HHS Public Access

Author manuscript

Headache. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Headache. 2017 November ; 57(10): 1522–1531. doi:10.1111/head.13193.

Structural Co-variance Patterns in Migraine: A Cross-sectional Study Exploring the Role of the Hippocampus

Catherine D. Chong[1], **Gina Dumkrieger**[1,2], and **Todd J. Schwedt**[1]

[1]Mayo Clinic, Arizona, Department of Neurology

[2]Arizona State University, School of Computing Informatics and Decision Systems Engineering

Abstract

Objective—To interrogate hippocampal morphology and structural co-variance patterns in migraine patients and to investigate whether structural co-variance patterns relate to migraine disease characteristics.

Background—Migraine is associated with structural alterations in widespread cortical and subcortical regions associated with the sensory, cognitive, and affective components of pain processing. Recent studies have shown that migraine patients have differences in hippocampal structure and function relative to healthy control subjects, but whether hippocampal structure relates to disease characteristics including frequency of attacks, years lived with migraine and symptoms of allodynia remains unknown. Furthermore, this study investigated hippocampal volume co-variance patterns in migraineurs, an indirect measure of brain network connectivity. Here, we explore differences in hippocampal volume and structural co-variance patterns in migraine patients relative to healthy controls and examine whether these hippocampal measures relate to migraine disease burden.

Methods—This study included 61 migraine patients and 57 healthy control subjects (healthy controls: median age=34.0, IQR=19.0; migraine patients: median age=35.0, IQR=17.5; p=0.65). Regional brain volumes were automatically calculated using FreeSurfer version 5.3. Symptoms of allodynia were determined using the Allodynia Symptom Checklist 12 (ASC-12). Structural covariance patterns were interrogated using pairwise correlations and group differences in correlation strength were estimated using Euclidian distance. A stepwise regression was used to investigate the relationship between structural co-variance patterns with migraine burden.

Results—Migraine patients had less left hippocampal volume (healthy controls: left hippocampal volume = 4276.8mm^3, SD= 425.3mm^3, migraine patients: left hippocampal volume= 4089.5mm^3, SD= 453.9mm^3, p= 0.02) and less total (right plus left) hippocampal volume (healthy controls: total hippocampal volume= 8690.8mm^3, SD= 855.1mm^3; migraine patients: total hippocampal volume= 8341.8mm^3, SD=917.9mm^3; p= 0.03) compared to healthy controls. Migraineurs had stronger structural covariance between the hippocampi and cortico-limbic regions in the frontal lobe (inferior opercular gyrus), temporal lobe (planum temporale, amygdala), parietal lobe

Catherine D. Chong, Assistant Professor of Neurology, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, Arizona 85054, Phone: 480-342-4196, Fax: 480-342-3083, Chong.Catherine@mayo.edu.

Conflict of Interest: None declared.

(angular gyrus, precuneus,) and the cerebellar white matter. Results of a stepwise regression showed that hippocampal volumes and the interactions between hippocampal volumes with the volumes of other cortico-limbic regions associate with migraine-related allodynia but not with headache frequency or years lived with migraine.

Conclusion—Migraineurs have less hippocampal volume and stronger hippocampal-cortico-limbic connectivity compared to healthy controls. Hippocampal volumes and measures of hippocampal volume connectivity with other cortico-limbic network regions associate with symptoms of allodynia.

Keywords

allodynia; hippocampus; magnetic resonance imaging; Migraine; structural covariance

Introduction

Mounting evidence from structural and functional neuroimaging studies of migraine indicate alterations in a broad network of brain regions associated with pain processing, including several studies that have shown alterations in the hippocampus [1-4]. However, the relationship between the hippocampus with other brain regions involved in pain processing and the precise role of the hippocampus in the pathophysiology of migraine remain insufficiently understood. One way of interrogating intrinsic brain connectivity is to investigate how brain regions co-vary with one another in size, or in function [5, 6]. Morphological features of the brain (such as regional estimates of brain volume or cortical thickness) are known to co-vary with one another in size and are thought to reflect the underlying functional organization of networks [7]. In healthy control populations, structural co-variance patterns are known to relate to mood, cognitive performance, and environmental factors [8], but whether structural co-variance patterns are altered by migraine has yet to be determined. The hippocampus, an integral component of the limbic system, is perhaps best known for its importance in memory and learning. However, recent evidence from human neuroimaging studies has implicated the hippocampus in mediation of emotional components of pain [9] and in playing a critical role in the transition from acute to chronic pain [10]. The purpose of this study was to interrogate whether migraine was associated with aberrant hippocampal morphometry and to determine if hippocampal connectivity, measured via structural co-variance techniques, differed amongst individuals with migraine compared to healthy controls.

