17, 22-28, 40]. Figure 1 presents the PRISMA flowchart. Publication year of the included studies ranged from 2011 to 2020. The 17 datasets included 872 patients with migraine (average sample size 51.3 [range 11-131], mean age 39.6 years [range 30.8-57.4 years], 721 females) and 949 HC subjects (average sample size 59.3 [range 11-309], mean age 44.2 years [range 29.1-58.7 years], 680 females). Of the 17 datasets, ten evaluated patients with episodic migraine, two evaluated patients with chronic migraine, two evaluated patients with episodic and chronic migraine, and the remaining three did not explicitly indicate the patient type. The information regarding migraine patients with aura or without aura from 13 datasets, illness duration from 14 datasets, and attack frequency per month from 12 datasets were available. MRI data were acquired mostly on 3.0 Tesla machines (15 of the 17 datasets) and 1.5 Tesla machines (2 of the 17 datasets). Fourteen of 17 datasets used FreeSurfer software packages, and 3 used Computational Anatomy Toolbox (CAT) to analyze regional CTh differences between patients and HC subjects. The demographic and clinical characteristics and imaging characteristics are listed in Table 1 and 2, respectively. The scores of quality assessment are shown in Table 1. Overall, all included studies reached a score of either ‘good’ or ‘moderate’.

Main CBMA

The main CBMA of all included datasets showed no significant brain clusters of regional CTh difference between patients with migraine and HC subjects (TFCE FWER corrected p < 0.05 and voxel extent ≥ 10).

Sensitivity analysis

The sensitivity analysis revealed that the result of no consistent difference in regional CTh between patients with migraine and HC subjects remained in all combinations of datasets.

Heterogeneity analysis and Publication bias analysis

The lack of significant brain clusters identified in the main CBMA prevented us from performing heterogeneity analysis and publication bias analysis.

Subgroup meta-analysis

Subgroup meta-analysis of datasets in patients with episodic migraine (n = 10), of datasets using 3.0 T MRI scanners (n = 15), and of datasets using FreeSurfer software packages demonstrated no significant findings (TFCE FWER corrected p < 0.05 and voxel extent ≥ 10). Other subgroup meta-analyses were not performed due to the insufficient datasets included.

Meta-regression analysis

Meta-regression analyses revealed that age, gender, aura, attack frequency per month, and illness duration were not moderators that influence the CBMA result of regional CTh difference across studies (TFCE FWER corrected p < 0.05 and voxel extent ≥ 10).

Discussion

To the best of our knowledge, this is the first CBMA of CTh studies in migraine. Using the SDM-PSI meta-analytical approach, our CBMA that included 17 datasets comprising 872 patients and 949 controls detected no statistically significant consistency of CTh alterations in patients with migraine relative to healthy controls. This lack of specific CTh alterations indicates that CTh analysis is not a reliable and reproducible metric as a potential biomarker of migraine. Although little is known about the exact reasons for the absence of consistency of CTh alterations in migraine, we will discuss the possible sources and factors from the variability of sample size and heterogeneous patient selection criteria to imaging collection and methodological differences across independent studies.

There is an increasing concern regarding the reliability and reproducibility in neuroimaging research [41]. A small sample size with low statistical power undermines the reliability of neuroscience [42]. A power calculation is applauded to estimate the appropriate sample size before the study initiation. A well-powered cross-sectional CTh study required approximately 50 subjects per group to detect a 0.25-mm CTh difference [43]. Sample size estimates were heterogeneous over the cortical surface [43]. Of the 17 datasets included in the CBMA, the sample sizes range from 11 to 166 (mean 51.3) in the patient groups and from 11 to 309 (mean 59.3) in the HC groups, of which the majority (n = 13) enrolled participants with small sample size less than 50 subjects per
group. Only three studies included in the CBMA conducted prior statistical power calculations with different sample sizes required [25–27]. The findings from these studies with small sample sizes were probably false that affected the generalizability of the obtained results. Although it is challenging in practice, data sharing or multi-center collaboration to increase the sample size (and therefore power) is highly needed [41, 42].

