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ORIGINAL ARTICLE

Altered structural brain network topology in chronic migraine

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Abstract
Despite its prevalence and high disease burden, the pathophysiological mechanisms underlying chronic migraine (CM) are not well understood. As CM is a complex disorder associated with a range of sensory, cognitive, and affective comorbidities, examining structural network disruption may provide additional insights into CM symptomology beyond studies of focal brain regions. Here, we compared structural interconnections in patients with CM ($n=52$) and healthy controls (HC) ($n=48$) using MRI measures of cortical thickness and subcortical volume combined with graph theoretical network analyses. The analysis focused on both local (nodal) and global measures of topology to examine network integration, efficiency, centrality, and segregation. Our results indicated that patients with CM had altered *global* network properties that were characterized as less integrated and efficient (lower global and local efficiency) and more highly segregated (higher transitivity). Patients also demonstrated aberrant *local* network topology that was less integrated (higher path length), less central (lower closeness centrality), less efficient (lower local efficiency) and less segregated (lower clustering). These network differences not only were most prominent in the limbic and insular cortices but also occurred in frontal, temporal, and brainstem regions, and occurred in the absence of group differences in focal brain regions. Taken together, examining structural correlations between brain areas may be a more sensitive means to detect altered brain structure and understand CM symptomology at the network level. These findings contribute to an increased understanding of structural connectivity in CM and provide a novel approach to potentially track and predict the progression of migraine disorders.
This study is registered on ClinicalTrials.gov (Identifier: NCT03304886).

Keywords Migraine · Structural MRI · Graph theory · Connectivity · Network topology · Morphometry

Introduction

Chronic migraine (CM) is a debilitating neurologic disorder affecting approximately 1–2% of the population worldwide (Natoli et al. 2010). Each month, individuals with CM experience at least 15 headache days with at least 8 being migraine days (Dodick et al. 2019). According to the International Classification of Headache Disorders-3 (IHS 2018), migraine is characterized by headache attacks that last 4–72 h, are unilateral in location, pulsating quality, accompanied by nausea and/or vomiting, and photophobia and phonophobia, among other features. Despite its prevalence and high disease burden, the pathophysiological mechanisms of CM are not fully understood. As migraine diagnoses are based on clinical history and exclusion of other headache disorders (Katsarava et al. 2012), there has been an increased interest in determining objective brain-based biomarkers using noninvasive magnetic resonance imaging (MRI) methods. Previous studies have assessed brain structure and function using MRI to provide insight into the neurobiological correlates of migraine; however, the majority of these studies have focused on episodic migraine, which is less severe with potentially different underlying pathophysiological mechanisms (Sprenger and Borsook 2012; Burstein et al. 2015; Chong et al. 2016; Chong et al. 2017a; Schulte and May 2016).

Recent studies have investigated cortical and/or subcortical brain structure in individuals with CM compared to

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healthy controls or patients with episodic migraine (EM) (Valfrè et al. 2008; Schwedt et al. 2015; Lai et al. 2016; Neeb et al. 2017; Coppola et al. 2017; Woldeamanuel et al. 2019). Objective measures based on brain structure are of practical use since these data can often be generated using conventional clinical MRI scans (Schwedt et al. 2015). The results of these studies have been mixed, with some providing evidence for altered gray matter in CM compared to control groups (Valfrè et al. 2008; Neeb et al. 2017), and others showing altered relationships between gray matter and clinical variables for patients with CM in the absence of group differences (Coppola et al. 2017; Woldeamanuel et al. 2019). As CM is a complex disorder associated with a range of clinical, sensory, cognitive, and affective symptoms (Aurora and Brin 2017; Coppola et al. 2017; Ferreira et al. 2018), examining structural network disruption may provide additional insights into topological patterns underlying CM symptomology beyond studies of focal brain regions.

There is now ample research showing that coordinated variations in structural brain morphology (e.g., cortical thickness and subcortical volume) differ across development and disease (Mechelli et al. 2005; Lerch et al. 2006; He et al. 2008; Bassett et al. 2008; Pereira et al. 2015; Watson et al. 2018; Wannan et al. 2019). Indeed, brain regions with highly correlated structure often comprise networks underlying behavioral and cognitive functions (Lerch et al. 2006). One framework that has been shown to be an ideal tool to examine networks of structural co-variance and offers an opportunity to understand integrative aspects of brain structure in individuals with migraine disorders is graph theory (Bullmore and Sporns 2009; Bressler and Menon 2010; Rubinov and Sporns 2010). Graph theory allows for the quantification of brain networks, represented by nodes (brain regions) and edges (connections) with a number of neurobiologically meaningful measures (Rubinov and Sporns 2010) and has recently been used to demonstrate both structural and functional connectivity alterations in individuals with EM (Liu et al. 2011, 2012, 2015; Zhang et al. 2017; Ren et al. 2019). In contrast to conventional studies of functional connectivity, connectivity as assessed by graph theory incorporates topological analysis, which combines algebraic topology and other tools from pure and applied mathematics to study the shape or architecture of complex networks (Anderson et al. 2018). Graph metrics can provide meaningful information about the organization of human brain networks in healthy and clinical populations based on how brain regions are connected at global and local levels to support efficient information segregation and integration, while mitigating energy and wiring costs (Watts and Strogatz 1998; Farahani et al. 2019).