This study explored hippocampal morphology in migraine patients and healthy controls using magnetic resonance imaging (MRI) data. Specifically, this study explored alterations in inter-regional brain volume correlations with the left and right hippocampus in migraineurs relative to healthy controls and determined whether alterations in volume co-variance patterns were related to migraine-specific factors such as headache frequency, years lived with migraine, and symptoms of allodynia.

Methods

Subjects

A total of 118 individuals (61 migraine patients and 57 healthy controls) were included in this study. Participants were recruited from Mayo Clinic Arizona and Washington University School of Medicine in St. Louis. All subjects signed informed consent prior to being enrolled in this study. This study was approved by the local institutional review boards. All subjects were compensated for their time. Exclusion criteria for healthy controls and migraine patients included history of neurological disorder other than migraine. Migraine patients were diagnosed with episodic or chronic migraine using the diagnostic criteria established by the International Classification of Headache Disorders (ICHD-II) guidelines [11]. 52 patients were diagnosed with episodic migraine and 9 patients were diagnosed with chronic migraine, 27 migraine patients had aura and 34 migraine patients had migraine without aura. All migraine patients had migraine for a minimum of 3 years and none of the migraine patients were taking opioids or were taking migraine preventive medication. Migraine patients were included if they were headache-free for at least 48 hours prior to testing. Healthy controls were included in this study if they never had headaches or had occasional tension-type headaches with a frequency <3 days per month. Imaging and questionnaire data were collected from healthy controls and migraine patients during a single 2½-hour appointment. For migraine patients, headache frequency was calculated as the average number of headaches experienced over a 30-day month. This was determined as follows: Patients were asked on how many days per month (given a 30 day month) they had a headache of any severity and on how many days per month they were completely headache-free. Subjects were told that the number of headache days per month and the number of headache-free days per month had to total 30 days. The days per month that patients said that they had a headache of any severity were considered ‘headache days’.

Levels of depression and anxiety were determined for all subjects using the Beck Depression Inventory (BDI) and the State/Trait Anxiety Inventory (STAI, Form Y-1 and Form Y-2), respectively [12, 13] Symptoms of cutaneous allodynia were evaluated using the allodynia symptom checklist (ASC-12) [14]. Subject demographics were compared between migraineurs and healthy controls using a Mann-Whitney U test or Fisher's exact test, as appropriate. Potential relationships between hippocampal volume and measures of depression and anxiety were interrogated using a Pearson correlation analysis.

Structural and functional imaging data of a subset of subjects who were included in this study have been previously published [15-21]. This is the first study to interrogate hippocampal volume co-variance patterns in cohort of migraine patients and healthy controls.

Imaging Acquisition Parameters

All imaging was conducted using 3-Tesla Siemens (Erlangen, Germany) scanners at Mayo Clinic Arizona and at Washington University School of Medicine. Washington University (Siemens MAGNETOM Trio; Scanner I): T1-weighted images: repetition time (TR)=2400 ms; echo time (TE)=3.16 ms: flip angle=8 degrees, $1\times1\times1mm^3$ voxels. T2-weighed images:

TE=88ms, TR=6280ms, flip angle=120 degrees, 1×1×4mm^3 voxels. Mayo Clinic (Siemens MAGNETOM Skyra, Scanner II): T1-weighted images; TR=2400 ms; TE=3.06 ms; flip angle=8 degrees, 1×1×1.3mm^3 voxels. T2-weighted images: TE=84ms, TR=6800 ms, flip angle=150 degrees, 1.×1.×4mm^3 voxels. Imaging data at Washington University School of Medicine were collected over a period of 24 months (from 2010 to 2012) and imaging data at Mayo Clinic were collected over a period of 18 months (from 2013 to 2014). During the time of imaging data acquisition, no scanner updates were performed at either location. All T1 and T2-weighted images were reviewed and subject data were excluded if structural abnormalities were detected during a typical clinical interpretation of the images.