Heterogeneous patient selection criteria make it difficult to define consistent migraine characteristic alterations of CTh. Migraine is a heterogeneous neurological disease. Some datasets only enrolled episodic migraineurs [12, 15, 16, 22, 24–26, 28], while some other datasets included both episodic and chronic migraineurs [13, 14] or only chronic migraineurs [11, 44]. Majority of the datasets (n = 14) in the CBMA included patients with mixed gender [10, 11, 13–17, 22, 25–28, 44], while two datasets only included female migraine patients [23, 24] and one only male migraine patients [12]. Some datasets only included patients with aura [16, 23, 25, 28] and without aura [13, 22, 24–26], while some other studies included both patients with migraine without aura and with aura [10, 11, 15, 17]. Individual studies showed that the observed regional pattern of CTh abnormalities in patients with migraine was influenced by age [10, 11], gender [12], gender [12], disease duration [11, 13–15], attack frequency [13–15, 44], pain intensity [14], the presence of aura [15–17], and photosensitivity [18]. In addition, two datasets were cross-sectional population-based studies [23, 27] and the rest are clinic-based studies that the former minimized the selection biases compared to the later. Migraine is a recurrent headache disorder characterized by a cycle of attacks including pain-attack ictal and pain-free interictal phases. Different patterns of morphometric GM changes detected via VBM and dynamic variations in the anatomical microstructure of the thalamus detected via diffusion tensor imaging between ictal and interictal phases were observed in migraine, which suggests that abnormal structural plasticity may be an important mechanism of migraine pathology [45, 46]. While no CTh studies have been conducted to explore headache phase-related cortical plasticity in migraine. An extensive literature has shown that a wide range of psychiatric disorders, especially anxiety and depression, can accompany migraine [4, 47–49]. Previous studies revealed cortical abnormalities in depression [35, 50, 51] and anxiety disorders [52–55]. However, these psychiatric problems are often under-diagnosed and have not been thoroughly assessed in CTh studies in migraine. Only a few studies in the CBMA included patients at the medication-free state [10, 16, 22]. Medication status and type are other potential confounders that may influence CTh findings in migraine; however, no CTh studies have attempted to evaluate such effects.

Differences in imaging collection and methodology of CTh analyses may also have contributed to the absence of consistency from CTh studies in migraine. Previous reports showed that results of CTh analyses can be influenced by scanner platform [56, 57], field strength [58–60], pulse sequence [58, 61, 62], the number of coil channels [61], scanner relocation [63], and imaging sites [56, 64]. As shown in Table 2, differences in scanner manufacturer and platform (Siemens, Philips, and GE), field strength (3.0 T and 1.5 T), head coil (8-, 12-, 32-, and 64-channel), MR sequence (MPRAGE, FFE, TFE, FLASH, and FSPGR), TR/TE, and voxel size (from 1.33 × 1.0 × 1.0 to 0.89 × 0.89 × 0.8 mm³) across studies were noted. Besides, variations in computing workstation types [65], operating systems [65, 66], processing pipelines and software packages [65, 67, 68], the extent of smoothing [69], and statistical strategies [10, 16, 17, 22] may produce inconsistent results. These differences make direct comparisons between the different studies difficult. A multi-center study from four academic headache centers used different MRI systems and vendors, MRI sequences, TR/TE, and voxel size [15], which were controlled in the subsequent analyses. However, most individual studies did not explicitly state the computing workstation types and operating systems used in the CTh analyses. It has been shown that variability at various levels of processing pipeline influences cortical thickness measurement [70]. The CTh studies in migraine included in the CBMA used divergent processing pipelines and software packages (different versions of FreeSurfer and CAT12), smoothing kernels, and statistical strategies were used. Specially, four studies revealed that the use of a more liberal uncorrected threshold produced more positive results [10, 16, 17, 22], which may be false positive. Moreover, there is increasing awareness that image quality can systematically bias the results [71–73]. Quality control of imaging data in the processing pipelines should be applied in all CTh studies to achieve reliable results [71, 72]. However, only three of the studies included in the CBMA explicitly conduct a visual inspection and manual correction of topological errors for quality control [10, 14, 15].

As discussed above, many potential confounders may contribute to the inconsistencies of CTh alterations in migraine, which merit attention in future studies. Of the 17 CTh datasets included in the CBMA, 9 reported null finding in patients with migraine relative to healthy controls using corrected thresholds for multiple comparisons [10–12, 16, 25–28]. Is migraine indeed not associated with CTh alterations? Are significant CTh alterations observed in the studies secondary, or specified to migraine subgroups, or just a reflection of structural plasticity of the migraine cycle? To answer these questions and to obtain reliable results, we need to design longitudinal population-based studies at different migraine phases that recruit homogeneous patients with appropriate sample size using standardized imaging collection protocols with high field strength, multi-echo sequence, and a high number of coil channels and latest well-validated processing and analysis pipelines controlling for the age, gender, comorbidities, and medication. Besides, longitudinal multimodal neuroimaging studies would contribute to elucidate whether CTh alterations are secondary to chronic functional abnormalities.

