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Altered Cortical Activation in Adolescents With Acute Migraine: A Magnetoencephalography Study

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Abstract

To quantitatively assess cortical dysfunction in pediatric migraine, 31 adolescents with acute migraine and age- and gender-matched controls were studied using a magnetoencephalography (MEG) system at a sampling rate of 6,000 Hz. Neuromagnetic brain activation was elicited by a finger-tapping task. The spectral and spatial signatures of magnetoencephalography data in 5 to 2,884 Hz were analyzed using Morlet wavelet and beamformers. Compared with controls, 31 migraine subjects during their headache attack phases (ictal) showed significantly prolonged latencies of neuromagnetic activation in 5 to 30 Hz, increased spectral power in 100 to 200 Hz, and a higher likelihood of neuromagnetic activation in the supplementary motor area, the occipital and ipsilateral sensorimotor cortices, in 2,200 to 2,800 Hz. Of the 31 migraine subjects, 16 migraine subjects during their headache-free phases (interictal) showed that there were no significant differences between interictal and control MEG data except that interictal spectral power in 100 to 200 Hz was significantly decreased. The results demonstrated that migraine subjects had significantly aberrant ictal brain activation, which can normalize interictally. The spread of abnormal ictal brain activation in both low- and high-frequency ranges triggered by movements may play a key role in the cascade of migraine attacks.

Perspective—This is the first study focusing on the spectral and spatial signatures of cortical dysfunction in adolescents with migraine using MEG signals in a frequency range of 5 to 2,884 Hz. This analyzing aberrant brain activation may be important for developing new therapeutic interventions for migraine in the future.

Keywords

Migraine; magnetoencephalography (MEG); pediatric; high-frequency oscillations; wavelet

Migraine is characterized by ictal episodes of moderate to severe episodic pain, which is described subjectively by patients, leaving few clues for assessing cortical dysfunction

objectively.^{9,25,26} Migraine sufferers are typically hypersensitive to multiple stimuli, including visual (photophobia), auditory (phonophobia), and sensory (cutaneous allodynia) stimuli during migraine attacks.^{10,16,31} The pain of many migraine sufferers worsens with physical activity.^{12,13} The exact neurobiological mechanisms of migraine expression remain speculative. A recent electroencephalographic study of migraine has revealed that migraine manifestation is a key factor that interferes with the natural maturation process of cerebral information processing.²⁹ These neurophysiological findings indicate that migraine is associated with cortical dysfunction.^{13,14} It seems that the cerebral cortex serves a primary role in the cascade of migraine attacks.¹⁵

Magnetoencephalography (MEG), a relatively new clinical neuroimaging modality, is well suited for the study of cortical dysfunction in migraine because it can noninvasively detect and localize neuromagnetic signals associated with functional brain activation.^{3,4,11,24} Previous studies of migraine using MEG have shown that migraine is associated with abnormal cortical excitability and that medications normalizing cortical excitability can reduce the incidence of migraine attacks.^{2,3,5} Brain activity in a low-frequency range including large waves associated with cortical spreading depression is typically studied in migraine.^{1,3} The highest frequency of abnormal brain signals (high-frequency oscillations) identified in migraine is approximately 450 to 750 Hz in the somatosensory system.⁸ Recent invasive recordings have shown that a brain with epilepsy generates very-high-frequency activation near 2,632 Hz.^{28,32} The examination of high-frequency brain activation may have the potential to provide key information about cortical dysfunction in migraine.

The objective of this study was to investigate the neuromagnetic signatures of aberrant brain activation in both low- and very-high-frequency ranges in adolescents with migraine.^{22,33} Instead of using conventional bandpass filters, this study was designed to use Morlet wavelet to analyze MEG data.^{36–38} In comparison to previous MEG publications,²⁸ the main innovation of the present study was the systematic analyses of neuromagnetic spectrograms in the 3 frequency ranges of 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz. This approach avoided possible bias by subjectively selecting a frequency range.^{3,5,28,34} The central hypothesis was that neuromagnetic activation in the developing brain with migraine could be identified in multiple frequency ranges. This hypothesis was based on the observation that brain activation in 1 to 30 Hz and 65 to 150 Hz in migraine has been identified using MEG.³³ To our knowledge, this is the first MEG study focusing on aberrant brain activation in 5 to 2,884 Hz in pediatric migraine.