Structural Data Post-Processing

All T1-weighted data were post-processed using FreeSurfer, version 5.3 (http://surfer.nmr.mgh.harvard.edu/) on a single Macintosh workstation running OS X Lion 10.7.5 software so as to avoid image post-processing irregularities stemming from the use of multiple workstations [22]. The T1-weighted scans were segmented according to standard techniques [23-25] which include skull stripping [26], Talairach transformation, segmentation of subcortical grey and white matter structures [25, 27], intensity normalization [28], brain boundary delineation, automated topology correction and surface deformation and reconstruction [23, 24]. Volumetric parcellations of 35 cortical regions and segmentations of 35 subcortical areas were calculated for the right and left hemisphere separately. For each subject, regional estimates were visually interrogated for errors prior to including subject data for further analysis. Whole brain subcortical segmentations were automatically calculated using the Fischl atlas [16] and cortical surface brain gyri and sulci parcellations were based on the Destrieux atlas [29].

Regional cortical and subcortical brain estimates were extracted from FreesSurfer and exported to R Statistical Software [30] for further analysis using the *core, ppcor, psych, mass* and *relaimpo* packages.

Brain Structural Co-variance Analysis

Regional brain volume correlations with the right and the left hippocampus were interrogated for each group (migraine patients and healthy controls) and controlled for age, sex, and scanner variability. Using a data-driven approach, only regions that significantly ($p<$ 0.05) correlated with the right or left hippocampus in either the migraine patients or healthy controls were included in subsequent analyses. First, the structural volume correlations of 160 regions with the left and right hippocampus were calculated for healthy controls and migraine patients. This included a total of 160*2*2; 640 tests. $P = 0.05/640$ was used as the cutoff for significance for this part of the analysis. For example, if in either group area x did not co-vary in size with the right or left hippocampus, then this area was not included in further analyses. This method ensured that areas were not further interrogated if they had no relationship to either the right or left hippocampus. Results were corrected for multiple comparisons using a Bonferroni correction. The resultant list contained 24 region pairs (all including either the left or right hippocampus). Subject cohort differences in correlation strength were estimated using Euclidian distance calculations. A paired z-test between independent correlations was applied to determine which correlations were significantly

different between cohorts [31]. To interrogate whether differences in structural co-variance patterns between migraineurs and healthy controls were related to clinical parameters, linear regression models were generated for headache frequency, years lived with migraine, symptoms of allodynia, anxiety scores, and depression scores. A stepwise linear regression using the Akaike Information criterion (AIC) was used to generate the models. The AIC is a measure of fit of a model, penalized for complexity. For the same set of data, a model with a lower degree of complexity (fewer regressors) and better fit will have a better (lower) AIC than a model with greater complexity and worse fit.

The regression models investigating potential relationships between MRI data and clinical parameters included each of the regional volume pairs that had significantly different structural covariance between migraineurs and healthy controls. The strength of the structural covariance and the volume of each region were included in the regression models. The stepwise regression method that was used iterated through 7 additional models (including the initial full model) before the reported model. In order to limit the number of variables that were included in the regression model, only regions for which migraineurs showed significantly stronger co-variance with either right or the left hippocampus (regions shown in Table 2) were included in the regression model. The relative importance of each regressor was estimated using the *relaimpo* package of R Statistical Software, which estimates the contribution of each regressor as the average of its contribution over all possible orderings of regressors. For example, if the correlation between the volume of the right hippocampus and volume of region “x” was found to be different between migraineurs and control groups, then right hippocampal volume, volume of region “x”, and the right hippocampus and volume “x” interaction were included as potential predictors in the regression models. This is to allow the relationship between the clinical measures and structural co-variance features to be explored through the interaction effects.

Results

Demographics

Subject demographics are listed in Table 1. Subject groups were well-balanced with one another and there were no significant group differences for age (healthy controls: median age= 34.0, IQR= 19.0; migraine patients: median age= 35.0, IQR=17.5; p= 0.65), sex (healthy controls: 43 females and 14 males; migraine patients: 47 females and 14 males; p= 1.00), anxiety at the time of testing (healthy controls: median state anxiety= 24.0, IQR= 8.0; migraine patients: median state anxiety= 24.0, IQR= 8.0; p= 0.24), or general anxiety (healthy controls: median trait anxiety= 27.0, IQR= 10.5; migraine patients: median trait anxiety= 30.0, IQR= 10.0; p= 0.73). There was a significant difference in the depression raw scores between groups, (migraineurs: median depression raw scores= 3.0, IQR= 6.0; healthy controls: median depression raw scores= 1.0, IQR= 3.0; p= 0.03) however the median raw scores of both groups were in the average, non-depressed range. Two scanners were used to perform the MRIs. Thirty-one (54.3%) healthy controls and 34 (55.7%) migraineurs were imaged on scanner I, while the remainder of subjects were imaged on scanner II. There was no difference between the ratios of migraine patients and healthy controls that were imaged on scanner I versus scanner II (p= 0.99). Migraine patients had on average 6.0 headache

days per month (median=6.0; IQR= 6.0) and an average of 16.0 years with migraine (median=16.0; IQR=15.0).