In the current study, we compare structural interconnections in patients with CM and healthy controls (HC) using MRI measures of cortical thickness and subcortical volume combined with graph theoretical network analyses. Using this approach, differences between groups could be assessed in a data-driven manner, without restricting analyses to specific brain regions or networks. However, given the sensory (e.g., pain, photophobia, phonophobia, allodynia), cognitive (e.g., processing speed, attention), and affective (e.g., depression, anxiety) symptoms that are observed in CM (Goadsby et al. 2017), we hypothesized altered structural topology at the local level would primarily involve brain regions previously shown to be involved in pain and sensory perception, cognitive control, and negative affect in patients with CM compared to controls.

Methods

Participants

Individuals were recruited from the Stanford Headache Clinic and surrounding community and were enrolled in a larger ongoing study examining biomarkers of chronic daily headache. Participants were eligible for the current study if they were at least 18 years of age, met diagnostic criteria fulfilling the International Classification of Headache Disorders (ICHD)-3 for CM as determined by a headache specialist, or were controls without the presence of migraine or other headache diagnoses. Participants were excluded from the current study if they had MRI contraindications, elected not to participate in the MRI scanning session, and/or had severe neurologic or psychiatric comorbidities such as epilepsy, neurodegenerative disorders, or schizophrenia.

Participants completed extensive self-report questionnaires based on validated tools (Lipton et al. 2016) on demographics, including age and sex, and clinical details such as frequency of headache days, headache severity, and headache medication use over the past 3 months. In addition, participants with CM were asked about lifetime duration of migraine and length of time with CM. The Stanford University Institutional Review Board approved this study. Informed consent was obtained from all individual participants included in the study.

MRI acquisition

Neuroimaging data were acquired at Stanford University's Lucas Center on a 3T GE Healthcare Discovery MRI system fitted with an eight-channel phased array head coil. T1-weighted 3D axial FSPGR IRprep images were obtained ($0.9 \times 0.9 \times 1.0$ mm^3 voxels; matrix: 256×256; field of view:

33 cm; echo time: minimum (2 ms); repetition time: 5.9 ms; flip angle: 15°; inversion time: 400 ms).

MRI preprocessing

FreeSurfer software (version 6.0, https://surfer.nmr.mgh.harvard.edu/fswiki) was used to provide measures of brain cortical thickness and subcortical volume (Dale et al. 1999; Fischl et al. 1999; Fischl and Dale 2000). For each participant, non-brain tissues were removed and brains were aligned to Talairach space (Talairach and Tournoux 1988). Tissue types were classified into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Since the literature shows a potential role for subcortical structures in chronic migraine pathophysiology (Schulte and May 2017; Aurora and Brin 2017; Schulte et al. 2017), we included both GM cortical thickness and subcortical volume measures in our analyses, as done previously (Bassett et al. 2008; Pereira et al. 2015). Preprocessed scans were visually inspected at each step using the FreeView interface in FreeSurfer. Seven subcortical structures per hemisphere, including the hippocampus, amygdala, thalamus, putamen, nucleus accumbens, pallidum, and caudate nucleus, in addition to the brainstem were automatically segmented and labeled according to probabilistic maps derived from a manually labeled training set (Fischl et al. 2002). Following segmentation, volumes of these structures were automatically calculated. To determine cortical thickness, the GM/WM boundary was deformed outward towards the GM/CSF boundary and thickness was calculated as the distance between these tissue boundaries at every point along a tessellated surface (Fischl and Dale 2000). Cortical models were then registered to a spherical atlas to account for sulcal and gyral structure and parcellated according to the Desikan-Killiany atlas, which divided each hemisphere into 34 cortical regions of interest (Desikan et al. 2006). As such, a total of 83 brain regions [68 cortical, 14 subcortical, and 1 midline (brainstem)] were submitted for further graph analyses.

Network construction and analysis

The cortical thickness and subcortical volumes of the 83 brain regions were extracted and included as nodes in structural network topology analyses using BRAPH (Brain Analysis using Graph theory; http://braph.org) software (Mijalkov et al. 2017). Prior to network construction, cortical thickness and subcortical volume values were adjusted by age and sex using linear regression to remove their potential confounding effects. Although not a specific aim of the current study, group differences in adjusted cortical thickness and subcortical volume values were examined exploratorily. Each brain node was assigned to one of the seven communities corresponding to anatomical proximity/function: 1. frontal, 2. limbic, 3. parietal, 4. temporal, 5. insula, 6. occipital, and 7. subcortical as demonstrated in Fig. 1b. Edges or "connections" between nodes were computed as Pearson correlations, with negative correlations set to zero. As such, in this study, connection strength corresponded to the structural correlation between brain regions examined across each group. Network analyses were conducted on binary undirected graphs, while controlling for densities ranging from 5 to 40% in steps of 0.5, in range with previous studies assessing network topology using GM (Mijalkov et al. 2017; Kaplan et al. 2019; Wannan et al. 2019). Fixing the density, or the fraction of edges that will be connected, was the preferred way to threshold in the current study, as it allows for the comparison of network architecture while controlling for differences in number of edges between groups. Importantly, hypothesis testing of significance across a range of densities helps to overcome the challenge of selecting one specific threshold or density since there is currently no way to establish the best value (Mijalkov et al. 2017).

