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Abnormal cortical activation in females with acute migraine: A magnetoencephalography study

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HIGHLIGHTS

- It is well known that cerebral cortex plays a key role in migraine attacks and movement makes migraine headaches worse; however, its neural mechanism is poorly understood.
- Finger movements produced cortical hyperexcitability in females with migraine during migraine attack in a frequency range of 5–1000 Hz.
- Neuromagnetic signal may help to identify neurophysiological biomarkers for studying mechanisms of migraine using MEG and may facilitate to develop new therapeutic strategies for migraine.

ABSTRACT

Objective: The objective of this study was to investigate functional abnormalities of the brain in females with migraine using magnetoencephalography (MEG) and a finger-tapping task.
Methods: Twenty-nine female patients with migraine (aged 16–40 years) and age- and gender-matched healthy controls were studied with an MEG system at a sampling rate of 6000 Hz. MEG recordings were performed during an attack in migraineurs with and without aura. Neuromagnetic brain activation was elicited by a finger-tapping task. The latency and amplitude of neuromagnetic responses were analyzed with averaged waveforms in the frequency range of 5–100 Hz. The Morlet wavelet and beamformers were used to analyze the spectral and spatial signatures of MEG data from subjects in two frequency ranges of 5–100 and 100–1000 Hz.
Results: The latency of motor-evoked magnetic fields evoked by finger movement was significantly prolonged in migraineurs as compared with controls. Neuromagnetic spectral power in the motor cortex in migraineurs was significantly elevated. There were significantly higher odds of activation in 5–30, 100–300 and 500–700 Hz frequency ranges in the ipsilateral primary motor cortices and the supplementary motor area in migraineurs as compared with controls.
Conclusions: Neuromagnetic signal abnormalities in this study suggest cortical hyperexcitability in females with migraine during migraine attack, which could be measured and analyzed with MEG signal in a frequency range of 5–1000 Hz.
Significance: These findings may help to identify neurophysiological biomarkers for studying mechanisms of migraine, and may facilitate to develop new therapeutic strategies for migraine by alterations in cortical excitability.

1. Introduction

Migraine is a common disabling headache disorder characterized by ictal episodes of moderate-to-severe focal pulsating

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headache (Coppola and Schoenen, 2012). Migraine sufferers are typically hypersensitive to visual (photophobia), auditory (phonophobia), and sensory (cutaneous allodynia) stimuli during migraine attack (Gelfand et al., 2010). Migraine frequently begins in childhood and the prevalence increases in adolescence and early adult life. The prevalence of migraine is the same in boys and girls before adolescence; it increases predominantly in females compared with males after puberty (Hershey, 2010). According to the World Health Organization, migraine has become one of the 20 most disabling diseases (Leonardi et al., 2005). The occurrence of frequent headaches can have a significant impact on the human quality of life (Gladstein and Rothner, 2010). It is therefore a public health problem having a great impact on both the individuals and the society.

The neurobiological mechanism underlying migraine attacks remains unclear. There are evidences that the cerebral cortex plays a key role in migraine attacks (Hershey, 2005, 2010; Hershey et al., 2007; Pietrini et al., 1987). Bowyer and colleagues have found that patients with migraine have cortical hyperexcitability (Bowyer et al., 2005). Neurophysiological reports have shown that migraine is associated with abnormal excitability in visual and somatosensory cortices (Bowyer et al., 2001; Gunaydin et al., 2006; Lang et al., 2004). Recent magnetoencephalography (MEG) studies revealed that children with migraine, during their headache attacks, have significantly prolonged latencies of neuromagnetic activation in a low-frequency range, with increased spectral power in high-frequency ranges (Xiang et al., 2013; Wang et al., 2010). The spread of abnormal brain activation triggered by movements seems to play an important role in the cascade of pediatric migraine attacks (Xiang et al., 2013). As age is an important factor in headache severity, duration, frequency, and subsequent secondary disability (Bohotin et al., 2002), it remains unknown if adult patients with migraine are also associated with motor cortical dysfunction during migraine attacks.