Hippocampal Volume Differences Between Migraineurs and Healthy Controls and Associations with Clinical Features

There were significant differences in total hippocampal volume (left hippocampal volume plus right hippocampal volume) between migraineurs and healthy controls (healthy controls: total hippocampal volume= 8690.8mm^3, SD= 855.1mm^3; migraine patients: total hippocampal volume= 8341.8mm^3, SD=917.9mm^3; p= 0.03) and there were significant group differences in left hippocampal volume (healthy controls: left hippocampal volume = 4276.8mm^3, SD= 425.3mm^3, migraine patients: left hippocampal volume= 4089.5mm^3, SD= 453.9mm^3, p= 0.02). Right hippocampal volume was not significantly different between groups: (healthy controls: right hippocampal volume=4414.1mm^3, SD= 455.1mm^3, migraine patients: right hippocampal volume= 4252.3mm^3, SD= 497.5mm^3, p= 0.07). There were no differences in total grey matter volume between groups (p=0.14), indicating that group differences in hippocampal volume were not driven by overall group differences in total cortex volume.

There was not a significant correlation (p<0.05) between right, left, or total hippocampal volume and levels of depression (BDI) or levels of anxiety (state/trait). Hippocampal volume was significantly correlated with allodynia symptom severity scores (left hippocampus: r= -0.286, p=0.025; right hippocampus: r = -0.302, p=0.018). There were not significant correlations between left or right hippocampal volumes with years lived with migraine (left hippocampus: r= -0.097, p=0.455; right hippocampus: r = -0.086, p=0.510) or with migraine frequency (left hippocampus: r= 0.057, p=0.661; right hippocampus: r= 0.022, p=0.866).

Structural Co-variance Differences Between Migraineurs and Healthy Controls

Nine hippocampal volume correlations (two involving the left hippocampus and seven involving the right hippocampus) differed significantly between migraineurs and healthy controls. Migraine patients had significantly stronger structural covariance between the left and right hippocampus with the left inferior frontal opercular gyrus and the right precuneus (see Table 2). Additionally, migraine patients had stronger structural covariance of the right hippocampus with the left planum temporale, left angular gyrus, bilateral amygdala and the right cerebellar white matter. There were no regions were migraine patients showed weaker structural covariance between either the left or right hippocampus and other brain regions.

Associations Between Hippocampal Volumes and Hippocampal Volume Interactions with Allodynia

There were significant associations between allodynia symptom severity scores with regional volumes and the interactions between the regional volumes with hippocampal volumes (p=0.04) (only regions that had hippocampal volume correlations differing between migraineurs and healthy controls were included in this analysis). Specifically, region-to-region volume interactions that significantly related to severity of allodynia included right hippocampal volume with left inferior frontal gyrus, left planum temporale, and right amygdala. Single volumes that related to severity of allodynia included the following: left

inferior frontal gyrus, left planum temporale, right cerebellar white matter, left amygdala, left angular gyrus and right hippocampus. The final regression model for variance in allodynia symptom severity scores that was attributed to regional volumes and their interactions had a R-squared value of 33.0 %, (see Table 3).

There were no significant associations between structural co-variance patterns with headache frequency or years lived with migraine (p>0.05).

Discussion

Migraine is associated with structural and functional alterations of regions mediating the cognitive, affective, sensory components of pain. Although the limbic network is a key circuit for pain processing, the role of the hippocampus in migraine-specific pain is insufficiently understood. The hippocampus is known to be involved in memory and learning, yet more recent evidence from animal and human studies suggest that the hippocampus also plays a role in chronic pain conditions [32, 33]. The main findings of this study were that migraineurs had less left and less total (left and right) hippocampal volume relative to healthy controls. Additionally, migraine patients showed a strengthening of structural co-variance patterns, suggestive of stronger connectivity, between the hippocampi and cortico-limbic regions. Hippocampal volumes and the interaction between hippocampal volumes with other cortico-limbic brain regions correlated with the severity of allodynia symptoms.