To assess differences between groups in network architecture, we examined local (nodal) and global measures of centrality (connections), segregation (densely interconnected groups allowing for specialized processing), and integration (the combining of specialized information from distributed brain regions) (Rubinov and Sporns 2010; Mijalkov et al. 2017). Specifically, local measures included degree, the total number of edges connected to a node; path length, the average distance from a node to all other nodes; closeness centrality, the inverse of the path length of a node; betweenness centrality, the fraction of all shortest paths in the graph that pass through a node; clustering coefficient, the fraction of triangles present around a node; global efficiency, the average of the inverse shortest path length from a node to all other nodes; and local efficiency, the global efficiency of a node calculated on the subgraph created by the node's neighbors (Rubinov and Sporns 2010; Mijalkov et al. 2017). With regard to global measures, which assess group differences in overall network architecture, degree, path length, global and local efficiency were also examined, in addition to modularity, the extent to which a graph can be divided into clearly separated communities; transitivity, the ratio of triangles and connected triples in the graph; and small-worldness, which combines high levels of local clustering among nodes of a network and short paths that globally link nodes of a network (Bullmore and Sporns 2009). While the selection of these precise graph measures is primarily exploratory, they represent some of the most commonly examined graph measures in network neuroscience and offer the opportunity to explore different aspects of structural brain organization.

Significant between-group differences on network measures were examined using non-parametric permutation tests with 1000 replications (He et al. 2008; Bassett et al. 2008; Mijalkov et al. 2017; Pereira et al. 2018)

