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Spatial Heterogeneity of Cortical Excitability in Migraine Revealed by Multi-Frequency Neuromagnetic Signals

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Abstract

To investigate the spatial heterogeneity of cortical excitability in adolescents with migraine, magnetoencephalography (MEG) recordings at a sampling rate of 6000 Hz were obtained from 35 adolescents with an acute migraine and 35 age- and gender-matched healthy controls during an auditory-motor task. Neuromagnetic activation from low- to high-frequency ranges (5–1,000 Hz) was measured at both sensor and source levels. The heterogeneity of cortical excitability was quantified within each functional modality (auditory vs. motor) and hemispherical lateralization. MEG data showed that high-frequency, not low-frequency neuromagnetic signals, revealed heterogeneous cortical activation in migraine subjects as compared with controls ($p < 0.001$). The alteration of the heterogeneity of cortical excitability in migraine was independent of age and gender. The degree of the neuromagnetic heterogeneity of cortical activation was significantly correlated with headache frequency ($r=0.71$, $p < 0.005$). The alteration of cortical excitability in migraine is spatially heterogeneous and frequency dependent, which has not previously been

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Authorship

J.X.: was responsible for (1) drafting/revising the manuscript for content, (2) study concept and design; K.L. was responsible for (1) data recording and analysis; (2) revising the manuscript; X.D. was responsible for (1) revision the manuscript for content; (2) study design; B.K. was responsible for (1) data analysis; (2) revising the manuscript for content; H.F. was response for (1) data recording and analysis; (2) study design; D.F.R. was responsible for (1) study concept; (2) revising the manuscript for content; J.R.A. was responsible for (1) study design and recruiting subject; (2) revising manuscript; J.E.K. was responsible for (1) study design; (2) data interpretation; H.L.O. was responsible for (1) study concept; (2) data interpretation; M.A.K. was responsible for (1) study concept; (2) data interpretation; S.W.P. was responsible for (1) study concept and design; (2) revising the manuscript for content; A.D.H. was responsible for (1) study concept and design; (2) data interpretation and revising the manuscript for content.

Potential Conflicts of Interest

The authors have no conflicts of interest to declare.

reported. The finding may be critical for developing spatially targeted therapeutic strategies for normalizing cortical excitability with the purpose of reducing headache attacks.

Perspective—This article presents a new approach to quantitatively measuring the spatial heterogeneity of cortical excitability in adolescents with migraine using MEG signals in a frequency range of 5–1000 Hz. The characteristics of the location and degree of cortical excitability may be critical for spatially targeted treatment for migraine.

Keywords

Migraine; Cortical Excitability; Headache; High-Frequency Oscillations (HFOs); Magnetoencephalography (MEG)

Introduction

Migraines are characterized by variable frequency, severity, duration, and headache characteristics, and are associated with a variety of focal cortical dysfunctions¹⁶. Headache and associated neural dysfunctions in migraine may manifest during early childhood and pose challenging diagnostic dilemmas¹⁵. Migraine sufferers are typically hypersensitive to multiple stimuli including visual (photophobia), auditory (phonophobia), and sensory (cutaneous allodynia) stimuli during migraine attacks^{12, 17, 34}. Though it is well recognized that the clinical manifestation of migraines is heterogeneous^{9, 26, 30}, the neurophysiological mechanism underlying the heterogeneous clinical manifestation remains largely unknown.

Recent reports have shown that cyclical changes of cortical excitability play a key role in migraine attacks^{16, 36}. Magnetoencephalography (MEG), a relatively new clinical modality for noninvasive assessment of functional brain activation, has been used to find that there are significant neuromagnetic abnormalities in the motor cortex of childhood migraine sufferers^{13, 37}. There is evidence that the auditory cortex exhibits decreased activation in some childhood migraine sufferers²⁴. Reports from functional magnetic resonance imaging (fMRI)²¹ and transcranial magnetic stimulation (TMS)²⁹ also reveal that migraine subjects have impaired cortical excitability. Neurophysiological and neuroimaging reports have provided ambiguous findings regarding cortical excitability. There have been reports of both hyper- and hypo-excitability in a variety of brain areas including somatosensory, motor, and visual cortices^{6, 10, 27}, although the cerebral mechanisms underlying the conflicting findings are unclear.

The assessment of cortical excitability is typically performed in one functional modality (e.g. motor, somatosensory or auditory)^{9, 29, 32, 37}. Despite the fact that alteration of cortical excitability plays a pivotal role in migraine, to our knowledge, no study to date has simultaneously assessed the relative cortical excitability in multiple systems. Since the identification of underlying cortical dysfunction in migraine can lead to future identification of neurophysiological biomarkers for studying migraine¹⁰, it is necessary to determine if the alteration of cortical excitability in migraine is a heterogeneous or homogenous change.