Hippocampal volume

In this study, migraine patients had less left hippocampal volume and less total (left and right) hippocampal volume compared to healthy controls. Similar findings were shown in a previous study investigating hippocampal morphology in migraine. Specifically, Borsook and colleagues found less hippocampal volume in high-frequency episodic migraine patients who had on average 8-14 headache days per month relative to low-frequency migraine patients who had on average 1-2 headache days per month [4]. Liu and colleagues [1] reported that fluctuations of hippocampal volume were associated with the frequency of migraine attacks and less hippocampal volume has also been reported in patients with myofascial pain and fibromyalgia relative to healthy control cohorts [34, 35]. Morphological changes in the hippocampus were found in a recent meta-analysis of fibromyalgia patients [36]. Interestingly, Apkarian and colleagues [10] found that hippocampal volumes were smaller in patients who later progressed from acute to chronic back pain relative to patients who recovered from back pain, perhaps suggesting that smaller hippocampal volume is associated with a predisposition to developing chronic pain. Although some data suggest that the hippocampus is related to emotional components of pain [37] we did not find a relationship between hippocampal volume and measures of depression or anxiety. However, as the average levels of depression and anxiety for migraine patients in this study were within the normal non-depressed and non-anxious ranges, our data might have lacked sensitivity for detecting such relationships. Contrary to the current findings, several studies have found more hippocampal volume in migraine patients and in patients with chronic pain relative to control populations. Hubbard et al.[38] and Neeb et al. [39] reported more

hippocampal volume in migraine patients and more hippocampal volume was reported in a study that investigated the brain morphology in patients with burning mouth syndrome [40]. Results of a meta-analysis of chronic pain studies found the hippocampus to be the only region that had larger volumes in patients compared to controls [41]. The heterogeneity of results might be reflective of differences between studies related to sample sizes, patient populations and data analysis techniques, thus suggesting the need for future validation studies.

Cortico-limbic connections are altered in migraine

Compared to healthy control subjects, migraine patients had stronger correlations between bilateral hippocampal volumes with frontal (inferior opercular gyrus), temporal (planum temporale, amygdala), parietal regions (angular gyrus, precuneus,) and cerebellar regions involved in pain processing. Particularly, migraine patients showed stronger structural covariance between the left inferior opercular gyrus and the right precuneus with the left hippocampus and the right hippocampus.

Evidence from the migraine and chronic pain literature corroborates our findings of a strengthening or perhaps reorganization of limbic and cortico-limbic functional pain networks. Several migraine studies found increased functional connectivity amongst limbic regions. Mainero et al. showed that high-frequency migraineurs as compared to low–frequency migraineurs had stronger functional connectivity amongst anterior insula, temporal pole and hippocampus, perhaps indicating a strengthening of functional connectivity patterns with increasing headache frequency. Yu et al. [42], demonstrated that relative to episodic migraine patients, chronic migraine patients had stronger functional connectivity between bilateral amygdala areas and the bilateral inferior temporal gyri, and Liu et. al. [1] found that in migraine patients there was a positive association between right hippocampal volume and good 2-year headache outcome (≥50% reduction of headache frequency). Furthermore, in patients with persistent back pain, functional connectivity strength between the hippocampus and the medial prefrontal cortex correlated with pain persistence over time yielding evidence to the notion that this functional circuit might be involved in the transition from acute to chronic pain [43]. Additionally, in pediatric patients with complex regional pain syndrome, those patients with higher levels of pain-related fear had stronger functional connectivity between the left amygdala and the right hippocampus [44].

Strengthening of hippocampal-cerebellar covariance patterns in migraine

A number of neuroimaging studies have shown structural and functional alterations in cerebellar regions in migraineurs [45-47] as well as increased connectivity during nociception between the cerebellum and brainstem regions and between the cerebellum and thalamic regions [47]. In the current study, we found that structural covariance patterns between the right hippocampus and the right cerebellar white matter were strengthened in migraineurs. However, the precise explanation for why stronger cerebellar-hippocampus connectivity is associated with migraine remains unclear.

Allodynia relates to morphometry changes in the cortico-limbic pain network

In migraine patients, hippocampal volumes and interactions between hippocampal volumes with other cortico-limbic regions significantly related to allodynia symptom severity but did not relate to headache frequency or to years lived with migraine. These results suggest that altered hippocampal volumes and aberrant connectivity between the hippocampus and other cortico-limbic brain regions are related to migraine-associated allodynia but are not directly impacted by the cumulative effects of recurrent migraines. Similar findings were observed in a study investigating complex regional pain syndrome in which pain intensity, but not pain duration was related to left posterior hippocampus and left amygdala volumes [48].

