Clinical Neurophysiology 127 (2016) 2855–2861

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Abnormal resting-state brain activity in headache-free migraine patients: A magnetoencephalography study

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ARTICLE INFO

Article history:
Accepted 19 May 2016
Available online 26 May 2016

Keywords:
Migraine
Magnetoencephalography
Resting-state
Gamma oscillation

HIGHLIGHTS

- We quantified resting-state brain activity from full-scale regions and frequency ranges in migraine.
- Migraine in headache-free phases showed increased gamma oscillations in left frontal and temporal regions.
- Abnormal resting-state brain activity may play a key role in the susceptibility of migraine attacks.

ABSTRACT

Objective: The aim of this study is to quantitatively assess the resting-state brain activity in migraine patients during the headache-free phase with magnetoencephalography (MEG).
Methods: A total of 25 migraine patients during the headache-free phase and 25 gender- and age-matched control patients were studied with a whole-head MEG system at eyes-closed resting-state. MEG data were analyzed in multifrequency range of 4–200 Hz.
Results: In a regional cortex analysis, the spectral power of gamma oscillations in left frontal and left temporal regions was significantly increased in migraine patients as compared to controls (all $p < 0.001$), but no significant difference was found between the two groups for the global channels. Analyses of source location showed that there were significant differences in the distribution of gamma oscillation between migraine subjects and controls ($p < 0.025$).
Conclusions: Migraine patients in resting-state had altered brain activities in spectral power value and source distribution that can be detected and analyzed by MEG.
Significance: Abnormal brain activities in the left frontal and temporal regions may be involved in pain modulation and processing of migraine. These findings provide new insights into the possible mechanisms of migraine attacks.

1. Introduction

Migraine is a common episodic neurological disorder characterized by recurrent unilateral throbbing headache and a host of complex pathophysiology including hypersensitivity to visual (photophobia), auditory (phonophobia) stimuli, nausea, emotional, and motor disturbances (Headache Classification Subcommittee of the International Headache, 2004; Noseda and Burstein, 2013; Pietrobon and Moskowitz, 2013) during migraine attacks. Even in the interictal period (headache-free phase), migraine patients also show hypersensitivity to sensory stimuli and abnormal processing of sensory information (Chen et al., 2011; Restuccia et al., 2012). Converging evidence shows that the abnormal cortical excitability serves a key role in the pathogenesis of migraine (Bowyer et al., 2005; Hershey et al., 2007; Vecchia and Pietrobon, 2012) and the mechanisms underlying the abnormal regulation of cortical function remain largely unknown.

The spontaneous oscillatory activity of resting-state represents a basic feature of the neuronal activity in the human brain. It is

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http://dx.doi.org/10.1016/j.clinph.2016.05.015
1388-2457/

crucial that the aberrant resting-state brain activity can provide a direct explanation of cerebral abnormality that result in the proneness of the brain-generating migraine attacks. Recent resting-state fMRI studies have found that migraine was associated with focal changes of blood oxygen level-dependent (BOLD) signal, and these regions were involved with nociceptive processing, such as in prefrontal cortex, anterior cingulate, and amygdala (Mainero et al., 2011; Yu et al., 2012; Xue et al., 2013). These findings provide deeper insights into the possible underlying mechanisms and their relationship to migraine attack susceptibility. However, BOLD signal does not reflect local variations in deoxyhemoglobin concentration and it is not a direct measure of neuronal activity.

Magnetoencephalography (MEG) is well suited for the study of brain function, because it is noninvasive, in vivo observations of the working brain as well as sensitive to subtle changes of neural activity (Hillebrand et al., 2005; Xiang et al., 2010; Lopes da Silva, 2013). Previous MEG studies have shown that the ictal time of migraine is associated with abnormal cortical excitability in visual, motor, and somatosensory cortices (Lang et al., 2004; Bowyer et al., 2005; Gunaydin et al., 2006; Xiang et al., 2013; Ge et al., 2015), but the spectral analysis of resting-state MEG in headache-free phases has been scarcely performed. The aim of this study was to quantify abnormal resting-state migraine brain activity at sensor and source levels with MEG system. As obvious difference of physiological characters between migraine with aura (MA) and migraine without aura (MwoA) (Manzoni and Torelli, 2008; Bashir et al., 2013), in this study, we selected MwoA patients. We quantified resting-state spatial and spectral brain activities from full-scale brain regions and wider frequency ranges in patients with interictal migraine. Finding of this study may contribute to a comprehensive understanding of altered brain activation in migraine patients and development of noninvasive brain stimulation techniques (transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)) on migraine treatment (Lipton and Pearlman, 2010; Antal et al., 2011; Rocha et al., 2015).