Methods

Subjects

Thirty-one subjects with an acute migraine (23 girls, 8 boys; mean age 15.1 years; standard deviation 1.6 years; age range, 12–17 years) were recruited from the Acute Headache Unit 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, 2nd Edition (ICHD-II)^{18,30} and 2) no other neurologic disorder. Controls were recruited to match the migraine subjects for age and gender and met inclusion criteria of 1) healthy without history of neurologic disorder, headache, or brain injury and 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 neurostimulator; devices containing electrical circuitry, generating magnetic signals; or having other metal that could produce visible magnetic noise in the MEG data and 2) noticeable anxiety (expressing worry about the tests with noticeable physical trembling or sweating) and/or inability to readily communicate with personnel operating the MEG equipment. The research protocol was reviewed by the institutional review board (IRB) at

CCHMC. An approval of the study by the IRB at CCHMC was granted. Informed consent, formally approved by the IRB at CCHMC, was obtained from each subject prior to testing.

The migraine subjects were prescreened by pediatric neurologists who specialized in headache. The clinical characteristics of migraine subjects were preliminarily assessed with a questionnaire developed in previous studies.¹⁷ The questionnaire included headache frequency, duration, severity, and information about prophylactic and acute medication.¹⁸ If migraine subjects met the criteria of the present study, a MEG researcher would then discuss the study with them. If a migraine subject showed interest in the study, IRB consent forms would be obtained. MEG data from the migraine subjects were recorded during their headache attacks and prior to initiation of treatment for patients who were referred to the Acute Headache Unit at CCHMC for treatment of an acute headache.

All the subjects with migraine who completed the MEG tests during an acute migraine attack phase (ictal) were also asked back for MEG tests during their headache-free phases (interictal). Sixteen of the 31 subjects with migraine (11 girls, 5 boys; mean age, 15.4 years; standard deviation 1.6 years; age range, 12–17 years) met our criteria and were also able to have MEG tests during their headache-free phases. In addition to the criteria described for ictal MEG tests, the following additional criteria were used for interictal MEG tests: 1) headache free for at least 1 week and 2) no medication taken for at least 3 days prior to the MEG tests.

Finger Tapping Paradigm

Participants performed a brisk finger tapping with either the right or the left index finger immediately after hearing a cue (500 Hz, square wave tone). Similar to that in previous reports,^{20,33} participants were instructed to press a response button with the index finger that was ipsilateral to the tone presented, while keeping other body parts still with eyes open and fixed to an arbitrary target during the tests. A trigger from the response button was sent to the MEG system for each finger tap. The stimuli consisted of 200 trials of square wave 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).^{20,33}

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, British Columbia, Canada) in the MEG Center at CCHMC. Before data acquisition began, electromagnetic coils were attached to the nasion and the left and right preauricular points of each subject. These 3 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 6,000 Hz. An acquisition window was set to 3,000 ms per trial, with 2,000 ms pretrigger. 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 data set was indicated as “bad” and an additional trial was recorded.

All subjects were introduced to the MEG facilities including the magnetic shielded room, MEG system, and the finger tapping box before they made their decision to take part in the study. Once subjects agreed to participate in the study, they would be asked to remove all possible metals from their bodies. After that, the subjects would be asked to lie on a specially designed MEG bed and a technologist would attach 3 fiducial coils to the nasion and the left and right preauricular points. Just before the MEG recordings, subjects would be

slid into the MEG dewar (or helmet) and their head position would be localized. For ictal migraine subjects, MEG data were recorded during the subjects' headache attacks. In the present study, 2 subjects dropped out as investigators were trying to slide them into the MEG dewar and 1 subject dropped out just before the MEG recording (the subject already put her head in the dewar). Thus, 3 subjects had to be excluded because they were not able to complete the task, probably because of the migraine attack (the 3 subjects were not included in the 31 migraine subjects in the present study).

Magnetic Resonance Imaging Scan

Three-dimensional magnetic resonance imaging (MRI) was obtained using a 3-T Philips Achieva scanner (Philips Healthcare, Andover, MA). Three fiducial marks were placed in identical locations to the positions of the 3 coils used in the MEG recordings with the aid of digital photographs to allow for an accurate coregistration of the 2 data sets. Subsequently, all anatomic landmarks were made identifiable in the MRIs. Pediatric brain templates developed by the Pediatric Neuroimaging Research Consortium³⁵ and MEG Center²⁰ at CCHMC were used for group comparison and visualization.