Limitations

There are several limitations to our study: It is possible that presence or absence of migraine family history in our subject cohorts might have had an influence on our results. Future studies will be necessary to further identify how family history of migraine influences structural co-variance patterns in migraine patients and healthy controls. Migraine patients and healthy control subjects were imaged using two 3-Tesla Siemens Scanners. Although equal proportions of healthy controls and migraine patients were imaged on both scanners, and the use of multiple scanners was included as a covariate in the statistical models, there is still potential that the use of multiple scanners influenced study results. Lastly, due to sample-size limitations, there is potential that the results of the current study might not replicate to the migraine population at large. Future studies, using larger subject populations will be needed to validate the current results. Several imaging studies have found that structural co-variance patterns strongly converge with functional connectivity patterns, which might suggest that both reflect common brain architectural networks [5, 49, 50]. Future studies, that interrogate both- hippocampal structural and functional co-variance patterns will be needed to better understand commonalties and differences in the brain network architecture.

Conclusion

Relative to healthy controls, migraineurs have less left hippocampal and less total hippocampal volume. In migraineurs, there was stronger connectivity between hippocampal and cortico-limbic regions, which related to allodynia symptom severity, but not to headache frequency, or to years lived with migraine. These results might indicate that strengthening of the hippocampal-cortico-limbic network relates to the severity of migraine-associated allodynia symptoms.

Acknowledgments

We would like to thank the participants and project coordinators from both recruitment sites (Mayo Clinic Arizona and Washington University) for their time and dedication to this study.

Funding: This work was supported by the National Institutes of Health (NIH) grant NIH K23NS070891.

References

1. Liu HY, Chou KH, Lee PL, et al. Hippocampus and amygdala volume in relation to migraine frequency and prognosis. Cephalalgia. 2016
2. Schwedt TJ, Chong CD, Chiang CC, et al. Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. Cephalalgia. 2014; 34(12):947–58. [PubMed: 24627432]
3. Gao Q, Xu F, Jiang C, et al. Decreased functional connectivity density in pain-related brain regions of female migraine patients without aura. Brain Res. 2016; 1632:73–81. [PubMed: 26688226]
4. Maleki N, Becerra L, Brawn J, et al. Common hippocampal structural and functional changes in migraine. Brain Struct Funct. 2013; 218(4):903–12. [PubMed: 22760159]
5. Kelly C, Toro R, Di Martino A, et al. A convergent functional architecture of the insula emerges across imaging modalities. Neuroimage. 2012; 61(4):1129–42. [PubMed: 22440648]
6. Mechelli A, Friston KJ, Frackowiak RS, et al. Structural covariance in the human cortex. J Neurosci. 2005; 25(36):8303–10. [PubMed: 16148238]
7. Lo CY, He Y, Lin CP. Graph theoretical analysis of human brain structural networks. Rev Neurosci. 2011; 22(5):551–63. [PubMed: 21861783]
8. Alexander-Bloch A, Giedd JN, Bullmore E. Imaging structural co-variance between human brain regions. Nat Rev Neurosci. 2013; 14(5):322–36. [PubMed: 23531697]
9. Reicherts P, Wiemer J, Gerdes AB, et al. Anxious anticipation and pain: the influence of instructed vs conditioned threat on pain. Soc Cogn Affect Neurosci. 2016
10. Vachon-Presseau E, Tetreault P, Petre B, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain. 2016; 139(Pt 7):1958–70. [PubMed: 27190016]
11. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004; 24(Suppl 1):9–160. [PubMed: 14979299]
12. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996; 67(3):588–97. [PubMed: 8991972]
13. Spielberger, CD., Gorsuch, RL., Lushene, R., et al. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.
14. Lipton RB, Bigal Me Fau - Ashina S, Ashina S Fau - Burstein R, et al. Cutaneous allodynia in the migraine population. (1531-8249 (Electronic)).
15. Schwedt TJ, Berisha V, Chong CD. Temporal lobe cortical thickness correlations differentiate the migraine brain from the healthy brain. PLoS One. 2015; 10(2):e0116687. [PubMed: 25679805]
16. Schwedt TJ, Chong CD. Correlations between brain cortical thickness and cutaneous pain thresholds are atypical in adults with migraine. PLoS One. 2014; 9(6):e99791. [PubMed: 24932546]
17. Schwedt TJ, Chong CD, Chiang CC, et al. Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. Cephalalgia. 2014
18. Schwedt TJ, Chong CD, Wu T, et al. Accurate Classification of Chronic Migraine via Brain Magnetic Resonance Imaging. Headache. 2015; 55(6):762–77. [PubMed: 26084235]
19. Chong CD, Dodick DW, Schlaggar BL, et al. Atypical age-related cortical thinning in episodic migraine. Cephalalgia. 2014
20. Chong CD, Gaw N, Fu Y, et al. Migraine classification using magnetic resonance imaging resting-state functional connectivity data. Cephalalgia. 2016
21. Chong CD, Plasencia JD, Frakes DH, et al. Structural alterations of the brainstem in migraine. Neuroimage Clin. 2017; 13:223–227. [PubMed: 28003961]
22. Gronenschild EH, Habets P, Jacobs HI, et al. The effects of FreeSurfer version, workstation type, and Macintosh operating system version on anatomical volume and cortical thickness measurements. PLoS One. 2012; 7(6):e38234. [PubMed: 22675527]
23. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999; 9(2):179–94. [PubMed: 9931268]