The objective of the present study was to investigate the heterogeneity of cortex excitability in adolescents with migraine, using an optimized paradigm specifically focusing on auditory

and motor cortices. We hypothesized that the alterations of cortical excitability are heterogeneous across the auditory and motor systems. The major methodological improvement upon previous studies was the quantification of the heterogeneity of cortical excitability by measuring brain activation at source levels. The main scientific innovation was the analyses of brain activation in a high-frequency range (up to 1000 Hz) in migraine, with additional spatial, spectral power, and frequency descriptions, as compared to conventional measurement of brain waveforms. Understanding the heterogeneity of cortical excitability in migraine is important for better understanding the heterogeneous nature of clinical migraine symptoms, and may yield a neurophysiological phenotype of headaches for personalized treatment and prevention (i.e. MEG-guided normalization of cortical excitability using TMS).

Materials and methods

Subjects

Thirty-five subjects diagnosed with acute migraine (26 females, 9 males; mean age 15.2 years; standard deviation 1.6 years; age range 11–17 years) were recruited from the Headache Center at Cincinnati Children's Hospital Medical Center (CCHMC). Inclusion criteria were: (1) migraine with or without aura as defined in the International Classification of Headache Disorders, 3rd edition (beta version)¹⁴; (2) no other neurological disorder. Controls were recruited to match the migraine subjects for age and gender and met inclusion criteria of: (1) healthy without history of neurological disorder, headache or brain injury; (2) age-appropriate hearing, vision, and hand movement. Exclusion criteria for all participants were: (1) presence of an implant, such as cochlear implant devices, a pacemaker or neuro-stimulator, devices containing electrical circuitry, generating magnetic signals, or having other metal that could produce visible magnetic noise in the MEG data; (2) noticeable anxiety (e.g. expressing worry about the tests; noticeable physical trembling; or sweating), and/or inability to readily communicate with personnel operating the MEG equipment. The research protocol was reviewed and approved by the Institutional Review Board (IRB) at CCHMC. Informed consent, formally approved by IRB at CCHMC, was obtained from each subject prior to testing.

The migraine subjects were evaluated for eligibility by neurologists who specialized in headache medicine. The clinical characteristics of migraine subjects were preliminarily assessed with a questionnaire developed in previous studies¹⁹. The questionnaire included headache frequency, duration, severity, and information about prophylactic and acute medication²⁰. If migraine subjects met the criteria of the present study, a researcher would then perform a more in-depth screening process and obtain IRB consent forms. MEG data from the migraine subjects were recorded during their headache attacks (or during episodes). Recordings were performed prior to initiation of treatment for patients who were referred to the Acute Headache Unit at CCHMC for treatment of an acute headache (from February 1st, 2009 to March 1st, 2015). The clinical characteristics of the subjects are shown in Table 1. All the subjects diagnosed with acute migraine who completed the MEG tests during their headache attack were also asked back for second MEG visit. Twenty-one of the 35 subjects with migraine were able to return for a follow-up MEG appointment.

Auditory-motor paradigm

Similarly to previous reports^{22, 35}, subjects were instructed to press a response button immediately after the presentation of a 500 Hz square wave tone. Subjects were instructed to use the index finger that was ipsilateral to the ear that the tone was played in, while keeping other body parts still with eyes open and fixed to a target on the screen in front of them during the tests (see Fig. 1). A trigger from the response button was sent to the MEG system for each button press. The stimuli consisted of 200 trials of tones, 100 trials per ear, which were presented randomly through plastic tubes and earphones. Stimulus presentation and response recording were accomplished with BrainX software, which was based on DirectX (Microsoft Corporation, Redmond, WA, USA)^{22, 35}.

MEG recording

The MEG signals were recorded in a magnetically shielded room (Vacuum-Schmelze, Hanau, Germany) using a whole head CTF 275-Channel MEG system (VSM MedTech Systems Inc., Coquitlam, BC, Canada) in the MEG Center at CCHMC. Before data acquisition began, electromagnetic coils were attached to the nasion, and to the left and right pre-auricular points of each subject. These three coils were subsequently activated at different frequencies for measuring participants' head positions relative to the MEG sensors. The sampling rate of the MEG recordings was 6000 Hz. An acquisition window was set to 3000 milliseconds (ms) per trial, with 2000 ms pre-trigger. Data were recorded with a noise cancellation of third order gradients. Subjects were asked to remain still. If head movement during a recording was beyond 5 mm, that dataset was indicated as “bad” and an additional recording was performed.

Magnetic resonance imaging (MRI) scan

Three-dimensional (3D) MRI was obtained using a 3T Philips Achieva scanner (Philips Healthcare, 3000 Minuteman Road, Andover, MA). Three fiducial marks were placed in identical locations to the positions of the three coils used in the MEG recordings, with the aid of digital photographs to allow for an accurate co-registration of the two data sets. Similarly to our previous reports³⁷, all anatomical landmarks were made identifiable in the MRIs.

Sensor level analysis

To analyze time-locked neuromagnetic responses, conventional averaging was applied to waveform data^{13, 24, 35}. To analyze phase-locked neuromagnetic oscillations (not necessarily time-locked), MEG waveforms were transformed to spectrograms, as described in detail in previous reports^{38, 39}. The spectral characteristics of MEG data were analyzed with spectrograms computed using the Morlet continuous wavelet algorithm with 600 frequency bins up to 1000 Hz (1 kHz) from time-series data³⁸. To measure neuromagnetic spectral power elicited by sound and finger movements, accumulated spectrograms from 100 trials for left or right tone or finger movement were computed separately. To quantify the neuromagnetic spectral power, we computed “global spectral power” by calculating the sum of the spectral power from all sensors over the target frequency ranges of 5–100 Hz and

100–1000 Hz. The details of the mathematical algorithms have been described in previous reports^{38, 39}.