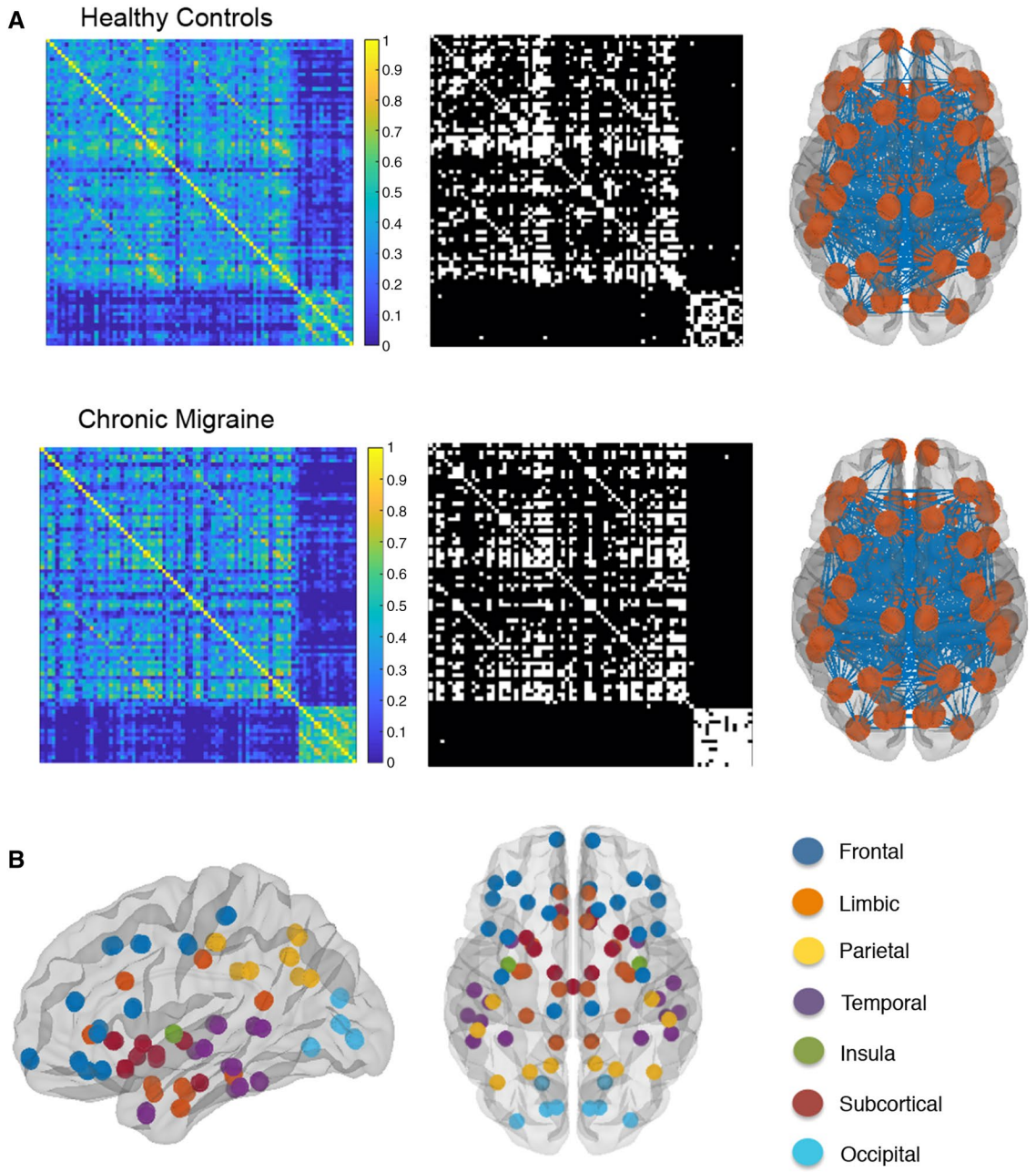

Fig. 1 **a** Structural brain networks in healthy controls and patients with chronic migraine. From left to right: weighted correlation matrices of 83 brain regions, binary correlation matrices fixed at 20% density, and corresponding brain graphs. **b** Brain nodes were assigned to one of seven communities corresponding to anatomical proximity/function: 1. frontal (dark blue), 2. limbic (orange), 3. parietal (yellow), 4. temporal (purple), 5. insula (green), 6. occipital (light blue), 7. subcortical (red). Communities are shown in sagittal (left) and axial (right) views

in combination with two-tailed *p* values based on 95% confidence intervals. Specifically, graph measures were first calculated separately for each the CM and control groups. Participants were then randomly reallocated to one of the groups and differences in graph measures at each network density were measured. This procedure was repeated 1000 times to build a distribution of between-group differences. As such, *p* values calculated the fraction of the difference distribution values that exceeded the difference value between the actual patient and control groups. To control for multiple comparisons, a false discovery rate (FDR) correction was applied across the 83

brain regions using the Benjamini–Hochberg procedure ($q < 0.05$) (Benjamini and Hochberg 1995).

Statistical analyses

Between-group differences in demographic variables were analyzed using Student's *T* test for normally distributed data, Mann–Whitney *U* test for non-normally distributed data, and Chi-squared test for categorical data using R software (https://www.r-project.org/).

Results

A total of 100 participants [48 HC (18 men, 30 women; mean age ± SD: 37.1 ± 14.2)] and 52 with CM (10 men, 42 women; mean age ± SD: 38.5 ± 12.8) were included in the study. Clinical details for the CM cohort are described in Table 1. The CM and control groups were cohort matched, so while age ($p = 0.61$) and sex ($\chi^2 = 3.3$, $p = 0.07$) were not statistically significant between groups, raw cortical thickness and subcortical volume values were adjusted by these variables to control for their potential influences. An exploratory analysis comparing adjusted cortical thickness and subcortical volumes between patients with CM and controls revealed no significant differences for any of the 83 brain regions included in the network analyses ($p > 0.05$, two-tailed).

The structural adjacency matrices and brain graphs of participants with CM and healthy controls are shown in Fig. 1a. Both groups demonstrated strong correlations between bilaterally homologous regions. Notably, the CM group had visibly higher correlations among subcortical structures, including those in the limbic system (e.g., amygdala, hippocampus) and brainstem as indicated by the brightness of the bottom right corners of the adjacency matrices.

Global network analyses

Compared to controls, patients with CM had significantly decreased global efficiency (p range < 0.025–0.049) and local efficiency (p range < 0.017–0.049) and increased transitivity (p range < 0.029–0.046) (Fig. 2). Transitivity, a global measure of segregation, showed the most widespread topological changes as it was increased across multiple densities. Global efficiency was found to be decreased primarily at lower densities (< 20%), while local efficiency was decreased at densities between 19 and 22%.

Local network analyses

Significant group differences (p range < 0.001–0.011, $q < 0.05$) in local (nodal) network topology are shown in