Time – Frequency Analysis

MEG waveforms were transformed to spectrograms, the time–frequency representations of MEG data.^{20,23} The spectral characteristics of MEG data were analyzed with spectrograms computed with Morlet continuous-wavelet algorithm using the following equation:

$$W(t, s) = c_{\sigma} \pi^{-\frac{1}{4}} e^{-\frac{1}{2}t^2} (e^{i\sigma t} - \kappa_{\sigma}).$$

Because frequency-temporal resolution changes with the sigma value, this study improved our time–frequency analysis method by dynamically changing the sigma value (the number of wave circles) according to frequency ranges.^{20,23} The present study did not include neuromagnetic signals below 5 Hz because the computation of low-frequency components needed more data points that might include premotor activation such as readiness magnetic fields. To quantify neuromagnetic signals in a wide frequency range with balanced temporal and frequency resolutions, the sigma values considered were 1, 3, and 6 for frequency ranges of 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz, respectively. With 600 frequency bins, the frequency resolution was 6.315, .667, .318 data points per Hz for the 3 frequency ranges, respectively. To measure magnetic spectral power elicited by finger movements, accumulated spectrograms from 100 trials for left or right finger movement were computed separately. The magnetic polarity was color-coded into the spectrogram, which was named as the polarity spectrogram (see Fig 1). The polarity spectrograms for all the MEG-measuring sensors were then displayed as contour maps for visualizing the spatial distribution of movement-elicited brain activation.

Sensor-Level Analysis

The spatial characteristics of movement-elicited neuromagnetic activation at sensor levels were estimated using polarity contour maps because polarity contour maps could demonstrate the source patterns. To quantify brain activation that was elicited by movement, the absolute spectral power was computed using the root-mean-square value without polarity information. To facilitate the measurements, we developed a toolbox that could automatically measure the mean and peak value for each frequency bin of all MEG sensors. We used this approach because the entire calculation could be done objectively by a computer. The automatic measurements of the peak value and mean values of spectrograms from all MEG sensors showed less interindividual variation among controls. The time

window for quantifying spectral power at sensor levels was 0–200 ms for all the 3 frequency ranges. The temporal resolution was 6 data points per millisecond for all of the 3 frequency ranges. The frequency bands for quantifying spectral power at sensor levels for the 3 frequency ranges were 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz, respectively. To ensure that our results were comparable with other reports using different frequency resolution, all spectral power presented in this study was normalized by frequency bins. Mathematically, the spectral power of a selected region was divided by the number of frequency bins, which was 600.

Source Level Analysis

Similar to our previous reports,^{38,39} wavelet-based beamformer was used in the source estimation. At each coordinate voxel in source imaging, our method computed coefficients W_θ using the unaveraged MEG data using the following equation:

$$W_\theta = \frac{C^{-1}B_\theta}{B_\theta^T C^{-1} B_\theta},$$

where C is the covariance matrix of the MEG data, and B is the forward solution for a unit current source at a location θ . To capture the dynamic spatiotemporal activity in the brain, we applied a sliding window in the source estimation. Multiple local spheres were used for magnetic forward computing. A customer-designed program, MEG Processor, was used to compute and visualize magnetic sources.^{21,23} According to a previous study³³ and the observation of spectral contour maps in the present study that showed dominant activation around the primary motor region, the time window and frequency ranges for source estimation was 0 to 200 ms for signals in the frequency ranges of 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz. The source analysis did not include neuromagnetic signals below 5 Hz because the computation of low-frequency spectral power required data points beyond the 0 to 200 ms time window. The highest frequency was governed by the Nyquist sampling theorem as well as floating data point error during the computing. The whole brain was scanned with a 3-mm resolution grid. In comparison to our previous reports,^{21,23} one methodological improvement in the present study was that the source power and goodness of fit were computed for each grid position (each voxel had 2 values). These approaches allowed us to compare neuromagnetic source power that could explain at least 85% of field variance with similar orientations.

Statistical Analysis

The comparisons of migraine subjects and controls for left and right finger movements were performed with Student t-tests. The effects of migraine on the latency, spectral power, and frequency range were analyzed using analyses of variance (ANOVAs). The fixed factor was the groups of migraine subjects versus controls. The dependent variables were latency, spectral power, and central frequency. The comparisons of ictal and interictal MEG data for left and right finger movements were performed with paired Student t-tests. The effects of headache attacks on the latency, spectral power, and frequency range were analyzed with ANOVA. The fixed factor was the groups of ictal versus interictal MEG data. The odds ratios of activity in brain areas other than the primary motor cortex among the ictal, interictal, and control groups were analyzed with Fisher exact tests. Because subjects performed left and right finger movements, the aforementioned statistical analyses were performed twice, once for right finger movement and once for left finger movement. $P < .05$ was considered significant.