To facilitate the measurements, we used a newly developed software package, MEG Processor, which automatically measured the mean and peak value for each frequency of the 600 bins for all MEG sensors^{38, 39}. This approach was ideal because the entire calculation was completed objectively by an optimized workflow^{24, 25}. The time window for quantifying spectral power at sensor levels was 0–200 ms for the frequency ranges of interest (5–100 Hz and 100–1000 Hz) for both auditory and movement elicited activation. To ensure that our results were comparable with previous reports³⁷ using different frequency resolution, all spectral power presented in this study was normalized by frequency bins. In comparison to previous reports³⁷, one methodological improvement in this study was the removal of the spectral baseline by subtracting the spectrograms computed with pre-trigger recording from auditory or motor response spectrograms for each subject (see Fig.1).

Source level analysis

Neuromagnetic sources were localized with volumetric source imaging^{38, 39}. The new method scanned each coordinate voxel^{24, 25}. In order to capture the dynamic spatiotemporal activity in the brain, we applied a sliding window to the source estimation. Multiple local spheres were used for computing the magnetic forward solution. A custom-designed program, MEG Processor, was used to localize magnetic sources^{23, 25}. According to a previous study³⁵, along with the observation of spectral contour maps in the present study that showed dominant activation around the primary motor and auditory regions, the time window and frequency ranges for source estimation were selected as 0–200 ms for signals in the two frequency ranges of 5–100 Hz and 100–1000 Hz. The highest frequency was governed by the Nyquist sampling theorem as well as floating data point error during computation³⁸.

Quantification of the heterogeneity of cortical excitability

To quantitatively measure the heterogeneity of cortical excitability, we developed a set of equations (See the following Equation 1 and 2 for examples).

$$AL- MR=abs(AL- MR) \quad (1)$$

$$AR- ML=abs(AR- ML) \quad (2)$$

In the equations, *A* represents auditory activation; *M* represents motor activation; *L* indicates left stimulation, and *R* indicates right stimulation. The combination of *AL* indicates auditory activation evoked/elicited by left stimulation while the combination of *MR* indicates motor activation evoked/elicited by right stimulation. *Abs* above indicates absolute value. By using two neural systems (auditory vs. motor) and two hemispheres (left vs. right), we were able to obtain six parameters with equal number of equations: *AR-AL*, *AR-MR*, *AR-ML*, *AL-MR*, *AL-ML* and *MR-ML*. For example, by using Equation 1, we could obtain an *AL-MR* value. An *AL-MR* value represents the differences between auditory activation elicited by left

sound stimulation and motor activation elicited by right finger tapping. In the present study, we used the same equation in the analyses of the MEG waveform amplitude, spectral power and source strength.

Statistical analysis

MEG measurements were statistically analyzed with pair-wise comparisons (*Student t*-test) and multiple analyses of variance (ANOVA). The fixed factors were group (migraine and control groups) and age (categorized by quartiles within the 11–17 range). The dependent variables were waveform amplitude, spectral power and source strength. The odds ratio of activity in brain areas among the migraine and control groups was analyzed with Fisher's exact tests. The correlation between headache frequency/severity and MEG parameters (waveform amplitude, spectral power, and source strength) were analyzed with the Spearman correlation. Significance was accepted at the level of $p < 0.05$ for one test. For multiple comparisons, a Bonferroni multiple comparison correction was applied. If multiple tests were to be taken into account then the significance threshold for any one of these tests were reduced from 0.05 to 0.025 (two parameters) or 0.008 (six parameters).

Results

Clinical characteristics

As shown in Table 1, 26 out of the 35 migraine subjects in the present study were female (26/35, 74%). Thirty out of the 35 migraine subjects had moderate to severe headache (30/35, 86%). Twenty-eight out of 35 migraine subjects had bilateral headache attacks (28/35, 80%). Eight of the 35 migraine subjects had aura (8/35, 23%), the other 27 migraine subjects did not have aura (27/35, 77%). Fourteen of the 35 migraine subjects had not used any preventive drug therapy (14/35, 40%), the other 21 migraine subjects used preventive drugs before MEG recordings (see Table 1 for details). The time between the medication intake and the MEG recording in the 21 migraine subjects was 34.2 ± 14.1 hours.