Several limitations to our CBMA must be considered. First, given the clinical heterogeneity of migraine and the lack of sufficient original studies, we were unable to conduct separate subgroup CBMA to identify the effects of potential moderators, such as migraine with aura vs. migraine without aura, male migraine vs. female migraine, and episodic migraine vs. chronic migraine. More CTh studies in migraine with homogeneous subtypes are needed to characterize the CTh patterns. Second, the present meta-analysis is coordinate-based rather than image-based or mixed coordinate- and image-based, which may lead to biased results. Future studies with imaging data sharing would be helpful to obtain more accurate results.

Conclusions

In conclusion, the present CBMA detected no consistent CTh alterations in patients with migraine relative to healthy controls. Our CBMA adds to the evidence of the replication crisis in neuroimaging research that is increasingly recognized [74, 75]. The current evidence suggests that CTh is not a reliable biomarker of migraine. Whether migraine is truly associated with CTh alterations is still argued. Many potential confounders, such as underpowered sample size, heterogeneous patient selection criteria, and differences in imaging collection and methodology, may contribute to the inconsistencies of CTh alterations in migraine, which merit attention before planning future research on this topic. Longitudinal population-based multimodal neuroimaging studies at different migraine phases that subtype homogeneous patients with well-powered sample sizes using standardized imaging collection protocols and well-validated
processing and analysis pipelines controlling for the age, gender, comorbidities, and medication are required to improve the reliability of the results that characterize CTh alterations in migraine.

**Abbreviations**

CAT: Computational Anatomy Toolbox; CBMA, coordinate-based meta-analysis; CNKI, China National Knowledge Infrastructure; CTh, cortical thickness; FFE, fast field echo; FLASH, fast low angle shot; FSPGR, fast spoiled gradient recalled echo sequence; FWHM, full width half maximum; FWER, family-wise error rate; GM, gray matter; HCs, healthy controls; MLE, maximum likelihood estimation; MNI, Montreal Neurological Institute; MPRAGE, Magnetization Prepared Rapid Gradient Echo; MRI, magnetic resonance imaging; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SBM, surface-based morphometry; SDM-PSI, Seed-based d Mapping with Permutation of Subject Images; SPGR, spoiled gradient-echo; TFCE, threshold-free cluster enhancement; TFE, turbo field echo; TR/TE, repetition time/echo time; VBM: voxel-based morphometry

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by the National Natural Science Foundation of China (81601161) and Jiangsu Commission of Health (LGY2018039, QNRC 2016466).

**Authors’ contributions**

JGZ, FC, and PLP conceived and designed the study. LQS, HRM, and YYS performed the experiments. LQS, JGZ, and HRM analyzed the data. LQS, HRM, and YYS prepared the manuscript. JZG, FC, and PLP reviewed and edited the manuscript. All authors read and approved the final manuscript.

**Acknowledgments**

We thank all the authors of the included studies.

**References**

8. Qubty W, Patniyot I, Migraine Pathophysiology: Pediatric Neurol, 2020
44. Lai KL et al., Cortical morphological changes in chronic migraine in a Taiwanese cohort: Surface- and voxel-based analyses. Cephalalgia, 2020:333102420920005
52. Zhao Y et al., Gray Matter Abnormalities in Non-comorbid Medication-naive Patients with Major Depressive Disorder or Social Anxiety Disorder. EBioMedicine, 2017; 21:228–235
70. Kharabian Masouleh S et al., Influence of Processing Pipeline on Cortical Thickness Measurement. Cereb Cortex, 2020