Results

Clinical Characteristics

As shown in Table 1, 23 (74%) of the 31 migraine subjects in the present study were girls; 27 (87%) of the 31 migraine subjects had moderate to severe headache; and 25 (80%) of the 31 migraine subjects had bilateral headache attacks.

MEG Data Characteristics

Of the MEG data recorded from 31 migraine subjects and 31 controls, MEG data from 27 migraine subjects and 27 controls showed a focal increase of spectral power around the primary motor cortex in all 3 analysis frequency ranges of 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz (Figs 1–3, the same color-coding and orientations are used). MEG data recorded from 4 migraine subjects (4/31, 13%) showed visually identifiable artifacts without a focal increase of spectral power around the primary motor cortex. To avoid possible misinterpretation of the data, we focused on the MEG data recorded from the 27 migraine subjects (20 girls, 7 boys) and the 27 controls (20 girls, 7 boys).

Behavior Data

The mean and standard deviation of the response time from 27 migraine subjects and 27 controls were 392.35 ± 184.72 versus 386.73 ± 156.52 ms for left and 363.01 ± 173.81 versus 365.36 ± 145.42 ms for right finger movements, respectively. There was no statistical difference between the 2 groups ($P > .05$).

Low-Frequency Brain Activation (5–100 Hz)

The polarity spectrograms in 5 to 100 Hz showed that 27 migraine subjects (27/27, 100%) and 27 controls (27/27, 100%) had at least 2 neuromagnetic components of focal increase of brain activation (Fig 1).

As shown in Table 2, the latencies of the 2 neuromagnetic components were significantly delayed in migraine subjects as compared to controls during left and right finger movements. Fig 4 shows the mean and standard error of the latencies of the 2 components. There was no significant difference between migraine subjects and controls in terms of averaged spectral power and the range of central frequency in 5 to 100 Hz (see Table 2).

The contour maps revealed that neuromagnetic activation in the ipsilateral hemisphere was predominantly observed in migraine subjects but not in controls during finger movements (see Fig 1). MEG source analyses revealed that the activation in the ipsilateral hemisphere area was predominantly found in migraine subjects but not in controls during finger movements (see Table 2). Migraine subjects had significantly higher odds of activation in the ipsilateral sensorimotor areas ($P < .01$). Fig 5 shows an example of magnetic source imaging in 5 to 100 Hz.

High-Frequency Brain Activation (100–1,000 Hz)

The polarity spectrograms in 100 to 1,000 Hz showed oscillatory components in 27 migraine subjects and 27 controls. Fig 2 shows an example of spectrograms in this frequency range. Of note, measuring the latency and central frequency was technically difficult as the polarity changed rapidly in the spectrograms (see Fig 2 for example).

Analyses of spectral power showed that migraine subjects had stronger spectral power than the controls in 100 to 200 Hz during finger movements (see Table 2). The results of

ANOVAs revealed that the spectral power during right finger movement was significantly affected by migraine ($F = 12.31$, $df = 1, 26$, $P < .002$).

The contour maps revealed that diffuse activation around the supplementary motor area (SMA) was observed predominantly in migraine subjects but not in controls (Fig 2). MEG source analyses showed that activation in the contralateral SMA was found predominately in migraine subjects but not in controls (Table 2). Migraine subjects had significantly higher odds of activation in the SMA ($P < .01$). Fig 5 shows an example of magnetic source imaging in 100 to 200 Hz.

Very-High-Frequency Brain Activation (1,000–2,884 Hz)

The polarity spectrograms in 1,000 to 2,884 Hz showed at least 1 oscillatory component in 27 migraine subjects and 27 controls. Fig 3 shows an example of spectrograms in this frequency range. Of note, measuring the latency was technically difficult as the spectral components were connected (see Fig 3 for example).

There were no significant differences in averaged spectral power and central frequency in the 1,000 to 2,884 Hz range between migraine subjects and controls (Table 2).

The contour maps of MEG signals in 2,200 to 2,800 Hz showed that activation in the occipital areas and ipsilateral sensorimotor areas was predominantly found in migraine subjects but not in controls (see Fig 3 for example). MEG source analyses showed that migraine subjects had significantly higher odds of activation in the occipital and ipsilateral sensorimotor cortices (Table 2). Fig 5 shows an example of magnetic source imaging in 2,200 to 2,800 Hz.