Waveform amplitude

MEG waveforms recorded from the 35 migraine subjects and controls showed at least one response (deflection) in the bilateral auditory cortices following auditory stimulation and at least one response in the contralateral motor cortex during finger tapping. As the first waveform peak (i.e. auditory M100, motor M1) was the most consistent neurophysiological response among the two groups of subjects, the quantification of waveforms focused on the first peak following either auditory stimulation or motor finger tapping. Fig.2 shows waveforms from a migraine subject and a control. Fig.3 shows the results of the group comparisons of the MEG measurements in both migraine subjects and controls. An ANOVA with repeated measures revealed that migraine significantly affected the level of the neuromagnetic difference between the auditory and motor activation in the left or right hemisphere, independent of age and gender ($p < 0.005$). The results suggested that cortical activation in the auditory and motor cortices in migraine was heterogeneous as compared with controls. In other words, the levels of the alteration of cortical excitability in migraine were heterogeneous, occurring predominantly in either auditory or motor cortex.

Spectral power

5–100 Hz—The spectrograms in the 5–100 Hz range revealed that migraine subjects had focal increased spectral power in 0–200 ms. Fig. 4 shows spectrograms in 5–100 Hz from a migraine subject and a control. Fig. 5 shows the results of group comparisons of the measurements of sensor-level spectral power in 5–100 Hz from all migraine and control subjects. An ANOVA with repeated measures revealed that migraine significantly affected the level of the neuromagnetic difference between the auditory and motor activation in the left or right hemisphere, independent of age and gender ($p < 0.005$). The results of spectral power in 5–100 Hz suggested that cortical activation in the auditory and motor cortices in migraine was heterogeneous as compared with controls.

100–1000 Hz—The spectrograms in the 100–1000 Hz range revealed that migraine subjects had increased spectral power in 0–200 ms. Fig. 6 shows spectrograms in 100–1000 Hz from a migraine subject and a control. Fig. 7 shows the results of group comparisons of the measurements of sensor-level spectral powers in 100–1000 Hz from all migraine and control subjects. An ANOVA with repeated measures revealed that migraine significantly affected the level of the neuromagnetic difference between the auditory and motor activation in the left or right hemisphere, independent of age and gender ($p < 0.0025$). The results of spectral power in 100–1000 Hz suggested that cortical activation in auditory and motor cortices in migraine was heterogeneous as compared with controls.

Source strength

5–100 Hz—MEG source analyses revealed that auditory activation in the occipital region was identified in 12 migraine subjects (12/35, 34%) but not in any controls. In addition, we noted that ipsilateral motor cortex activation was found in migraine subjects (9/35) but not in controls. Compared with controls, migraine subjects had significantly higher odds of activation in the occipital region following auditory stimulation ($p < 0.01$) and ipsilateral motor cortex during finger tapping ($p < 0.01$).

Fig. 8 shows magnetic source imaging (MSI) in 5–100 Hz from a migraine subject and a control. Fig. 9 shows the results of group comparisons of the measurements of source strengths in 5–100 Hz from all migraine and control subjects. An ANOVA with repeated measures revealed that migraine significantly affected the level of the neuromagnetic difference between the auditory and motor activation, independent of age and gender ($p < 0.0025$). The results of source strength in 5–100 Hz suggested that cortical activation in the auditory and motor cortices in migraine was heterogeneous as compared with controls. In other words, the alteration of cortical excitability in migraine was spatially selective, which predominantly occurs in either auditory or motor cortex. Further analysis revealed that the level of the neuromagnetic difference between the auditory and motor activation in the same hemisphere was also significantly increased in migraine subjects as compared with controls. This observation suggests that the heterogeneity of cortical excitability had a hemispherical effect although predominant factor was from the auditory and motor systems. In other words, different neural systems (auditory vs. motor) and different hemispheres (left vs. right) resulted in the heterogeneity of cortical excitability in migraine.

100–1000 Hz—MEG source analyses revealed that the auditory activation in the occipital region was identified in some migraine subjects (13/35, 37%) but not controls. In addition, activation in ipsilateral motor cortex was found in migraine subjects (12/35, 34%) but not in controls. Compared with controls, migraine subjects had significantly higher odds of activation in occipital region following auditory stimulation ($p < 0.01$) and ipsilateral motor cortex during finger tapping ($p < 0.01$).

Fig.10 shows MSI in 100–1000 Hz from a migraine subject and a control. Fig. 11 shows the results of group comparisons of the measurements of source strengths in 100–1000 Hz from all migraine and control subjects. An ANOVA with repeated measures revealed that migraine significantly affected the level of the neuromagnetic difference between the auditory and motor activation, independent of age and gender ($p < 0.001$). The results of source strength in 100–1000 Hz suggested that the alteration of cortical excitability in the auditory and motor cortices in migraine was spatially selective, which was spatially heterogeneous as compared with controls. Even in the same hemisphere, the alteration of auditory and motor cortical excitability was spatially selective.

Neuromagnetic correlates of clinical manifestations

The analyses of waveform amplitude and clinical data revealed that there was correlation between frequency of headaches per month and the difference between auditory and motor activation in the left or right hemisphere (*AR-ML*: $r=0.43$, $p < 0.05$; *AL-MR*: $r=0.42$, $p < 0.05$). There were no significant correlations between other clinical manifestations and the measurements of waveform amplitude.

The analyses of spectral power in 5–100 Hz and clinical data revealed a significant correlation between the frequency of headaches per month and the difference between auditory and motor activation in the left or right hemisphere (*AR-ML*: $r=0.53$, $p < 0.05$; *AL-MR*: $r=0.52$, $p < 0.05$). There were no significant correlations between other clinical manifestations and the measurements of spectral power in 5–100 Hz.