24. Fischl B, Liu A, Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging. 2001; 20(1): 70–80. [PubMed: 11293693]
25. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33(3):341–55. [PubMed: 11832223]
26. Segonne F, Dale AM, Busa E, et al. A hybrid approach to the skull stripping problem in MRI. Neuroimage. 2004; 22(3):1060–75. [PubMed: 15219578]
27. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex. 2004; 14(1):11–22. [PubMed: 14654453]
28. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging. 1998; 17(1):87–97. [PubMed: 9617910]
29. Destrieux C, Fischl B, Dale A, et al. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage. 2010; 53(1):1–15. [PubMed: 20547229]
30. Team, RC. R: A language and envoronment for statistical computing. Vienna, Austria: 2013.
31. Sections of Psychiatry, Neurology, Study of Disease in Children, and Epidemiology, Joint Discussion No. 2: Discussion on the Mental Sequelæ of Encephalitis Lethargica. Proc R Soc Med. 1925; 18(Joint Discuss):17.
32. Mutso AA, Radzicki D, Baliki MN, et al. Abnormalities in hippocampal functioning with persistent pain. J Neurosci. 2012; 32(17):5747–56. [PubMed: 22539837]
33. Liu MG, Chen J. Roles of the hippocampal formation in pain information processing. Neurosci Bull. 2009; 25(5):237–66. [PubMed: 19784080]
34. Niddam DM, Lee SH, Su YT, et al. Brain structural changes in patients with chronic myofascial pain. Eur J Pain. 2017; 21(1):148–158. [PubMed: 27352085]
35. McCrae CS, O'Shea AM, Boissoneault J, et al. Fibromyalgia patients have reduced hippocampal volume compared with healthy controls. J Pain Res. 2015; 8:47–52. [PubMed: 25674013]
36. Shi H, Yuan C, Dai Z, et al. Gray matter abnormalities associated with fibromyalgia: A meta-analysis of voxel-based morphometric studies. Semin Arthritis Rheum. 2016; 46(3):330–337. [PubMed: 27989500]
37. Ploghaus A, Narain C, Beckmann CF, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci. 2001; 21(24):9896–903. [PubMed: 11739597]
38. Hubbard CS, Khan SA, Keaser ML, et al. Altered Brain Structure and Function Correlate with Disease Severity and Pain Catastrophizing in Migraine Patients. eNeuro. 2014; 1(1):e20.14. [PubMed: 25893216]
39. Neeb L, Bastian K, Villringer K, et al. Structural Gray Matter Alterations in Chronic Migraine: Implications for a Progressive Disease? Headache. 2017; 57(3):400–416. [PubMed: 28028808]
40. Khan SA, Keaser ML, Meiller TF, et al. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain. 2014; 155(8):1472–80. [PubMed: 24769366]
41. Smallwood RF, Laird AR, Ramage AE, et al. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain. 2013; 14(7):663–75. [PubMed: 23685185]
42. Chen Z, Chen X, Liu M, et al. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. J Headache Pain. 2017; 18(1):7. [PubMed: 28116559]
43. Mutso AA, Petre B, Huang L, et al. Reorganization of hippocampal functional connectivity with transition to chronic back pain. J Neurophysiol. 2014; 111(5):1065–76. [PubMed: 24335219]
44. Simons LE, Pielech M, Erpelding N, et al. The responsive amygdala: treatment-induced alterations in functional connectivity in pediatric complex regional pain syndrome. Pain. 2014; 155(9):1727–42. [PubMed: 24861582]
45. Moulton EA, Schmahmann JD, Becerra L, et al. The cerebellum and pain: passive integrator or active participator? Brain Res Rev. 2010; 65(1):14–27. [PubMed: 20553761]
46. Demir BT, Bayram NA, Ayturk Z, et al. Structural Changes in the Cerebrum, Cerebellum and Corpus Callosum in Migraine Patients. Clin Invest Med. 2016; 39(6):27495. [PubMed: 27917786]