Tables

Table 1. Demographic and clinical characteristics of CTh studies included in the meta-analysis
<table>
<thead>
<tr>
<th>Study</th>
<th>Migraine type</th>
<th>Sample (female)</th>
<th>WoA/WA</th>
<th>Age (years, SD)</th>
<th>Duration (years, SD)</th>
<th>Attack frequency/month (SD)</th>
<th>Medication</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datta et al., 2011</td>
<td>EM</td>
<td>Patients 28 (24)</td>
<td>0/28</td>
<td>35 (6)</td>
<td>19.1 (NA)</td>
<td>4.1 (5.6)</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 28 (24)</td>
<td>28/0</td>
<td>35 (7)</td>
<td>15 (NA)</td>
<td>3.4 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 28 (24)</td>
<td></td>
<td>33 (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maleki et al., 2012</td>
<td>EM</td>
<td>Patients 11 (0)</td>
<td>NA/NA</td>
<td>42.7 (9.3)</td>
<td>≥ 3 years</td>
<td>NA</td>
<td>medicated</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 11 (0)</td>
<td></td>
<td>43 (9.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Messina et al., 2013</td>
<td>NA</td>
<td>Patients 63 (42)</td>
<td>31/32</td>
<td>37.2 (NA)</td>
<td>17 (NA)</td>
<td>&lt;1/month, 8 patients</td>
<td>19 medicated</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 18 (13)</td>
<td></td>
<td>36.9 (NA)</td>
<td></td>
<td>1-3/month, 32 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chong et al., 2014</td>
<td>EM</td>
<td>Patients 27 (22)</td>
<td>18/9</td>
<td>33.6 (12.3)</td>
<td>16 (9.2)</td>
<td>6.4 (3.0)</td>
<td>medication-free</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 32 (25)</td>
<td></td>
<td>35.3 (11.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hubbard et al., 2014</td>
<td>EM/CM</td>
<td>Patients 17 (13)</td>
<td>NA/NA</td>
<td>41.71 (12.2)</td>
<td>12.53 (8.41)</td>
<td>11.65 (10.07)</td>
<td>14 medicated</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 18 (14)</td>
<td></td>
<td>38.89 (11.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al., 2014</td>
<td>EM/CM</td>
<td>Patients 56 (56)</td>
<td>56/0</td>
<td>35.7 (9.5)</td>
<td>10.9 (5.8)</td>
<td>10.1 (5.7)</td>
<td>medicated</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 34 (34)</td>
<td></td>
<td>34.2 (9.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maleki et al., 2015</td>
<td>EM</td>
<td>Patients 46 (46)</td>
<td>46/0</td>
<td>34.7 (10.4)</td>
<td>15.6 (9.5)</td>
<td>&lt;2/month, 13 patients</td>
<td>majority medicated</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 46 (46)</td>
<td></td>
<td>34.1 (10.6)</td>
<td></td>
<td>2-6/month, 17 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hougaard et al., 2016</td>
<td>EM</td>
<td>Patients 60 (42)</td>
<td>0/60</td>
<td>33.36 (NA)</td>
<td>9.5 (6.23)</td>
<td>3.36 (2.55)</td>
<td>medication-free</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 60 (42)</td>
<td></td>
<td>33.39 (NA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2017</td>
<td>EM</td>
<td>Patients 32 (24)</td>
<td>32/0</td>
<td>38.3 (10.16)</td>
<td>14.96 (NA)</td>
<td>NA</td>
<td>medication-free</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 32 (24)</td>
<td></td>
<td>38.8 (10.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaist et al., 2018</td>
<td>NA</td>
<td>Patients 166 (166)</td>
<td>0/166</td>
<td>48.0 (6.6)</td>
<td>48.0 (7.7)</td>
<td>NA</td>
<td>NA</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 137 (137)</td>
<td></td>
<td>48.0 (7.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petrusic et al., 2018</td>
<td>EM</td>
<td>Patients 48 (36)</td>
<td>0/48</td>
<td>39.3 (11.2)</td>
<td>18.5 (10.5)</td>
<td>0.68 (0.93)</td>
<td>medication-free</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 30 (23)</td>
<td></td>
<td>39.6 (12.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husøy et al., 2019</td>
<td>NA</td>
<td>Patients 80 (60)</td>
<td>NA</td>
<td>57.4 (4.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 309 (124)</td>
<td></td>
<td>58.7 (4.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magon et al., 2019</td>
<td>EM</td>
<td>Patients 131 (109)</td>
<td>93/38</td>
<td>30.8 (9.0)</td>
<td>14.1 (8.5)</td>
<td>3.3 (2.5)</td>
<td>3 medicated</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 115 (81)</td>
<td></td>
<td>29.1 (7.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woldeamanuel, 2019</td>
<td>CM</td>
<td>Patients 30 (24)</td>
<td>17/13</td>
<td>40 (14)</td>
<td>26 (13)</td>
<td>27 (12)</td>
<td>medicated</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls 30 (24)</td>
<td></td>
<td>40 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Patients</td>
<td>Controls</td>
<td>CTh</td>
<td>Age (SD)</td>
<td>Hct (SD)</td>
<td>SD (SD)</td>
<td>Migraine-free?</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>Masson et al., 2020</td>
<td>EM</td>
<td>0/19 (13)</td>
<td></td>
<td>33.6 (11.5)</td>
<td>32.7 (8.7)</td>
<td>16.8 (7.4)</td>
<td>3.3 (1.1)</td>
<td>medication-free?</td>
</tr>
<tr>
<td>Lai et al., 2020</td>
<td>CM</td>
<td>NA/NA (23)</td>
<td></td>
<td>33.2 (9.8)</td>
<td>32.4 (8.3)</td>
<td>13.2 (8.8)</td>
<td>24.0 (5.3)</td>
<td>medicated</td>
</tr>
</tbody>
</table>