The analyses of spectral power in 100–1000 Hz (0.1–1.0 kHz) and clinical data revealed that there was the correlation between frequency of headaches per month and the difference between auditory and motor activation in the left or right hemisphere (*AR-ML*: $r=0.53$, $p < 0.025$; *AL-MR*: $r=0.52$, $p < 0.025$). There were no significant correlations between other clinical manifestation and the measurements of spectral power in 100–1000 Hz.

The analyses of source strength in 5–100 Hz and clinical data revealed that there was correlation between frequency of headaches per month and the difference between auditory and motor activation in the left or right hemisphere (*AR-ML*: $r=0.61$, $p < 0.005$; *AL-MR*: $r=0.62$, $p < 0.005$). There were no significant correlations between other clinical manifestation and the measurements of source strength in 5–100 Hz.

The analyses of source strength in 100–1000 Hz (0.1–1.0 kHz) and clinical data revealed that there was correlation between frequency of headaches per month and the difference between auditory and motor activation in the left or right hemisphere (*AR-ML*: $r=0.64$, $p <$

0.005; *AL-MR*: $r=0.71$, $p < 0.005$). There were no significant correlations between other clinical manifestation and the measurements of source strength in 100–1000 Hz.

There were no significant differences between migraine subjects with aura and subjects without aura in terms of waveform amplitude/latency and spectral power at sensor levels. However, we observed that migraine subjects with auras had activation in the occipital region in 6 subjects (6/8, 75%), while migraine subjects without auras had activation in the occipital regions in 7 subjects (7/27, 26%). Compared with migraine subjects without aura, migraine subjects with aura had significantly higher odds of activation in 100–1000 Hz in the occipital region ($p < 0.02$) during the finger tapping task. We also noted that migraine subjects with aura were more likely to show activation in 100–1000 Hz the ipsilateral sensorimotor region (5/8, 63%) as compared with migraine subjects without aura (7/27, 26%). However, there was no statistical significance ($p = 0.06$) in terms of odds ratio. There was no significant difference between migraine subjects with aura and subjects without aura in terms of source strength.

There were no significant differences between migraine subjects, who were and who were not on preventive drug therapy in terms of waveform amplitude/latency and spectral power in 5–100 Hz or 100–1000 Hz. There was a numerical trend that preventive drug could minimize the level of the neuromagnetic difference between the auditory and motor activation in 5–100 Hz ($p = 0.063$) and 100–1000 Hz ($p = 0.054$), however, the statistical significance did not reach the acceptable criteria. There was no statistical difference between the two groups in terms of odds ratio of activation out of the primary motor cortex during the finger tapping tasks.

Neuromagnetic characteristics during no episode state

Of the 35 migraine subjects who had MEG tests during their headache attacks (ictal MEG), 21 subjects completed the second MEG recording. At the time of this second visit, 18 of the 21 subjects were not having headache attacks (interictal, headaches were well controlled), while the other 3 subjects were still having headache attacks (headaches were not well-controlled). There were no significant differences between the two groups of patients in terms of the second MEG measurements, probably due to limited number of subjects, who still had headache attacks in our follow-up MEG tests. Comparisons of MEG data from headache-free subjects and the controls showed that there were no significant differences between headache-free subjects and controls in terms of waveform latency/amplitude and spectral power ($p > 0.05$). However, comparisons of the second MEG measurements (interictal MEG) with the first MEG measurements (ictal MEG) from the same group of migraine subjects revealed that there were significant differences between the two MEG measurements in terms of latency and amplitude of MEG responses ($p < 0.01$), spectral power ($p < 0.005$) and source strength ($p < 0.002$). An ANOVA with repeated measures revealed that headache attacks significantly affected the level of the source strength difference between the auditory and motor activation in the left or right hemisphere, independent of age and gender ($p < 0.01$).

Discussion

Building on previous reports^{13, 38, 39}, the present study analyzed cortical excitability with waveform amplitude, spectral power, and source strength. We used the three methods in the present study because each method has its own strength. The measurement of waveform amplitude mainly reveals time-locked brain activation, while the assessment of spectral power in accumulated spectrograms mainly reveal phase-locked oscillatory activation³⁹. However, both waveform and spectral analyses are at sensor levels with limited information about the spatial location; therefore, source imaging was used to quantify the spatial heterogeneity³⁹.

The results of the present study provide new evidence that cortical excitability in migraine is significantly altered as compared with age- and gender-matched controls during adolescence. That is, typically cortical excitability is relatively consistent across the left and right hemisphere, as well as across motor and auditory modalities. However, in migraine, cortical excitability varies based on modality and hemisphere. The results also indicate that the measurements of source strength revealed more abnormalities than that of the conventional measurements of waveform amplitudes. One possible explanation is that the measurements of waveform amplitudes were at the sensor level, which might be significantly affected by noise (e.g. environmental and subject noise). On the other hand, the measurements of source strength spatially filter any noise. We postulate that analyses of source strength had fewer confounding factors than those of the analyses of waveform amplitude. Therefore, analyses of MEG signals at source levels may be the optimal direction for the future MEG study of migraine.

