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Widespread inter-ictal excitability changes in patients with temporal lobe epilepsy: A TMS/MEG study

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Summary
Purpose: Transcranial magnetic stimulation (TMS) has been used to elucidate the altered balance between excitatory and inhibitory circuits in the motor cortex in epilepsy; however, TMS could not well assess excitability changes beyond the motor cortex. This study aimed to address the spatial profile of cortical excitability changes in patients with temporal lobe epilepsy (TLE) by using TMS and magnetoencephalography (MEG).
Methods: Eighteen patients with TLE and 18 healthy control subjects were recruited. Resting motor threshold (RMT) and intracortical inhibition (ICI) were measured to reflect motor cortical excitability by using TMS. A whole-head MEG was applied to record auditory and somatosensory evoked responses to paired-pulse stimuli. A paired-pulse inhibition (PPI) ratio, defined as the amplitude ratio between responses to the second and the first stimuli, was used to assess the auditory and somatosensory cortical excitability. A high PPI ratio suggests an increase in cortical excitability, while a low ratio indicates a decrease in excitability.
Results: Compared to control subjects, TLE patients exhibited increased RMT in motor cortex and higher PPI ratios for auditory P50m and somatosensory P35m responses. Notably, patients with a lower seizure frequency tended to exhibit a higher RMT or a lower P35m PPI ratio.

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Conclusions: Present data suggest that the cortical excitability alteration in focal epilepsy is widely distributed beyond the epileptic focus and the profiles of excitability change correlate with clinical severity in terms of seizure frequency. Combined MEG and TMS studies provide new insight into the inter-ictal cortical excitability profiles in patients with epilepsy.

Introduction

Epilepsy is a common neurological disorder characterized by recurrent seizures that occur as a result of excessive excitation or inadequate inhibition of cortical neurons (Brown et al., 1996). Changes in cortical excitability in patients with epilepsy have been reported (Manganotti et al., 2001). Studies also indicated altered metabolic rate (Witte and Bruehl, 1999; Thoma et al., 2005) in cortical areas apart from epileptogenic zone, suggesting that the imbalance between excitatory and inhibitory circuits in epilepsy is not confined to the epileptogenic zone but involves distant areas, and epileptogenic zone may lead to functional and physiologic changes in remote cortical areas (Witte and Bruehl, 1999; Hamer et al., 2005; Wright et al., 2006).

Transcranial magnetic stimulation (TMS) is a non-invasive means by which inter-ictal cortical excitability in epilepsy can be explored (Ziemann et al., 1998; Macdonell et al., 2002). Despite TMS offers a promising method to elucidate effects of antiepileptic drugs (AEDs) (Reutens et al., 1993; Manganotti et al., 1999; Badawy et al., 2010a) on motor cortex excitability in epilepsy patients (Caramia et al., 1996; Badawy et al., 2007, 2010b), it could not provide reliable excitability evaluation for non-motor cortical areas. Given that the focal epileptogenic zone might influence distant cortical areas (Witte and Bruehl, 1999; Hamer et al., 2005; Wright et al., 2006), it is of importance to develop an approach to directly determine the excitability patterns in different brain regions and accordingly to evaluate whether the inter-ictal excitability profiles would reflect clinical seizure frequency in patients with focal epilepsy.

Magnetoencephalograhy (MEG) has been used to examine auditory (Pantev and Lutkenhoner, 2000; Naatanen et al., 2007) and somatosensory (Hari and Forss, 1999; Kakigi et al., 2000) cortical processing in humans. A widely used approach to assess cortical excitability is paired-pulse paradigm, in which two stimuli are presented with a short interstimulus interval (ISI). The response to the second stimulus (R2) is normally smaller than the first one (R1) (Huttunen et al., 2008), this is known as the so-called paired-pulse inhibition (PPI). Using this approach, the balance between cortical excitation and inhibition can be evaluated by measuring the ratio between the strengths of R2 and R1 (R2/R1). A high PPI ratio indicates either an increase in excitation or a decrease in inhibition of the target region of the brain. The electroencephalographic reactivity in auditory cortex (Lukhanina et al., 2010) or somatosensory cortex (Frasson et al., 2001) can be evaluated when corresponding paired-pulse sensory stimuli were delivered to the subjects. Some recent MEG studies have also applied paired-pulse paradigm to investigate cortical excitability in auditory (Edgar et al., 2005; Hanlon et al., 2005; Thoma et al., 2005) and somatosensory (Edgar et al., 2005; Thoma et al., 2007; Cheng and Lin, 2013; Hsu et al., 2013) cortices.

To assess excitability patterns in different brain regions in focal epilepsy, we applied TMS as a tool to investigate motor cortex excitability, and, additionally, a whole head MEG system was used to evaluate excitability in auditory and somatosensory cortices by measuring PPI ratio. An inevitable weakness of previous clinical epilepsy research is the heterogeneity between patients with different epilepsy syndrome. Clinically, partial-onset epilepsies account for about 60% of all adult epilepsy cases, and temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. To reduce the heterogeneity between different patients, the present study specifically evaluated cortical excitability in different brain regions (motor, auditory, and somatosensory cortices) in patients with TLE. We aimed to address the spatial profile of cortical excitability change in TLE and the relation between the excitability profile and seizure frequency. Moreover, we attempted to provide another approach to measure excitability in non-motor cortical areas in epilepsy patients by using MEG system.

Methods

Participants

Eighteen patients with TLE (7 males; mean age: 32.5 ± 2.2 years) and 18 healthy control subjects (11 males; mean age: 26.3 ± 0.6 years) were recruited in the current study. The diagnosis of epilepsy syndrome and the hemisphere of seizure onset were determined on the basis of the clinical history, electroencephalographic (EEG) assessment, and neuroimaging data. Epileptic syndromes were classified according to the Commission on Classification and Terminology of the International League Against Epilepsy (1981). Patients with any other neurological or psychological disorders, cardiac pacemaker or vagal nerve stimulator were excluded. All of the patients were taking multiple AEDs (Table 1). Fifteen of the TLE patients and 17 of control subjects underwent TMS assessment. Auditory cortical excitability was assessed in 11 TLE patients and 17 control subjects. Somatosensosensory cortical excitability was investigated in 10 TLE patients and 10 control subjects. The study was approved by the Ethical Committee of the Taipei Veterans General Hospital, Taipei, Taiwan (VGHIRB No. 2012-06-038B). Written informed consent was obtained from each participant.