Neuromagnetic Activation and Medications

Of the 27 migraine subjects, 12 subjects claimed that they had not used any medication for at least 1 week prior to the MEG study (“No-drug” group). Nineteen of the 27 migraine subjects reported that they had used medication or nutraceuticals prior to the MEG study (“Drug” group). The time between last medication taken and the MEG study was 34.5 ± 13.9 hours for the Drug group. Table 1 shows the detailed information about medication. Any medication used after the MEG tests was not analyzed because it was irrelevant to the present study. Of the 12 subjects in the No-drug group, 11 subjects showed activation in the contralateral primary motor cortex. Of the 19 subjects in the Drug group, 16 subjects showed activation in the contralateral primary motor cortex. Because MEG data in 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz in the analysis frequency ranges of 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz, respectively, were localized in the primary motor cortex contralateral to moving fingers, the comparisons between No-drug and Drug groups were then focused on 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz.

In the analysis frequency range of 5 to 100 Hz, there were no latency differences of the 2 spectral components in 5 to 30 Hz between No-drug and Drug groups (the first component elicited by the left finger: 40.5 ± 12.3 vs 42.0 ± 13.4 ms, $P > .05$; the first component elicited by the right finger: 37.8 ± 7.0 vs 39.1 ± 8.5 ms, $P > .05$; the second component elicited by the left finger: 121.6 ± 45.2 vs 119.5 ± 51.6 ms, $P > .05$; the second component elicited by the right finger: 117.3 ± 34.7 vs 124.0 ± 42.8 ms, $P > .05$, respectively).

In the analysis frequency range of 100 to 1,000 Hz, the spectral power in 100 to 200 Hz did not reveal significant differences between the No-drug and Drug groups in terms of spectral power during the left ($2.62 \pm .67$ vs $2.65 \pm .81$ fT/Hz, $P > .05$) and right (3.4 ± 2.1 vs 3.4 ± 1.2 fT/Hz, $P > .05$) finger movements. There was no statistical difference between the 2 groups in terms of odds of activation in the occipital cortex ($P > .05$).

In the analysis frequency range of 100 to 1,000 Hz, MEG data in 2,200 to 2,800 Hz did not reveal significant differences of spectral power between No-drug and Drug groups during the left ($1.28 \pm .79$ vs $1.25 \pm .83$ fT/Hz, $\pm > .05$) and right ($1.32 \pm .87$ vs $1.36 \pm .91$ fT/Hz, $P > .05$) finger movements. There were no significant differences in the odds of activation in the occipital and ipsilateral sensorimotor cortices between the 2 groups ($P > .05$).

Interictal Versus Ictal Neuromagnetic Changes

Of the 27 migraine subjects who had MEG tests during their headache attacks (ictal MEG), 16 subjects completed the MEG tests during their headache-free phases (interictal MEG). Interictal MEG data from 14 of the 16 migraine subjects showed clear neuromagnetic activation in the primary motor cortex contralateral to moving fingers in 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz in the analysis frequency ranges of 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz, respectively. The comparisons among interictal, ictal, and control groups were then focused on 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz.

In the analysis frequency range of 5 to 100 Hz, the latency of the first interictal component was significantly shorter than that of the ictal component during the left (26.8 ± 5.2 vs 39.8 ± 12.4 ms, $P < .001$) and right (25.7 ± 4.8 vs 38.9 ± 7.6 ms, $P < .001$) finger movements. However, there were no significant differences in the latencies between the interictal and control MEG data during the left (26.8 ± 5.2 vs 25.6 ± 4.8 ms, $P > .05$) and right (25.7 ± 4.8 vs 25.4 ± 4.7 ms, $P > .05$) finger movements. The comparison of spectral power in 5 to 30 Hz did not reveal statistical differences between the interictal and control groups during the left (3.5 ± 1.2 vs $3.4 \pm .8$ fT/Hz, $P > .05$) and right (3.3 ± 1.1 vs $3.2 \pm .7$ fT/Hz, $P > .05$) finger movements as well as the interictal and ictal groups during the left (3.5 ± 1.2 vs 3.9 ± 1.4 fT/Hz, $P > .05$) and right (3.3 ± 1.1 vs 3.7 ± 1.3 fT/Hz, $P > .05$) finger movements.

In the analysis frequency range of 100 to 1,000 Hz, the interictal spectral power was significantly lower than the ictal spectral power in 100 to 200 Hz during the left ($1.34 \pm .62$ vs $2.83 \pm .72$ fT/Hz, $P < .005$) and right ($1.18 \pm .58$ vs $3.09 \pm .94$ fT/Hz, $P < .002$) finger movements. Interestingly, the interictal spectral power in 100 to 200 Hz was also lower than that of controls during the left ($1.34 \pm .62$ vs $2.13 \pm .35$ fT/Hz, $P < .01$) and right ($1.18 \pm .58$ vs $2.09 \pm .41$ fT/Hz, $P < .05$) finger movements. Similar to ictal MEG data, measuring the latency in interictal MEG data in 100 to 1,000 Hz was technically difficult as the polarity changed rapidly in the spectrograms.