One of the main findings of the present study was the significant elevation of the difference between auditory and motor activation in migraine versus controls. The abnormalities were prominent in the source data. The neuromagnetic difference between the auditory and motor activation suggests that the relative activation in the auditory and motor cortices was increased as compared with controls. This finding is important because it may explain some conflicting results in previous reports¹⁰. Specifically, many previous reports based on TMS^{6, 8} and transcranial direct current stimulation (tDCS)^{1, 33} have revealed alteration of cortical excitability in migraine. However, it remains unclear if migraine is associated with hyper- or hypo-excitability in the cortex¹⁰. According to our data, cortical excitability in migraine was due to heterogeneity; that is cortical hyper-excitability might be observed in one modality (e.g. motor), but not in another modality (e.g. auditory) in some subjects. Intracortical inhibitory and excitatory networks in the brain caused by the regional cortical excitability changes^{5, 11, 28}, may cause some brain areas to appear hyper- and hypo-excitable.

The study of high-frequency brain activation in migraine is still a new area³⁷ as many previous reports focused on aberrant low-frequency brain activation in migraine⁴. The present study provides evidence that the relative activation of high-frequency signals in migraine sufferers is significantly altered as compared with controls. This observation is significant because recent advances in neuroscience suggest that synaptic specialization turns interneuron networks into gamma frequency oscillators³. Specifically, the origin of

high-frequency signals may be generated by GABAergic cortical interneurons. Consequently, the hyper-activation may indicate an imbalance among excitatory and inhibitory cortical circuits that could predispose migraineurs to periodic headache attacks^{3, 31}. Of note, high-frequency oscillatory patterns may shed a light on pathogenesis of migraine.

The frequency-dependent changes of auditory and motor activation in migraine as compared with controls have not previously been reported. Though both low- and high-frequency signals could reveal the same abnormalities, the p-values from high-frequency signals appeared to be higher than that of the low-frequency signals in at least one parameter. To our knowledge, this is the first study of relative changes of the auditory and motor systems in both low- and high-frequency ranges in adolescents with migraine using MEG. Though the cerebral mechanisms underlying the differences remain unclear, increased relative activation might be a result of cortical hyperexcitability^{6, 7, 31}. It seems that different frequencies may favor different types of connections and/or different spatio-temporal levels of information integration. Specifically, low-frequency signals might involve many groups of neurons over large brain areas, whereas high-frequency signals with short-duration time windows might be better suited to local, neighboring cortico-cortical interactions. Since cortical excitability is the target of new treatments⁴, the finding of frequency-dependent cortical alterations in migraine might be useful in the selection of spatial targets for treatment. MEG study of cortical excitability may play an important role in developing better and more effective therapeutic interventions for migraine in the future¹⁸.

The finding of enhanced neuromagnetic differences among auditory and motor activation in the left and right hemispheres is relevant to clinical management of pediatric migraine for several reasons. First of all, the enhanced neuromagnetic differences among auditory and motor activation in the left and right hemispheres are new biomarkers for assessing the abnormality of cortical excitability, which is different from the conventional measurements of waveforms showing neural responses to auditory or motor tasks^{13, 24}. MEG is a noninvasive technology that can be used to quantify these neuromagnetic differences non-invasively and safely. Secondly, the enhanced neuromagnetic differences among auditory and motor activation in the left and right hemispheres indicate that the alteration of cortical excitability in migraine is heterogeneous or focal. Consequently, clinical treatment, such as TMS, may selectively target the affected region or functional neural network, which may lead to better clinical outcomes¹⁶. In other words, this finding may be very important in developing spatially targeted therapeutic interventions for migraine in the future^{8, 30}. Third, the measurements of auditory and motor functions in the pediatric populations imply that the evaluation of a single functional modality (e.g. auditory or motor) may not be appropriate for evaluating migraine biomarkers. Instead, it is important and feasible to assess multiple functional modalities (e.g. auditory, motor, etc.) to pinpoint the impaired neural system. Consequently, we may use the MEG data to neurophysiologically phenotype migraines so as to better diagnose and treat migraine patients, who typically have heterogeneous clinical manifestations. Though it remains unclear why there are heterogeneous impairments in the auditory and motor system, the variation of neuromagnetic abnormalities among subjects may allow us to phenotype migraines, which may eventually lead us to more individualized prevention and treatment strategies and better clinical outcomes.

We noted that the difference between auditory and motor activation in the left or right hemisphere showed the most significant changes. One reasonable postulation is that the heterogeneity of cortical excitability resulted from different functional systems (auditory vs. motor) and different hemispheres (left vs. right). According our data, different functional systems play a major role in the heterogeneity of cortical excitability, because the difference between auditory and motor activation was consistently identified in waveform, spectral and source analyses. The increase of the difference between auditory and motor activation likely resulted from the selective elevation of cortical excitability in either auditory or motor cortex. Our results are consistent with previous reports². Aygul and colleagues have found that left-handedness and left-dominant eyes were not significantly correlated with migraine in women². In men, the incidence of left-handedness and left-eye dominance was significantly higher in migraine subjects than in controls². Since there were only 5 left-handed migraine subjects in the present study, the correlation between hemispherical lateralization and the MEG measurements is debatable. However, we consider the hemispherical variation support for the heterogeneity of cortical abnormalities in migraine.

