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Timely event-related synchronization fading and phase de-locking and their defects in migraine

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HIGHLIGHTS

- 10 Hz alpha event-related oscillation was investigated during passive oddball stimulation in patients with migraine and compared with control subjects.
- Alpha event-related synchronization (ERS) appeared around 100 ms and faded to zero (phase de-locking) around 300 ms after deviant sounds in control subjects.
- In migraine patients, timely ERS fading and alpha phase de-locking at 300 ms after deviant sounds are defective.

ABSTRACT

Objective: To investigate the characteristics of event-related synchronization (ERS) fading and phase de-locking of alpha waves during passive auditory stimulation (PAS) in the migraine patients.
Methods: The subjects were 16 adult women with migraine and 16 normal controls. Electroencephalographic (EEG) data obtained during PAS with standard (SS) and deviant stimuli (DS) were used. Alpha ERS fading, the phase locking index (PLI) and de-locking index (DLI) were evaluated from the 10 Hz complex Morlet wavelet components at 100 ms (t100) and 300 ms (t300) after PAS.
Results: At t100, significant ERS was found with SS and DS in the migraineurs and controls ($P = 0.000$). At t300 in the controls, ERS faded to zero for DS while in the migraineurs there was no fading for DS. In both groups the PLI for SS and DS was significantly reduced, i.e. de-locked, at t300 compared to t100 ($P = 0.000$). In the migraineurs, the DLI for DS was significantly lower than in the controls ($P = 0.003$).
Conclusion: The alpha ERS fading and phase de-locking are defective in migraineurs during passive auditory cognitive processing.
Significance: The defects in timely alpha ERS fading and in de-locking may play a role in the different attention processing in migraine patients.

1. Introduction

Migraine is a common recurrent headache syndrome with vulnerability to pain. Advanced neuroimaging has identified widespread brain defects in executive function, visual processing, motor tasks and heat sensation in persons with migraine, and the cortical or subcortical structural alterations associated with each of these defects have also been identified (Rocca et al., 2003; Granziera et al., 2006; Moulton et al., 2008; Schmitz et al., 2008; Schwedt and Dodick, 2009). These alterations have been associated with interictal electrophysiological deficits (Ambrosini et al., 2003; de Tommaso et al., 2004; Zohsel et al., 2008; Demarquay et al., 2011; Mickleborough et al., 2011) and indicate that migraineurs have overactive regulatory mechanisms and

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abnormally sensitive responses to environmental factors. These are believed to be associated with enhanced cortical excitability (Ambrosini et al., 2003; Pietrobon and Striessnig, 2003; Brighina et al., 2009).

The roles of alpha event-related synchronization/event-related desynchronization (ERS/ERD) in modulating cognitive processing and event-related phase resetting have been highlighted in relation to brain inhibition/activation and timing, respectively (Pfurtscheller and Lopes da Silva, 1999; Klimesch et al., 2007; Mouraux and Iannetti, 2008; Klimesch, 2012). The time window during which significant inhibitory ERS appears after auditory stimulation is thought to be small, namely about 100 ms, which is the time window of the well-known N1 component (Klimesch et al., 2007). This is because early sensory–semantic information processing and early semantic processes need to be shaped by inhibitory top-down processes. It has been shown that alpha ERD appears at about 200 ms, and peaks at around 350–650 ms after stimulus, though the time course of ERD depends on the type of stimulus, the type and duration of the task, and the frequency band (Sterman, 1996; Woertz et al., 2004). Early alpha ERS has to be faded out before significant ERD appears. Therefore for normal sensory cognitive processing, not only the appearance of early inhibitory ERS but also its timely fading seems to be mandatory. However, there have been no previous investigations of the timely ERS fading during cognitive processing in normal subjects and of whether ERS fades at the appropriate time in migraine patients.

Increased alpha ERS not only inhibits the tonic firing of cortical neurons resulting in inhibition but also entrains most of the neurons and causes their outer membrane potentials to follow the phase of the alpha oscillation. Thus alpha phase is known to influence the responsiveness of cortical neurons: responsiveness is maximal when sensory information arrives at the corresponding cortex during the surface negative phase of the alpha cycle and vice versa (Dustman and Beck, 1965; Valeriani et al., 2009). Thus ERS can allow precise timing of cortical cognitive processing through maximizing cortical responsiveness by resetting the ERS-negative phase to the desired time window.