Table 1 Summary of CM clinical features

Clinical details	CM
Headache days/month for past 3 months	25.2 ± 5.9
Lifetime duration (years)[a]	23.6 ± 13.7
Headache intensity (0–10)[b]	6.1 ± 1.8
CM duration (years)	9.8 ± 9.3
Aura present (%)[b]	Yes: 26 (50)
	No: 25 (48)
Family history (first degree)[a]	Yes: 25 (48)
	No: 12 (23)
	Do not know: 12 (23)
Medication Overuse (%)	Yes: 29 (56)
	No: 21 (40)
	Data not available: 2 (4)
Use of prophylactic meds (%)[c]	Yes: 24 (46)
	None indicated: 19 (37)
Type	
Nutraceuticals	10 (42)
Anti-depressants	10 (42)
Botox	8 (33)
Anti-hypertensives	6 (25)
Anti-epileptics	6 (25)
Use of abortive meds (%)[c]	Yes: 40 (77)
	None indicated: 3 (6)
Type	
Non-opioid analgesics (including NSAIDS, Tylenol)	27 (68)
Triptans	20 (50)
Opiates	10 (25)
Combination analgesics	11 (28)
Benzodiazepines	3 (8)
Ergotamine	2 (5)
Other	7 (18)
Type unknown	2 (5)
Use of 'other treatments' (%)[c]	Yes: 34 (65)
	None indicated: 9 (17)
Use of supplements[c]	Yes: 17 (33)
	No: 26 (50)
Comorbidities (%)[c]	Yes: 17 (33)
	No: 7 (13)
	Data not available: 28 (54)
Diagnosis	
Depression	10 (59)
Anxiety	8 (47)
Posttraumatic stress disorder	5 (29)
Irritable bowel syndrome	5 (29)
High blood pressure	4 (24)
Other	11 (65)

Values represent mean ± standard deviation or number (percentage of total or amount of amount that indicated 'yes', where appropriate)

'Other treatments' include physical therapy, acupuncture, chiropractic, among others

NSAIDS nonsteroidal anti-inflammatory drugs

[a]Data not available for 3 participants

[b]Data not available for 1 participant

[c]Data not available for 9 participants

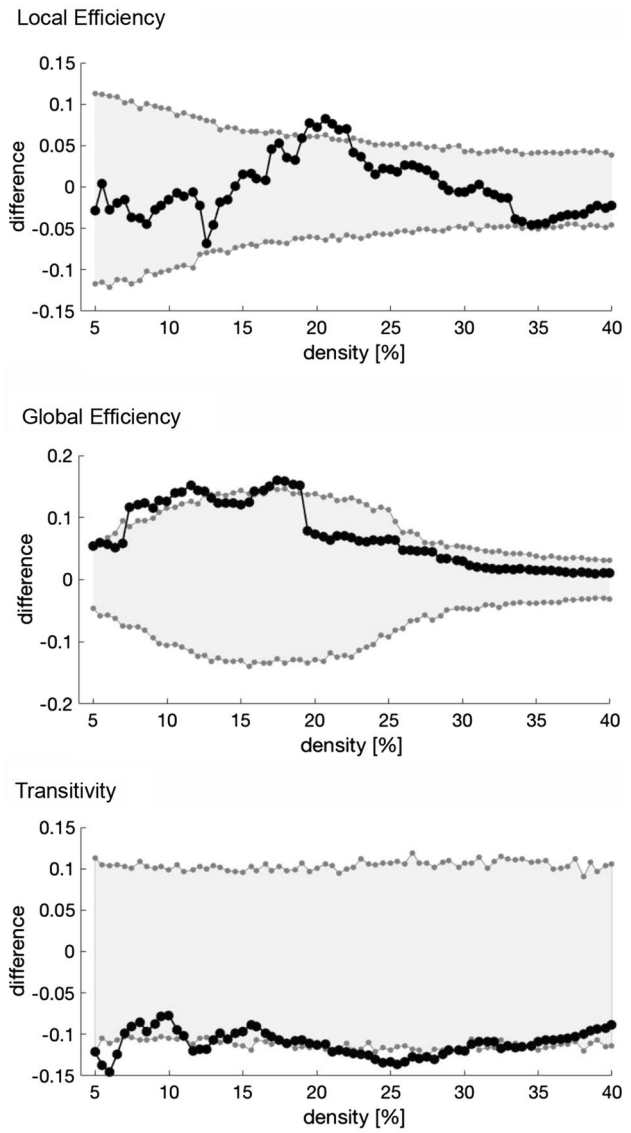

Fig. 2 Significant group differences in global measures. Compared to healthy controls, patients with CM had significantly lower local efficiency (top), global efficiency (middle), and higher transitivity. The black circles show differences between groups and the smaller gray circles show the upper and lower bounds of the 95% confidence intervals (shaded gray). Black circles falling outside of the confidence intervals indicate statistically significant values ($p < 0.05$)