No significant difference was observed in MEG measurements of those patients who were on preventive drug therapy versus who were not. This result might have been due to the fact that the time between medication intake and the MEG recordings was relatively long (34.2 ± 14.1 hours) in the present study. Consequently, the effect of medications on neuromagnetic activation might have already subsided. In addition, we consider that if a preventive drug normalized the cortical excitability for a patient, their diagnosis might have improved so greatly as to yield their ineligibility in the study. Therefore, we expect that patients that were still experiencing severe enough migraines likely benefited more modestly from preventative medication, as reflected by their MEG recordings. The neuromagnetic improvements from episode period (ictal) to no-episode period (interictal) recordings indicates that the elevated heterogeneity of cortical excitability during episodes can be decreased outside of headache attacks. There was no difference between migraine subjects and controls during the interictal period, which suggests that cortical excitability can return to normal in patients with migraine. These observations are consistent with previous reports³⁷.

The correlations between the elevations of the heterogeneity of cortical excitability and the frequency of headache attacks are intriguing. It seems that the variation of headache frequency is resulted from the heterogeneity of cortical excitability in various brain regions. We postulate that the heterogeneity of cortical excitability in migraine plays a key role in the heterogeneous nature of migraine clinical symptoms. It would be interesting to use neuromagnetic signatures of the heterogeneity of cortical activation to neurophysiological phenotype of headaches for personalized treatment and prevention in the future.

The present pilot study has some limitations. First, the low migraine sample size may make interpretation of results more difficult. For example, since only 8 of the subjects with migraine had aura (see Table 1), neuromagnetic difference between migraine with and without aura cannot be conclusively determined. Similarly, neuromagnetic difference between treatment controlled and treatment uncontrolled requires more subjects in our follow-up assessments. The present study provides evidence supporting increased cortical

excitability in migraine as compared with controls, but how these neural signatures of migraine differs from those of epilepsy remains unknown^{36, 37}. As the present study focused on the auditory and motor systems, the spatial information leading to emphasis on heterogeneity is limited to the two functional modalities. Therefore, it is necessary and important to increase the number of migraine subjects to generalize conclusions for all migraine patients in clinical practice in the future.

Conclusions

The results of the present study provide evidence that alteration of cortical excitability in the auditory and motor systems in migraine is heterogeneous and spatially selective. The heterogeneity of cortical excitability resulted from functional modalities (auditory vs. motor) and hemispherical lateralization (left vs. right). It is also frequency-dependent, which might be related to the modulating effects of local and global neural networks at different frequencies. The finding of significant correlations between degree of heterogeneity and clinical headache frequency suggests that MEG measurements of the heterogeneity of cortical excitability may play a key role in developing spatially targeted treatment for normalizing focal cortical excitability for reducing migraine headache attacks in the future.

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Figure 1. Sound-cue and finger tapping paradigm

A tone is sent to the participant's left or right ear in a randomized order. The subject is instructed to press a button on her/his left side when the tone is sent to the left ear, and press a button on her/his right side when the tone is sent to the right ear. Each tone and finger-tapping trial sends a unique signal (trigger) to the MEG system in real-time, and the MEG system will record and store the unique signal to the MEG dataset for analysis of auditory and movement-related neuromagnetic responses. The pre-trigger baseline is designed to record background brain activity and noise.

Figure 2. MEG waveforms

Typical responses from the most significant channels of MEG waveforms show neuromagnetic activation evoked by auditory stimulation (M100 and M200) and finger movement (M1 and M2). “Migraine” indicates the MEG data were recorded from a migraine subject, while “Normal” indicates the MEG data were recorded from a healthy control.

Figure 3. Group comparisons of MEG waveforms

“A” indicates auditory activation; “M” indicates motor activation; “R” indicates right stimulation; “L” indicates left stimulation. For example, “AR-ML” indicates the difference between auditory activation evoked by right sound stimulation and motor activation evoked by left finger tapping. Each bar represent the mean and standard error (SE) of the values. “Migraine” indicates the data recorded from migraine subjects, while “Normal” indicates the data recorded from healthy controls. The unit of amplitude is fT. “*” indicates $p < 0.005$.

Figure 4. Accumulated spectrograms in 5–100 Hz

The spectrograms show the spectral components between 5 and 30 Hz and between 70 and 80 Hz. Compared with the healthy control (“Normal”), the migraine subject (“Migraine”) shows elevated activation (green arrows). The X-axis (horizontal) indicates latency in millisecond (ms); the Y-axis (vertical) indicates frequency in Hz.

Figure 5. Group comparisons of spectral power in 5–100 Hz

“A” indicates auditory activation; “M” indicates motor activation; “R” indicates right stimulation; “L” indicates left stimulation. For example, “AR-ML” indicates the difference between auditory activation evoked by right sound stimulation and motor activation elicited left finger tapping. Each bar represent the mean and standard error (SE) of the values.