47. Mehnert J, Schulte L, Timmann D, et al. Activity and connectivity of the cerebellum in trigeminal nociception. Neuroimage. 2017; 150:112–118. [PubMed: 28192274]

48. Barad MJ, Ueno T, Younger J, et al. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. J Pain. 2014; 15(2):197–203. [PubMed: 24212070]

49. Clos M, Rottschy C, Laird AR, et al. Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. Neuroimage. 2014; 99:269–80. [PubMed: 24844743]

50. Wang J, Yang Y, Fan L, et al. Convergent functional architecture of the superior parietal lobule unraveled with multimodal neuroimaging approaches. Hum Brain Mapp. 2015; 36(1):238–57. [PubMed: 25181023]

Table 1

Subject Characteristics for migraine patients and healthy controls.

	Migraine Patients (*n*=61)	**Healthy Controls (*n*=57)**	***p*-value**
Age (Median, IQR)	35.0 (17.5)	34.0 (19.0)	0.65
Sex (f/m)	47/14	43/14	1.00
STATE (Median, IQR)	24.0 (8.0)	24.0 (8.0)	0.24
TRAIT (Median, IQR)	30.0 (10.0)	27.0 (10.5)	0.73
BDI (Median, IQR)	3.0 (6.0)	1.0 (3.0)	0.03
ASC-12 with Headache (Median, IQR)	4.0 (6.0)	0.0 (0.0)	<0.001
Headache Frequency (Median, IQR)	6.0 (6.0)	n/a	n/a
Years with Migraine (Median, IQR)	16.0 (15.0)	n/a	n/a
Aura (yes/no)	27/34	n/a	n/a

f=female, m=male, State/Trait = State and Trait anxiety inventory; BDI= Beck Depression Inventory, Headache Frequency= number of days with headache per month; ASC-12=Allodynia Symptom Checklist measuring the sensation of pain experienced by non-painful skin stimulation during a headache; Years with Migraine=number of years lived with migraine; IQR=Interquartile Range

Table 2

Right and left hippocampal volume correlations that are stronger in migraine patients. Regions in bolded print indicate areas that show stronger connectivity to the left **and** to the right hippocampus.

R. Hippocampal volume correlations to:	***Regional brain volumes***	***Healthy Controls (r)***	***Migraine Patients (r)***	***p-value***
	l. inferior frontal gyrus (opercular part)	0.252	0.641	0.008
	r. amygdala	0.606	0.797	0.041
	l. amygdala	0.512	0.799	0.005
	r. precuneus	0.323	0.666	0.013
	l. planum temporale	0.304	0.625	0.027
	l. angular gyrus	0.351	0.634	0.043
	r. cerebellar white matter	0.358	0.651	0.033
L. Hippocampal volume correlations to:				
	l. inferior frontal gyrus (opercular part)	0.347	0.646	0.032
	r. precuneus	0.41	0.686	0.032

l=left; r=right. Brain regions are listed according to the Destrieux Atlas naming conventions. Planum Temporale=Temporal-parietal junction, r= strength of region-pair correlations for migraine patients and healthy controls.

Table 3

Volume interactions and single region volumes that significantly relate to severity of allodynia. R-squared describes the amount of variation explained by the model; the contribution of each term to the R-squared was calculated using the *relaimpo* package within R Statistical Software.

Two-volume Interactions	***% Allodynia Severity Variance Explained by Term***
l. planum temporale and r. hippocamus	5.3%
l. inferior frontal gyrus (opercular part) and r. hippocampus	3.7%
l. amygdala and r. hippocampus	2.5%
Single Volumes	
l. planum temporale	5.6%
r. cerebellar white matter	4.8%
l. inferior frontal gyrus (opercular part)	3.5%
l. angular gyrus	2.8%
r. hippocampus	2.6%
l. amygdala	2.2%
Total Allodynia Severity Variance Explained by Model (R-squared)	**33.0%**