In the analysis frequency range of 1,000 to 2,884 Hz, there were no statistical differences between the interictal and ictal spectral power in 2,200 to 2,800 Hz during the left ($1.13 \pm .72$ vs $1.26 \pm .83$ fT/Hz, $P > .05$) and right ($1.16 \pm .74$ vs $1.34 \pm .95$ fT/Hz, $P > .05$) finger movements. There were no statistical differences between the interictal spectral power of migraine patients and that of controls during the left ($1.13 \pm .72$ vs $1.09 \pm .63$ fT/Hz, $P > .05$) and right ($1.16 \pm .74$ vs $1.18 \pm .57$ fT/Hz, $P > .05$) finger movements. Measuring the interictal latency in 1,000 to 2,884 Hz was technically difficult as the spectral components were connected.

Discussion

Building on previous reports,^{20,21,33} the present study investigated cortical dysfunction in adolescents with migraine using a finger tapping paradigm and a high-sampling-rate MEG system. Similar to that in previous reports,¹⁹ adolescents with migraine seemed to have shorter durations of headache and more bilateral headaches as compared to adults with migraine. There were no statistical differences in MEG measurements between the subgroups of migraine subjects (Drug and No-drug groups). This result might have been due to the time between last medications taken and the MEG recordings in the Drug group being

relatively long (~34.5 hours) in the present study. Consequently, the effect of medications on neuromagnetic activation might have already subsided because of the relatively long time.²²

From a methodological point of view, this study moved 1 step further by analyzing neuromagnetic signals above 1,000 Hz using wavelet and beamforming.^{20,33} The results have demonstrated that the development of MEG methods has made it possible to detect the spatial, spectral, frequency, and temporal signatures of aberrant cortical activation in migraine in multiple frequency ranges, including very-high-frequency brain activation.²³

The analyses of neuromagnetic signals in 5 to 100 Hz have demonstrated that the latency of spectral components in 5 to 30 Hz in migraine subjects was significantly delayed as compared to controls. This latency finding is consistent with previous reports using conventional measurements of waveform responses.³³ In comparison to the conventional measurements of waveforms, the measurements of spectrograms in the present study also provided frequency descriptions of the neuromagnetic components, which are novel.

The analyses of neuromagnetic spectrograms in 100 to 1,000 Hz have demonstrated that the neuromagnetic spectral power in 100 to 200 Hz in migraine subjects was significantly increased as compared to controls during finger movements. The increases of brain activation in 100 to 200 Hz may reflect the activation of the cortical-subcortical networks during the onset of discrete movements or may signal the direct modulation of outputs from the subthalamic nucleus to the basal ganglia, thereby facilitating movement execution.⁶ A significant increase of brain activation in the 100 to 200 Hz range suggests that the cortical excitability is altered in migraine. This finding is consistent with previous MEG studies.^{3,33} Functional MRI has also been used to investigate brain activation patterns in migraine subjects with a simple motor task; functional MRI results have shown that migraine subjects have greater activation in the primary motor cortex as compared with controls.²⁷ Worth noting, both the present study and previous publications support the notion of increased cortical excitability in the brain with migraine during headache attacks.

The analyses of spectrograms in 1,000 to 2,844 Hz have demonstrated that the location of brain activation in 2,200 to 2,800 Hz in children with migraine was significantly different from that of the controls. In comparison to controls, migraine subjects had a significantly higher likelihood of activation in the SMA and the occipital and ipsilateral sensorimotor cortices. There are reports showing that the brain generates signals around 2,632 Hz in the somatosensory cortex²⁸ and 2,500 Hz in the epileptic regions.³² However, those previous reports are based on invasive intracranial recordings and are limited to patients with intractable epilepsy who are surgical candidates.^{28,32} This is the first report showing very-high-frequency neuromagnetic signals (>1,000 Hz) in migraine subjects using noninvasive MEG. The spatial information revealed by very-high-frequency neuromagnetic signals in migraine subjects seems to be unique and cannot be obtained with the conventional low-frequency brain waves. The distinct spatial patterns suggest extended propagating activation of excitation rather than a local static source in the motor cortex. Because the MEG results were based on 100 trials, which were time-locked to finger tapping, we postulate that the aberrant activation in the widespread regions beyond the primary motor cortex was triggered by finger movements.