“Migraine” indicates that the data were recorded from migraine subjects, while “Normal” indicates that the data were recorded from healthy controls. The unit of spectral power is fT²/Hz. “*” indicates $p < 0.005$; “**” indicates $p < 0.0025$.

Figure 6. Accumulated spectrograms in 100–1000 Hz

The spectrograms show the spectral components in 100 to 200 Hz. Compared with healthy controls (“Normal”), migraine subjects (“Migraine”) shows elevated activation (green arrows). The X-axis (horizontal) indicates latency in millisecond (ms); the Y-axis (vertical) indicates frequency in Hz.

Figure 7. Group comparisons of spectral power in 100–1000 Hz

“A” indicates auditory activation; “M” indicates motor activation; “R” indicates right stimulation; “L” indicates left stimulation. For example, “AR-ML” indicates the difference between auditory activation evoked by right sound stimulation and motor activation evoked by left finger tapping. Each bar represent the mean and standard error (SE) of the values.

“Migraine” indicates that the data were recorded from migraine subjects, while “Normal” indicates that the data recorded from healthy controls. The unit of spectral power is fT^2/Hz .

“***” indicates $p < 0.0025$.

Figure 8. Magnetic source imaging (MSI) showing brain activation in 5–100 Hz

The data were recorded from a migraine subject (“Migraine”) and a healthy control (“Normal”). Neuromagnetic signals evoked by the sound-cue and finger-tapping task are localized to the primary auditory and motor cortices for the migraine subject and the control. However, neuromagnetic signals are also localized to the middle occipital and the ipsilateral sensorimotor cortices in the migraine subject (green arrows), but not in the healthy control. “R” indicates right auditory stimulation or right finger tapping; “L” indicates left auditory stimulation or left finger tapping.

Figure 9. Group comparisons of source strength in 5–100 Hz

“A” indicates auditory activation; “M” indicates motor activation; “R” indicates right stimulation; “L” indicates left stimulation. For example, “AR-ML” indicates the difference between auditory activation evoked by right sound stimulation and motor activation evoked by left finger tapping. Each bar represent the mean and standard error (SE) of the values. “Migraine” indicates that the data were recorded from migraine subjects, while “Normal” indicates that the data were recorded from healthy controls. Since the sources are statistically determined, there is no unit. “*” indicates $p < 0.005$; “***” indicates $p < 0.0025$.

Figure 10. Magnetic source imaging (MSI) showing brain activation in 100–1000 Hz

The data were recorded from a migraine subject (“Migraine”) and a healthy control (“Normal”). Activation in the middle occipital region and the ipsilateral sensorimotor cortex are only identified in the migraine subject (green arrows), but not in the healthy control. “R” indicates right auditory stimulation or right finger tapping; “L” indicates left auditory stimulation or left finger tapping.

Figure 11. Group comparisons of source strength in 100–1000 Hz

“A” indicates auditory activation; “M” indicates motor activation; “R” indicates right stimulation; “L” indicates left stimulation. For example, “AR-ML” indicates the difference between auditory activation evoked by right sound stimulation and motor activation evoked by left finger tapping. Each bar represent the mean and standard error (SE) of the values. “Migraine” indicates the data recorded from migraine subjects, while “Normal” indicates the data recorded from healthy controls. Since the sources are statistically determined, there is no unit. “*” indicates $p < 0.005$; “**” indicates $p < 0.0025$; “***” indicates $p < 0.001$.

Table 1

Clinical characteristics of migraine subjects

<i>Parameters</i>		<i>Migraine</i>	<i>Control</i>
Age (years) (mean $\pm$ SD) [#]		15.2 $\pm$ 1.6	15.3 $\pm$ 1.4
Gender (female/male)		26/9	26/9
Handedness (right/left)		30/5	30/5
Patients with aura (with/without)		(8/27)	N/A *
Frequency of headache per month (mean $\pm$ SD)		7.4 $\pm$ 3.7	N/A
Years of suffering from migraine (mean $\pm$ SD)		3.6 $\pm$ 2.9	N/A
Duration of headache (hours) (mean $\pm$ SD)		9.2 $\pm$ 4.8	N/A
Severity of headache (on scale: 0~10) (mean $\pm$ SD)		6.7 $\pm$ 2.6	N/A
Pain Type (Number of subjects; Multiple descriptions were allowed)	Throbbing	21	N/A
	Pressure	17	N/A
	Constant	9	N/A
	Sharp	6	N/A
	Squeezing	5	N/A
	Stabbing	4	N/A
	Others	3	N/A
Medications for preventive treatment before MEG tests (Number of subjects; Multiple drugs/nutraceuticals might be used)	None	14	N/A
	Amitriptyline	9	N/A
	Divalproate	2	N/A
	Levetiracetam	3	N/A
	Topiramate	10	N/A
	Vitamine D	4	N/A
	Coenzyme Q10	12	N/A
	Riboflavin	8	N/A

[#] SD: standard deviation;

* N/A: not available.