Previous studies have shown that the appearance of N1 in the average ERP was in part due to constant alpha phase resetting, i.e., phase locking (Makeig et al., 2002; Klimesch et al., 2004; Gruber et al., 2005; Hanslmayr et al., 2007). For efficient cognitive performance, the exact timing of the N1 in relation to early cognitive processing is critical and, in this regard, early alpha phase locking can be important. In fact, in a cognitive performance test, good performers had higher alpha phase locking indexes than poor performers (Klimesch et al., 2004; Hanslmayr et al., 2005).

Once the early phase locking occurs and the corresponding cognitive step is carried out successfully, it is questionable whether alpha phase locking continues. Persistent locking is not desirable since persistence implies continued entrainment of cortical neurons to the alpha oscillation, which would disturb the cascade of cognitive processing during the period of phase locking. It is thus clear that phase locking must be completely, or at least partially, released (de-locked) after the early locking.

Alpha ERS is known to increase during internal attention control when learned responses must be withheld or when sensory information must not be processed. We noticed that the internal attention control occurs under the experimental conditions of the passive oddball paradigm in auditory modality, during which subjects are instructed to ignore a sound stimulus (Mertens and Polich, 1997; Wang and Wang, 2001; Chen et al., 2007; Ko et al., 2012). Since the auditory information must not be processed intentionally by the subjects, it is likely that this paradigm is appropriate for inducing ERS. Since no specific reaction is required from the subject, the effort to discriminate between auditory stimuli should be minimized. This should decrease the likelihood of the appearance of ERD, which would shorten the natural course of early ERS. Thus the passive oddball paradigm is appropriate for evaluating not only normal ERS induction but also normal ERS fading during the early attention period. Furthermore, since the standard sound (SS) is unexpectedly switched to the stimulus of the deviant odd sound (DS), the experiment provides the opportunity to study the response of alpha ERS fading and phase de-locking to a shift of attention to DS.

We hypothesized that migraine patients might have altered responses unlike in normal controls that early ERS had to be faded out before ERD and that early alpha phase locking would be significantly de-locked during the period of ERS fading. The altered responses might be related with the altered cerebral auditory processing in migraine patients. To address this issue, we examined the timing of ERS fading and de-locking of alpha waves to SS or DS in migraine patients during passive auditory stimulation, and compared them with the responses of normal controls.

2. Methods

2.1. Participants

The patients were 16 women (mean age: 22.9 ± 2.0 years) diagnosed as migraine with aura or without aura according to the International Classification of Headache Disorders (ICHD) 2nd Edition (Headache Classification Subcommittee of the International Headache, 2004). The controls were 16 age-matched healthy female volunteers (mean age: 22.6 ± 2.0 years). All patients and controls were given a standardized interview using a structured questionnaire and clinically evaluated by a neurology specialist. The patients included were taking no prophylactic migraine medication, had not previously overused analgesic drugs for headache, but had only intermittently used relief medications such as acetaminophen, NSAIDs and triptans. No participants had psychiatric or other neurological disorders or a history of drug abuse or dependency, and all had normal auditory function. They were all informed of the procedure, and gave informed consent in accordance with the guidelines of the institutional review board of Korea University Medical Center.

2.2. Task procedures

Stimuli were presented as auditory oddball paradigms, composed of 3 blocks of 1000 Hz standard sounds ($P = 0.8$, $n = 960$) and 1030 Hz deviant sounds ($P = 0.2$, $n = 240$). Tone duration was 100 ms, inter-stimulus interval (ISI) was 1000 ms. EEG recordings were obtained during a ±72 h headache-free period, confirmed by follow up telephone interview. 27 Electrodes were placed for recording according to the international 10–20 system with extended coverage of the lower temporal region (F9/10, T9/10, P9/10). The reference electrode was Pz. Impedance was below 5 kΩ and the band pass filter was 0.1–70 Hz. Sampling rate was 400 Hz. EOGs were recorded from two electrodes at the outer canthus of each eye for horizontal movements and one electrode under the left eye for vertical movements. Participants sat in a comfortable chair listening to the sounds through earphones and were instructed to read a book to ignore auditory stimuli during the task.

2.3. EEG processing

EEG data were preprocessed by EEGLAB version 8.035b, an open source toolbox operated in the MATLAB environment (version R2010a, Math Works, Natick, MA) (Delorme and Makeig, 2004). The data were re-referenced to average reference. Trial epochs