2. Methods

2.1. Subject

A total of 25 right-handed migraine patients were selected from the Headache Clinic of Nanjing Brain Hospital. The diagnosis of migraine was performed in accordance with the International Classification of Headache Disorders, Second Edition (ICHD-2) of 2004 (Headache Classification Subcommittee of the International Headache, 2004). Patients with other neurological diseases were excluded. The healthy controls did not have histories of migraine and other headache attacks in the past years. Exclusion criteria for all participants were the presence of ferromagnetic implant, brain injury history, inability to keep still, and use of medicine within 1 month before the test (except for prophylactic or acute medication in migraine patients).

The Medical Ethics Committee of the hospital approved the study protocol and each participant provided written informed consent.

2.2. Clinical and neuropsychiatric evaluation

The migraine patients were accessed with a questionnaire about their clinical characteristics of migraine before testing. The contents of clinical assessment included gender, age, aura, disease history, headache frequency (times/latest month), duration of the latest headache attack, headache locus, and headache accompanying symptoms such as phonophobia, photophobia, nausea, or vomit. The intensity of headache pain was assessed by the visual analog scale (VAS), while migraine-related impact was assessed by the migraine disability assessment questionnaire (MIDAS). The prophylactic and/or acute medication for migraine treatment was given at least 3 days before the MEG tests. In order to determine the potential effect of drug used on our results, we compared power value between migraine patients who did and did not use drug in the last month. Certain migraine patients reported laterality of the headache attack. The cranial side reported to experience the most headache attack during the latest month was selected as the symptomatic (S) side, and the headache-free side was selected as the nonsymptomatic (NS) side.

2.3. MEG recordings

The MEG recordings were collected in a magnetically shielded room using a whole-head CTF 275-channel MEG system (VSM Medical Technology Company, Canada) at Nanjing Brain Hospital MEG Center, China. Patients were required to have headache and aura free for at least 72 h before sampling and no one had a migraine symptom occurrence during or on the day following the testing. During the MEG recording, each participant was instructed to lay supine comfortably, close eyes, and maintain still head and body during the entire procedure (average duration ~120 s). Three small coils were attached to reference landmarks on the participant (left and right preauricular points, plus nasion) to check head position during recording. Head position changes up to approximately 1.5 cm were ignored. The sampling rate of MEG recording was 6000 Hz (this high sampling rate was used for another task study). Noise cancellation of the recording data was performed with third-order gradients.

2.4. MRI scan

Magnetic resonance imaging (MRI) data were obtained from each participant using a 1.5-T scanner (Sigma, GE, USA). Three marks were placed in the same position with the three coils used in the previous MEG recordings to acquire an accurate coregistration of the MEG and MRI data. The anatomical information was subsequently identified from the analysis of the MEG and MRI data.

2.5. MEG data processing

MEG data were analyzed using MEG Processor, a program that enables to visualize and compute MEG data (Xiang and Xiao, 2009). MEG data were resampled to 1000 Hz for improving the computational efficiency. High-pass (1 Hz) and low-pass (250 Hz) filters were used in MEG data processing. Morlet continuous wavelet transform was used to transform waveform data into a time–frequency spectrogram. Wavelet transform can be expressed as

$$G(t) = C_\sigma \pi^{-\frac{1}{4}} e^{-\left(\frac{1}{2}\right)t^2} (e^{i\sigma t} - k_\sigma),$$

where t is time, k_σ is admissibility, C_σ is normalized constant, and σ indicates the standard deviation of the Gaussian curve in the time domain. The detailed mathematical algorithms and parameters used were described in previous reports (Xiang et al., 2004, 2013; Kotecha et al., 2009). In order to measure magnetic spectral power effectively in a relative long time, accumulated spectrograms were computed by combining all the segments of time–frequency representations spectra. The accumulated spectrum can be described by the following equation:

$$Aft(s,f) = \sum_{t=1}^{T}\sum_{f=1}^{F} G(t,f),$$

where Atf indicates an accumulated spectrum, s is the time slice of the spectrum, f is frequency bands, T is time points, and F is the