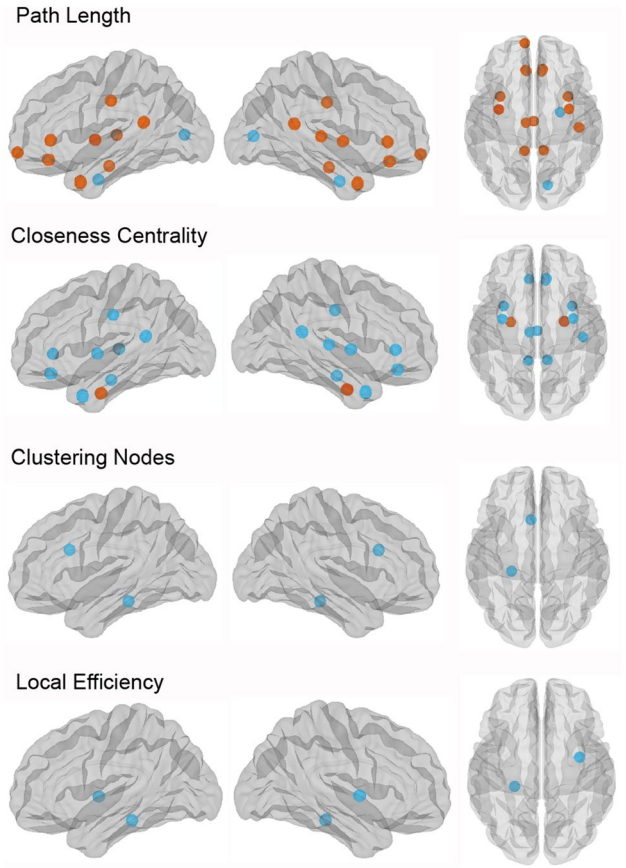

Fig. 3 Significant group differences in nodal measures ($p < 0.05$, FDR corrected). Orange nodes indicate larger values in CM compared to controls and blue nodes indicate larger values in controls compared to patients with CM

Fig. 3 and Table 2. Several group differences were observed in frontal, temporal, and brainstem regions. However, the most prominent group differences (bolded structures in Table 2) were located in the limbic and insular cortices. Local path length and closeness centrality demonstrated the most widespread topological differences with patients showing primarily greater path lengths compared to controls, and controls demonstrating primarily greater closeness centrality compared to patients. Additionally, significant differences in clustering were observed in two limbic structures—the left caudal anterior cingulate and the left parahippocampal gyrus, with controls showing higher clustering. Lastly, controls had higher local efficiency compared to patients in the left parahippocampal gyrus and the right insula.

Discussion

Using a graph theoretical approach to analyze GM network topology, we demonstrate both global and local differences in brain organization between individuals with CM and control participants. We found that patients with CM had disrupted global network properties characterized by lower global and local efficiency and higher transitivity. Additionally, patients with CM demonstrated aberrant local network topology characterized by higher path length, lower closeness centrality, lower clustering, and lower local efficiency. These differences not only were most prominent in the limbic and insular cortices but also occurred in frontal, temporal, and brainstem regions. Moreover, structural network topology differences occurred in the absence of group

Table 2 Brain regions contributing to group differences in nodal analyses

Local measure	Brain region	Community
Path Length (CM > HC)	**L insula**	**Insula**
	L PCC	Limbic
	L temporal pole	**Temporal**
	L rostral ACC	Limbic
	L isthmus	Limbic
	L frontal pole	Frontal
	L medial OFC	Frontal
	R isthmus	**Limbic**
	R rostral ACC	**Limbic**
	R insula	**Insula**
	R medial OFC	Frontal
	R temporal pole	Temporal
	R transverse temporal	Temporal
	Brainstem	**Subcortical**
Path Length (HC > CM)	R entorhinal	Limbic
	R pericalcarine	Occipital
Closeness Centrality (CM > HC)	**L entorhinal**	**Limbic**
	R entorhinal	**Limbic**
Closeness Centrality (HC > CM)	L insula	Insula
	L PCC	Limbic
	L isthmus	Limbic
	L medial OFC	Frontal
	R temporal pole	Temporal
	R insula	Insula
	R rostral ACC	Limbic
	R isthmus	Limbic
	R medial OFC	Frontal
	R temporal pole	Temporal
	R transverse temporal	Temporal
	Brainstem	Subcortical
Clustering (CM > HC)	None	
Clustering (HC > CM)	**L caudal ACC**	**Limbic**
	L parahippocampal	**Limbic**
Local Efficiency (CM > HC)	None	
Local Efficiency (HC > CM)	**L parahippocampal**	**Limbic**
	R insula	**Insula**

Brain regions from nodal analyses that significantly differed between patients with CM and controls ($p < 0.05$ (FDR corrected))

Bolded structures indicate regions of greatest difference as detected using BRAPH software

difference in adjusted cortical thickness and subcortical volumes. Compared to conventional structural MRI studies of individual brain regions, examining structural correlations between brain areas can reveal insight into potential pathophysiological mechanisms underlying CM at the network level and may provide a more sensitive means to assess altered brain structure. Taken together, our results suggest that aberrant structural brain networks in CM are more weakly integrated, less efficient, less central, and abnormally segregated (Rubinov and Sporns 2010).

Weaker network integration in CM

Global efficiency, local efficiency, and path length are measures of integration, which characterize the ease by which brain areas communicate and are based on the concept of a path (Rubinov and Sporns 2010). Shorter paths imply stronger integration, while longer paths imply weaker integration as information flow between brain regions has a longer distance to travel. These measures of integration can be assessed at both the global (average across nodes) and local (nodal) levels (Mijalkov et al. 2017). In the current study, the results of the global network analyses revealed significantly decreased global and local efficiency in patients with CM compared to controls. Disruptions in local efficiency primarily occurred in the left parahippocampal and right insular cortices as evidenced by nodal local efficiency, which are regions involved in multiple cognitive and affective processes (Aminoff et al. 2013). While characteristic (global) path length was not significantly different between groups, local path length was significantly higher in patients with CM in the insular, limbic, frontal, and temporal cortices and brainstem. As local path length describes the average shortest path length between a node and all other nodes (Cheng et al. 2012), higher path length often indicates less efficient communication between nodes and the rest of the brain.