One of the most important findings is that MEG signals in the 5 to 100 Hz, 100 to 1,000 Hz, and 1,000 to 2,884 Hz could reveal different aspects of migraine-related abnormalities, such as response latency, spectral power, and brain regions, respectively. To our knowledge, this is the first study of brain activation in the 3 frequency ranges in adolescents with migraine using MEG. According to our observations, low-frequency neuromagnetic signals are

probably generated from a large brain area whereas high-frequency brain signals are probably generated from a small area. In other words, high-frequency neuromagnetic signals are highly localized and may provide precise spatial information about cortical dysfunction. This observation is consistent with previous reports on epilepsy with MEG, confirmed by invasive recordings.^{36,38} This finding may be very important in developing spatially targeted therapeutic interventions for migraine in the future.^{7,26}

The comparisons of ictal and interictal MEG data from the same group of subjects showed that most of the ictal abnormalities (eg, MEG data in 5 to 100 Hz and 1,000 to 2,884 Hz) normalized between headache attacks. The MEG findings are very important because the results suggest that the abnormal cortical activation during a headache attack may return to normal in between attacks. From a neurophysiological point of view, these findings imply that the impairments of cortical excitability in childhood migraine during headache attacks are reversible. In other words, these findings imply that aberrant ictal brain activation might be caused by cortical dysfunction, which may normalize as migraine attacks subside. The ictal neuromagnetic activation was also significantly different from interictal neuromagnetic activation in neuromagnetic signals in 100 to 200 Hz. It remains unclear to what extent the additional brain activation (eg, ipsilateral cortical activation) may be concomitant to the experienced pain and autonomous symptoms. Of note, further investigation is necessary.

In summary, this study has demonstrated that the brains of migraine subjects during headache attack phases are associated with aberrant activation in both low- and high-frequency ranges. The main novel findings of the present study were 1) the identification of very-high-frequency brain activation in migraine subjects using MEG; 2) the determination of increased ictal cortical activation beyond the primary motor cortex in migraine subjects during finger tapping; 3) the observation of the effect of migraine on the source power of motor cortical activation in migraine subjects; and (4) the confirmation of the normalization of brain activation during the headache-free phase in migraine subjects. These findings support the notion that migraine is a neurologic disorder caused by cortical dysfunction.^{7,26}

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Figure 1.

Polarity spectrograms and contour maps of MEG data in 5 to 100 Hz recorded from a migraine subject and a control during finger movements. The polarity spectrograms (*upper row*) show the spectral components in 5 to 30 Hz, which are indicated by numerals 1, 2, and 3. The migraine subject has activation outside of the primary motor cortex (*white arrows*). The green asterisk (*) in the contour maps indicates the position of the corresponding spectrogram that is shown above the contour maps.

Figure 2.

Polarity spectrograms and contour maps of MEG data in 100 to 1,000 Hz recorded from a migraine subject and a control during finger movements. The polarity spectrograms (*upper row*) show the focal increase of spectral power indicated by *black arrows*. The migraine subject has activation outside of the primary motor cortex (*white arrows*). The green asterisk (*) in the contour maps indicates the position of the corresponding spectrogram that is shown above the contour map.

Figure 3.

Polarity spectrograms and contour maps of MEG data in 1,000 to 2,884 Hz recorded from a migraine subject and a control during finger movements. The polarity spectrograms (*upper row*) show the focal increase of spectral power in a very-high-frequency range (~2,640 Hz). The migraine subject has activation outside of the primary motor cortex (*white arrows*). The *green asterisk (*)* in the contour maps indicates the position of the corresponding spectrogram that is shown above the contour map.

Figure 4.

The latencies of the first and second spectral components in 5 to 30 Hz in migraine subjects and controls. Abbreviations: 1 LFM, the first component elicited by left finger movements; 2 LFM, the second component elicited by left finger movements; 1 RFM, the first component elicited by right finger movements; 2 RFM, the second component elicited by right finger movements; SE, standard error. * $P < .01$; ** $P < .001$.

Figure 5.

Magnetic source imaging showing the locations of finger movement-elicited neuromagnetic activation in 5 to 30 Hz, 100 to 200 Hz, and 2,200 to 2,800 Hz in a migraine subject (Migraine) and a control (Control). The primary motor cortex in the contralateral hemisphere is activated in both the migraine subject and the control. The supplementary motor area, the ipsilateral sensorimotor cortex, and the occipital cortex are activated only in the migraine subject (green arrows). Abbreviations: R, right; L, left.