The involvement of motor cortex in migraine has drawn attention recently (Esposito et al., 2012; Conforto et al., 2012; Wang et al., 2010). It is well known that movement makes migraine headaches worse, and one subset group of migraine patients shows hemiplegia (Scherer et al., 1997); however, its neural mechanism is poorly understood. Reports on nonfamilial migraine with unilateral motor symptoms (MUMSs) showed that a syndrome of severe migraine with accompanying give-way weakness is common in tertiary care headache centers (Young et al., 2007). An increasing list of transcranial magnetic stimulation (TMS) reports indicates that motor cortical dysfunction may play an important role in the pathogenesis of attacks of migraine (Aurora et al., 1999; Conforto et al., 2012; Conte et al., 2010; Fumal et al., 2003; Khedr et al., 2006; Maertens et al., 1992). From a therapeutic point of view, high-frequency repetitive TMS (rTMS) of the motor cortex can normalize aberrant intracortical inhibition during migraine (Brighina et al., 2010). Neurophysiologically, rTMS of the motor cortex can also modulate pain-related evoked responses in migraine (de Tommaso et al., 2010). Of note, a clearer understanding of motor cortical activation in patients with migraine is scientifically and clinically important.

The objective of the present study was to investigate motor cortical dysfunction in female adults with migraine using MEG and a finger-tapping task. We focused on females because the majority of patients with migraine are females and the ratio of migraine in female and male is approximately 3:1 (Hershey, 2012; Buse et al., 2012). A finger-tapping task was used because the task could activate the motor cortex without causing significant head movement. Our central hypothesis is that neuromagnetic activation in the motor cortex in females with migraine is significantly altered as compared with controls. To our knowledge, this is the first MEG study focusing on abnormalities of brain activation in the 5–1000-Hz frequency range in female adults with migraine using waveforms, spectrograms, and magnetic source imaging (MSI). Findings of this study may contribute to a better understanding of the mechanisms of migraine, and to the development of new therapeutic strategies in the future.

2. Methods

2.1. Subjects

Twenty-nine female patients with acute migraine (mean age: 30.59 years; standard deviation: 5.75 years, range: 16–40 years) were recruited from Nanjing Brain Hospital (see Table 1). Six of them had aura, while the remaining did not. Twenty-nine age-matched healthy female controls (mean age 30.59 years; standard deviation 5.75 years, range: 16–40 years) were recruited. All subjects >18 years of age signed a consent form. For subjects <18 years of age, their parents/guardians signed a consent form. This study and the consent form were approved by the Institutional Review Board at Nanjing Brain Hospital before undertaking the study.

The inclusion criteria were (1) migraine with or without aura as defined in the International Classification of Headache Disorders, 2nd Edition (ICHD-II) and (2) no other neurologic disorder. Controls were recruited to match the migraine subjects for age and gender and met inclusion criteria of (1) no history of neurologic disorder, headache, or brain injury and (2) age-appropriate hearing and hand movement. Exclusion criteria for all participants were (1) presence of an implant (e.g., braces or pacemaker) which could produce visible magnetic noise in the MEG data; (2) demonstration or expression of noticeable anxiety and/or inability to communicate readily with personnel operating the MEG equipment; (3) inability to keep still; and (4) subjects with claustrophobic tendencies or pregnancy (for MRI scans).

2.2. Tasks

All subjects were asked to perform a brisk index finger tapping with either right or left index finger while hearing a cue (500 Hz, 30 ms square tone). Subjects were instructed to press the response button with the index finger that was ipsilateral to the tone presented (Wang et al., 2010; Xiang et al., 2001, 2013). Other body parts were kept still and the eyes kept open, fixed to an arbitrary target during the paradigm. A trigger was sent to the MEG system from the response box when the button was pressed. The stimuli consisted of 200 trials of square tones and 100 trials per ear, and were presented randomly through a plastic tube and earphones. The stimulation presentation and response recording were accomplished with BrainX software, which was based on DirectX (Microsoft Corporation, Redmond, WA, USA) (Huo et al., 2011; Wang et al., 2010; Xiang et al., 2001, 2013). The entire procedure took about 15 min.

2.3. MEG recording

The MEG signals were recorded in a magnetically shielded room (MSR) using a whole head CTF 275-Channel MEG system (VSM MedTech Systems, Inc., Coquitlam, BC, Canada) in the MEG Center at Nanjing Brain Hospital. Before data acquisition commenced, all subjects were asked to remove all possible metals from their body. After that, electromagnetic coils were attached to the nasion and left and right preauricular points of the subject. These three coils were subsequently activated at different frequencies for measuring subjects' head positions relative to the MEG sensors. Subjects were asked to lie still comfortably in a supine position during the entire procedure, with arms resting on either side. The sampling rate of