In the current study, the majority of brain structures demonstrating higher path length, including the insula, frontal pole, cingulate cortex (rostral, posterior, isthmus), medial orbitofrontal cortex, temporal pole, and transverse temporal gyrus, have previously been shown to contribute to high (86%) classification accuracy of patients with CM versus healthy controls using cortical thickness measures (Schwedt et al. 2015). Building upon this important finding, the current study demonstrated weaker network integration of these brain regions in patients with CM. In addition to aiding in the classification of CM, the brain areas with longer path length have specifically been shown to be involved in the multi-dimensional experience of pain and its modulation (Davis and Moayedi 2013). In particular, these altered cortical networks contribute to affective-motivational [anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC)], attention/arousal (ACC, PFC), and pain/sensory modulation (brainstem) functions (Treede et al. 1999; Davis and Moayedi 2013; Chong et al. 2017b). Previous studies of migraine, including CM, have identified these brain areas as having abnormal structure and function (Rocca et al. 2006; Valfrè et al. 2008; Kim et al. 2008; Sprenger and Borsook 2012; Schwedt et al. 2013; Hubbard et al. 2014; Chong et al.

2017b; Neeb et al. 2017; Messina et al. 2018), with some regions (e.g., medial PFC) showing associations with pain catastrophization and clinical features including migraine duration, attack frequency, and migraine pain intensity (Hubbard et al. 2014). Other brain regions demonstrating higher path length, including the temporal pole and transverse temporal gyri participate in multisensory, including auditory, processing. Phonophobia is among the symptoms required for a diagnosis of migraine according to the ICHD-3, and longer paths to the transverse temporal gyri may reflect less efficient auditory processing/modulation. The temporal pole is involved in multisensory integration of auditory, visual, olfactory, and somatosensory information (Schwedt et al. 2015), and aberrant network topology involving this brain region may be related to sensory sensitivity during migraine attacks and/or in triggering migraine attacks (Moulton et al. 2011).

The brain regions demonstrating higher nodal path length in the current study have also been shown to be involved in descending pain modulation via cognitive and affective processes (Wiech and Tracey 2009). Specifically, cognitive (e.g., attention, expectation) and affective (e.g., contextual anxiety, anger) states can influence how pain is perceived; negative mood, for example, is commonly associated with increased pain perception (Wiech and Tracey 2009). Importantly, many of the regions demonstrating weaker network integration in the current study are part of the limbic system, including the ACC, insula, and parahippocampal cortex. The limbic system plays a role in negative emotional response and is important for encoding emotional and motivational aspects of pain (Bushnell et al. 2013). Recent evidence suggests a role for the limbic system particularly in CM. In a recent study examining endogenous μ-opioid neurotransmission using positron emission tomography, it was determined that patients with CM have increased μ-opioid neurotransmission during persistence and worsening of an ongoing migraine attack and with pain sensitivity (thermal allodynia), particularly in the limbic system (amygdala and parahippocampal cortex), compared to patients with episodic migraine (Jassar et al. 2019).

The modulation of auditory, visual, and somatosensory perceptions can also occur by attention and emotion. Frontal, limbic, and insular cortices can exert a top–down influence on nociceptive signals via connections to the brainstem (e.g., periaqueductal gray, rostral ventromedial medulla). In a recent study by Coppola and group (Coppola et al. 2019), it was shown that compared to healthy controls, patients with CM had weaker functional connectivity at rest, between two major cognitive networks—the dorsal attention system and the executive control network. Interestingly, the authors also demonstrated that the higher the severity of headache, the higher the strength of the dorsal attention system connectivity and the lower the strength of the central executive network. As both of these networks are involved in higher-order cognitive functions, aberrant top–down influences may specifically contribute to the modulation of headache severity in patients with CM. While the precise means by which weaker network integration in the current study relates to pain and/or sensory modulation via cognition and/or negative affect is speculative, future studies may aim to elucidate these relationships by focusing on structural brain interconnections and symptoms common to migraine including allodynia, photophobia, and phonophobia, among others.

Corroborating these findings of lower network integration in CM, the majority of brain regions with longer path length also had lower closeness centrality; a related measure described as the inverse of the average shortest path length from one node to all other nodes in the network (Sporns et al. 2007; Rubinov and Sporns 2010). Measures of centrality are rooted in the idea that central nodes participate in many short paths within a network; so in the current study, lower centrality can be indicative of lower efficiency of networks involving the brainstem, limbic, insular, frontal, and temporal cortices in CM (Sporns et al. 2007).