Table 1**Clinical Characteristics of Migraine Subjects**

Parameters	Measurements
Gender (female/male)	23/8
Age (years) (mean $\pm$ SD)	15.1 $\pm$ 1.6
Frequency of headache per month (mean $\pm$ SD)	7.6 $\pm$ 3.5
Years of suffering from migraine (mean $\pm$ SD)	3.6 $\pm$ 2.8
Duration of headache (hours) (mean $\pm$ SD)	9.1 $\pm$ 4.8
Severity of headache (on scale: 0~10) (mean $\pm$ SD)	6.7 $\pm$ 2.5
Pain type (number of subjects; multiple descriptions were allowed)	
Throbbing	19
Pressure	14
Constant	8
Sharp	5
Squeezing	4
Stabbing	3
Others	3
Medications for acute treatment before MEG tests (number of subjects; multiple drugs might be used)	
No-Drug *	12
Ibuprofen	17
Naproxen sodium	7
Sumatriptan	2
Rizatriptan	6
Eletriptan	2
Zolmitriptan	1
Axert	1
Maxalt	1
Dihydroergotamine(DHE)	3
Excedrin	3
Percocet	1
Medications for preventive treatment before MEG tests (number of subjects; multiple drugs/nutraceuticals might be used)	
No-Drug *	12
Amitriptyline	8
Divalproate	2
Levetiracetam	2
Topiramate	9
Vitamine D	3
Coenzyme Q10	11
Riboflavin	7

Abbreviation: SD, standard deviation.

* No-Drug: subjects claimed that they did not using any medications for at least 1 week prior to MEG tests.

Table 2

The Main Dependent Variables Analyzed in the MEG Spectrograms for Ictal Migraine Subjects and Controls

Analysis Frequency	Measured Variables	Moved Finger	Migraine	Control	P Value
5–100 Hz	Latency 1 (ms)	Left	41.4 ± 13.2	25.7 ± 4.9	<.001
		Right	33.9 ± 6.8	25.4 ± 4.6	<.002
	Latency 2 (ms)	Left	120.3 ± 42.8	97.8 ± 28.7	<.02
		Right	117.1 ± 32.4	81.2 ± 19.3	<.02
	Significant frequency (Hz)	Left	5–30	5–30	>.05
		Right	5–30	5–30	>.05
	Source power (fT/Hz)	Left	3.6 ± 2.8	3.4 ± .9	>.05
		Right	3.5 ± 2.4	3.2 ± 1.1	>.05
100–1,000 Hz	Location	Left	Right MA (27/27)	Right MA (27/27)	>.05
		Right	Left MA (14/27)	Left MA (2/27)	<.01
		Left	Left MA (27/27)	Left MA (27/27)	>.05
		Right	Right MA (14/27)	Right MA (3/27)	<.01
	Latency (ms)	Left	NM	NM	N/A
		Right	NM	NM	N/A
	Significant frequency (Hz)	Left	100–200	100–200	>.05
		Right	100–200	100–200	>.05
1,000–2,884 Hz	Source power (fT/Hz)	Left	2.76 ± .62	2.13 ± .35	<.005
		Right	2.68 ± .59	2.09 ± .41	<.002
	Location	Left	Right MA (27/27)	Right PM (27/27)	>.05
		Right	Right SMA (18/27)	Right SMA (4/27)	<.01
		Left	Left MA (27/27)	Left MA (27/27)	>.05
		Right	Left SMA (18/27)	Left SMA (3/27)	<.01
	Latency (ms)	Left	NM	NM	N/A
		Right	NM	NM	N/A
1,000–2,884 Hz	Significant frequency (Hz)	Left	2,639 ± 14	2,640 ± 12	>.05
		Right	2,635 ± 15	2,642 ± 11	>.05
	Source power (fT/Hz)	Left	1.26 ± .74	1.08 ± .64	>.05
		Right	1.31 ± .83	1.17 ± .59	>.05
	Location	Left	Right MA (27/27)	Right MA (27/27)	>.05
		Right	Right MA (27/27)	Right MA (27/27)	>.05
	Latency (ms)	Left	NM	NM	N/A
		Right	NM	NM	N/A

Analysis Frequency	Measured Variables	Moved Finger	Migraine	Control	P Value
			Left MA (16/27)	Left MA (6/27)	<.003
			Occipital (15/27)	Occipital (0/27)	<.01
		Right	Right MA (27/27)	Right MA (27/27)	>.05
			Left MA (16/27)	Left MA (6/27)	<.003
			Occipital (10/27)	Occipital (0/27)	<.01

Abbreviations: MA, primary motor area; NM, not measurable; N/A, not applicable.