CT, cortical thickness; EM, episodic Migraine; CM, chronic migraine; WoA, patients with migraine without aura; WA, patients with migraine with aura; SD, standard deviation; controls, headache-free controls; NA, not available; a, migraine with aura; b, migraine without aura; *, 12 points in total

Table 2. Imaging characteristics of the CTh studies included in the meta-analysis
<table>
<thead>
<tr>
<th>Study</th>
<th>MRI scanner</th>
<th>Field strength</th>
<th>Head coil</th>
<th>MRI sequence</th>
<th>TR/TE (mm/mm)</th>
<th>Voxel size (mm³)</th>
<th>Software</th>
<th>FWHM (mm)</th>
<th>Analytic model</th>
<th>Covariate</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datta et al., 2011</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>8-channel</td>
<td>MPRAGE</td>
<td>1620/3.09</td>
<td>1 x 1 x 1</td>
<td>FreeSurfer</td>
<td>10</td>
<td>random-effect models/t-test</td>
<td>age and gender</td>
<td>P &lt; 0.05 (FDR)</td>
</tr>
<tr>
<td>Maleki et al., 2012</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>8-channel</td>
<td>MPRAGE</td>
<td>2100/2.74</td>
<td>1.33 x 1.0 x 1</td>
<td>FreeSurfer</td>
<td>10</td>
<td>Vertex-wise GLM</td>
<td>NA</td>
<td>P &lt; 0.05 (MCS)</td>
</tr>
<tr>
<td>Messina et al., 2013</td>
<td>Inter, Philips</td>
<td>3.0 Tesla</td>
<td>NA</td>
<td>FFE</td>
<td>25/4.6</td>
<td>0.89 x 0.89 x 0.8</td>
<td>FreeSurfer</td>
<td>v4.5</td>
<td>Vertex-wise GLM</td>
<td>age, gender, whole-hemisphere average cortical thickness and cortical surface area</td>
<td>P &lt; 0.01 (FDR)</td>
</tr>
<tr>
<td>Chong et al., 2014</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>12-channel</td>
<td>MPRAGE</td>
<td>2400/3.16</td>
<td>1 x 1 x 1</td>
<td>FreeSurfer</td>
<td>v5.3</td>
<td>Vertex-wise GLM</td>
<td>depression, anxiety, and migraine burden</td>
<td>P &lt; 0.02 (MCS)</td>
</tr>
<tr>
<td>Hubbard et al., 2014</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>12-channel</td>
<td>MPRAGE</td>
<td>2500/3.44</td>
<td>0.9 x 0.9 x 1</td>
<td>FreeSurfer</td>
<td>v5.3</td>
<td>Vertex-wise GLM</td>
<td>age</td>
<td>P &lt; 0.05 (RFT)</td>
</tr>
<tr>
<td>Kim et al., 2014</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>12-channel</td>
<td>MPRAGE</td>
<td>1780/2.34</td>
<td>1 x 1 x 1</td>
<td>FreeSurfer</td>
<td>v5.1</td>
<td>Vertex-wise GLM</td>
<td>age</td>
<td>P &lt; 0.05 (MCS)</td>
</tr>
<tr>
<td>Maleki et al., 2015</td>
<td>Siemens</td>
<td>3.0 Tesla</td>
<td>NA</td>
<td>MPRAGE</td>
<td>2100/2.74</td>
<td>1.33 x 1.0 x 1</td>
<td>FreeSurfer</td>
<td>5</td>
<td>Vertex-wise GLM</td>
<td>age and TIV</td>
<td>P &lt; 0.05 (MCS)</td>
</tr>
<tr>
<td>Hougaard et al., 2016</td>
<td>Inter, Philips</td>
<td>3.0 Tesla</td>
<td>32-channel</td>
<td>TFE</td>
<td>9900/4.6</td>
<td>1 x 1 x 1</td>
<td>FreeSurfer</td>
<td>10</td>
<td>Vertex-wise GLM</td>
<td>age, gender, disease duration, and attack frequency</td>