Of interest, patients with CM demonstrated significantly shorter path lengths in two brain regions: the right entorhinal cortex and the right pericalcarine gyrus. The entorhinal cortex is part of the limbic system and previously contributed to the high classification accuracy of patients with CM versus controls as discussed above (Schwedt et al. 2015). The entorhinal cortex has been shown to play a role in pain amplification related to anxiety and anticipation (Ploghaus et al. 2001; Tracey and Mantyh 2007). As shorter path lengths can be indicative of greater ease of communication between a given region and the rest of the brain, the shorter path length of the entorhinal cortex may reflect enhanced communication of anxiety and anticipation of migraine attacks and/or the pain associated with them. Importantly, the entorhinal cortex also demonstrated higher closeness centrality in patients with CM, supporting this finding. Shorter path lengths of the pericalcarine gyrus of the visual cortex may potentially explain symptoms of aura in our CM cohort as half of the patients indicated they have this symptom. This finding could also be related to symptoms of photophobia in CM, which is part of the migraine diagnostic criteria. Future studies may elect to compare CM patients with and without aura to better understand these relationships.

Altered network segregation in CM

Clustering and transitivity are two measures that can provide insight into the brain's tendency to segregate into relatively independent neighborhoods or communities. Network segregation is important as it allows for specialized processing within brain regions that are densely connected (Rubinov and Sporns 2010). While transitivity is a variant

of clustering, reflecting connectivity of a given region to its neighbors, it differs from clustering because it is not impacted by nodes of less importance (i.e., those with lower degree) (Rubinov and Sporns 2010). In the current study, patients with CM had increased transitivity globally across a number of densities. Increased transitivity is often associated with greater functional specialization and describes a greater tendency for nodes to form numerous strongly connected communities (Ingalhalikar et al. 2014). In the case of CM, increased transitivity suggests that network regions are more highly connected within communities, but as no group differences in modularity were observed, global inter-community connectivity likely did not differ from healthy controls. Interestingly, local clustering was significantly greater in healthy controls compared to patients with CM in two limbic regions: the left caudal ACC and the left parahippocampal gyrus. As such, these brain regions had high connectivity with neighboring brain regions and low connectivity with distant brain regions. Higher clustering coefficients represent a network's resilience against random node damage and can be considered an estimate of robustness (Stam and Reijneveld 2007; Hashmi et al. 2014). The caudal ACC is one of the most frequently activated brain regions in functional neuroimaging studies of pain (Davis and Moayedi 2013) and the parahippocampal gyrus has previously been implicated in the stress model of chronic pain, which shows a relationship between prolonged stress and function of the hippocampal complex (Vachon-Presseau et al. 2013). Taken together, it is possible that disrupted network topology of these brain regions in patients with CM is related to sustained stress and persistent pain.

Study limitations

There are some important limitations that should be considered when interpreting the results of the current study. First, brain nodes were derived from the Desikan-Killiany atlas, which is commonly used to parcellate gray matter using FreeSurfer software. While the selection of this atlas allowed for the comparison of our results with previous studies of CM (e.g., (Schwedt et al. 2015)), future studies assessing network topology using finer parcellation schemes are warranted. Additionally, in the current study, connection strength corresponded to the structural correlations between gray matter regions. While these correlations can result from white matter tracts physically connecting brain regions or from connectivity based on correlations in functional data (Gong et al. 2012; Alexander-Bloch et al. 2013; Pereira et al. 2015), these measures were not directly assessed. Future studies may elect to combine imaging modalities to further describe network topology in patients with CM. Another limitation is that the majority of patients with CM were using medications at the time of this study. While the patients included in the current study represent a naturalistic cohort, the precise effects of these medications on brain structure were not directly assessed and could have impacted the findings. Lastly, correlations with clinical variables including levels of depression and anxiety were not assessed. This is because the approach we used for the assessment of network topology does not provide a network measure for each subject, just one for each group (Tijms et al. 2016; Pereira et al. 2018). It is well established that depression and anxiety are highly comorbid with migraine disorders. In fact, among patients with episodic migraine, depression is associated with an increased risk of developing CM (Ashina et al. 2012). The degree to which these affective measures (and/or other behavioral measures) are associated with alterations in network topology in CM can be the subject of future studies.

Conclusions

Here, we provide evidence for altered structural network topology in patients with CM compared to healthy controls using MRI measures of gray matter combined with graph theoretical network analysis. Our results suggest that aberrant structural brain networks in CM are more weakly integrated, less efficient, less central, and abnormally segregated. These differences were most prominent in the limbic and insular cortices but also spanned frontal, temporal, and brainstem regions. Compared to conventional structural MRI studies of individual brain regions, examining structural correlations between brain areas may be a more sensitive means to detect altered brain structure and can reveal insight into topological patterns underlying CM symptomology at the network level. In summary, our findings contribute to an increased understanding of structural connectivity in CM and provide a novel approach to potentially track and predict the progression of migraine disorders.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institu-

tional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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