<td>P &lt; 0.05 (PBNPA)</td>
</tr>
<tr>
<td>Zhang et al., 2017</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>12-channel</td>
<td>MPRAGE</td>
<td>2530/2.34</td>
<td>1 x 1 x 1</td>
<td>CAT12</td>
<td>15</td>
<td>Voxel-wise t-test</td>
<td>NA</td>
<td>P &lt; 0.05 (FDR)</td>
</tr>
<tr>
<td>Gaist et al., 2018</td>
<td>Verio, Siemens</td>
<td>3.0 Tesla</td>
<td>32-channel</td>
<td>FLASH</td>
<td>18.7/2.2</td>
<td>NA</td>
<td>FreeSurfer</td>
<td>v6.0.0</td>
<td>Vertex-wise GLM</td>
<td>age</td>
<td>P &lt; 0.05 (MCS)</td>
</tr>
<tr>
<td>Petrusic et al., 2018</td>
<td>Signa, GE</td>
<td>1.5 Tesla</td>
<td>8-channel</td>
<td>FSPGR</td>
<td>8.12/3.6</td>
<td>0.47 x 0.47 x 1.4</td>
<td>FreeSurfer</td>
<td>v5.3</td>
<td>Vertex-wise GLM</td>
<td>age and gender</td>
<td>P &lt; 0.05 (MCS)</td>
</tr>
<tr>
<td>Husøy et al., 2019</td>
<td>Signa, GE</td>
<td>1.5 Tesla</td>
<td>8-channel</td>
<td>MPRAGE</td>
<td>10.2/4.1</td>
<td>1.2 (slice thickness)</td>
<td>FreeSurfer</td>
<td>v5.3</td>
<td>Vertex-wise GLM</td>
<td>age and gender</td>
<td>P &lt; 0.05 (FDR)</td>
</tr>
<tr>
<td>Magon et al., 2019</td>
<td>Trio, Siemens; Signa, GE; Achieva, Philips</td>
<td>3.0 Tesla</td>
<td>8 or 12-channel</td>
<td>NA</td>
<td>3.99/9000, 2.98/2300, 4.6/9000, 1.5/6300, 2.98/2300</td>
<td>1 x 1 x 1</td>
<td>FreeSurfer v5.3</td>
<td>NA</td>
<td>Vertex-wise ANCOVA model</td>
<td>age, gender and MRI scanner</td>
<td>P &lt; 0.05 (FDR)</td>
</tr>
<tr>
<td>Woldeamanuel, 2019</td>
<td>Discovery, GE</td>
<td>3.0 Tesla</td>
<td>8-channel</td>
<td>IR-FSPGR</td>
<td>5.9/2</td>
<td>0.9 x 0.9 x 1</td>
<td>FreeSurfer</td>
<td>v5.3.0</td>
<td>Vertex-wise GLM</td>
<td>age</td>
<td>P &lt; 0.00 (FDR)</td>
</tr>
<tr>
<td>Masson et al., 2020</td>
<td>Prisma, Siemens</td>
<td>3.0 Tesla</td>
<td>64-channel</td>
<td>MPRAGE</td>
<td>3500/2.25</td>
<td>0.9 x 0.9 x 0.9</td>
<td>CAT12</td>
<td>15</td>
<td>Voxel-wise t-test</td>
<td>age and gender</td>
<td>P &lt; 0.05 (TFCE, FWE)</td>
</tr>
<tr>
<td>Lai et al., 2020</td>
<td>Trio, Siemens</td>
<td>3.0 Tesla</td>
<td>32-channel</td>
<td>MPRAGE</td>
<td>2530/3.03</td>
<td>1 x 1 x 1</td>
<td>CAT12</td>
<td>20</td>
<td>Voxel-wise t-test</td>
<td>age and gender</td>
<td>P &lt; 0.05 (FDR)</td>
</tr>
</tbody>
</table>

CTh, cortical thickness; MRI, magnetic resonance imaging; TR/TE, repetition time/echo time; FWHM, full width half maximum; MPRAGE, magnetization prepared rapid gradient echo; FDR, false discovery rate; GLM, general linear model; MCS, Monte Carlo Simulation; NA not available; FFE, fast field echo; TIV, T1-weighed image.
Figures

Study selection process following the PRISMA flowchart

CTh = cortical thickness, HC = healthy control, ROI = region of interest
Study selection process following the PRISMA flowchart. CTh = cortical thickness, HC = healthy control, ROI = region of interest.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx