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Causal influence of epileptic network during spike-and-wave discharge in juvenile myoclonic epilepsy

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Summary Electroencephalographic (EEG) characteristic of juvenile myoclonic epilepsy (JME) is spike-and-wave discharge (SWD), which is dominant in the frontal region. However, activity in the parietal area, including the precuneus, has also been documented for several seconds before and during SWD. The aim of this study was to identify the role of the parietal region, especially the precuneus, and to clarify the causal dynamics among cortical regions during SWD. EEGs were obtained from seven patients with JME. Each SWD was divided into six distinct temporal phases: *spike onset*, *spike peak*, *slow-wave onset*, *slow-wave ascending*, *slow-wave peak*, and *slow-wave descending* phases. Based on the cortical current source distribution and the results of a previous study, we selected the medial frontal, orbitofrontal, anterior cingulate, and mesial temporal cortices and the precuneus as regions of interest (ROIs). To assess epileptic networks and the causal relationships among ROIs during SWD, the directed transfer function (DTF), a measure of multivariate causality, was calculated for each phase of SWD. During *spike onset*, the maximal outdegree region in all patients was the precuneus. The *spike-peak* and *slow-wave onset* phases did not show a consistently dominant outflow region. Outflow from the anterior cingulate cortex was dominant in four patients during the *slow-wave ascending* phase, and the precuneus showed the maximal outdegree in six patients during the *slow-wave peak*. In the *slow-wave descending* phase, four patients showed maximal outflow from the temporal

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cortex. Our findings suggest that the precuneus is likely a key region for SWD despite the small amount of neural activity observed. The precuneus was the region with the maximal outdegree during both the *spike onset* and *slow-wave peak* phases, indicating that SWD in JME is initiated and sustained by a network involving the frontal cortex, precuneus, and thalamus.

Introduction

Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized epilepsy (IGE) syndrome, accounting for 5—10% of all cases of epilepsy (Janz and Christian, 1957; Janz, 1985; Vollmar et al., 2011). The characteristic features of JME are myoclonic jerks on awakening, generalized tonic—clonic seizures, and less frequent absence seizures. In terms of electroencephalography (EEG), the hallmark of JME consists of bilateral, synchronous, widespread spike or polyspike and wave complexes, which are commonly assumed to occur without lateralizing or localizing features (Nordli, 2005).

Combined EEG and functional magnetic resonance imaging (fMRI) studies in patients with IGE, including JME, have shown a clear spike-and-wave discharge (SWD)-associated increase in the blood oxygenation level-dependent (BOLD) signal in the thalamus and a decrease in the BOLD signal in the parietal and frontal cortical regions, which is consistent with the default mode network (DMN) of the human brain (Archer et al., 2003; Gotman et al., 2005; Hamandi et al., 2006; Labate et al., 2005). Time-course analyses of the BOLD signal during SWD have shown BOLD increments starting approximately 5—10 s before the onset of SWD in the precuneus (PCN)/posterior cingulate cortex (PCC) and medial/lateral parietal cortex (Benuzzi et al., 2012) as well as in the orbital/medial frontal cortex (Bai et al., 2010). Additionally, a recent magnetoencephalograpihc (MEG) study showed that low-frequency sources were sequentially activated in the frontal and occipital regions prior to the first generalized spikes (Gupta et al., 2011).

An fMRI study using dynamic causal modeling suggested that activity in the PCN gates SWD in IGE in the thalamocortical network (Vaudano et al., 2009). The posteromedial cortical region, including the PCN and PCC, showed the highest degree of interactions with the rest of the DMN, suggesting that this area plays a pivotal role in the network. This finding indicates that the posterior cortex may influence SWD generation such that it drives the SWD network under pathological circumstances.

Although EEG-fMRI studies have been used for the localization of SWD in IGE (Aghakhani et al., 2004; Gotman et al., 2005; Moeller et al., 2008a), fMRI reflects the BOLD signal, which is indirectly related to the underlying neuronal activity and cannot describe instantaneous neural activities of SWD because the BOLD signal is an accumulation of signals over several seconds (Archer et al., 2003; Blumenfeld, 2005; Sullivan and Dlugos, 2004). Additionally, most EEG-fMRI studies oversimplify the hemodynamic response function (HRF) related to brain activity, as most activity cannot be measured by the standard HRF used for conventional fMRI analyses of SWD in IGE (Blumenfeld, 2012).

Recently, as epilepsy has been considered network disorder, epileptic brain networks have been evaluated using mathematical measures of connectivity (Amor et al., 2009; Gupta et al., 2011; Killory et al., 2011; Kramer and Cash, 2012; Zhang et al., 2011). In our study, we adopted a directed transfer function (DTF), which is a type of multivariate application of Granger causality (Kamiński and Blinowska, 1991), since DTF can efficiently estimate causal interactions among multiple EEG signals. DTFs have been extensively used in the analysis of epileptic networks (Ding et al., 2007; Franaszczuk and Bergey, 1998; Lu et al., 2012; Wilke et al., 2011). A series of studies have demonstrated that the DTF technique can be used to identify ictal onset zones from intracranial EEG recordings in cases of mesial and lateral temporal lobe epilepsies as well as in cases of neocortical extra-temporal lobe epilepsies. In addition, it was recently reported that seizure activity in patients with symptomatic generalized epilepsy, such as Lennox—Gastaut syndrome, can be localized using DTF analysis (Jung et al., 2011).

In the present study, to assess epilepsy networks and the causal relationship among cortical regions during SWD in patients with JME, we first identified cortical current sources and applied DTF on these current sources during SWD. We also tried to elucidate the role of the PCN in gating SWD during the ictogenesis of JME.

Methods

Subjects

Seven patients with a clinical diagnosis of JME were included in this study. The diagnosis of JME was based on electroclinical criteria as per the International League Against Epilepsy (ILAE) classification (Commission of ILAE, 1989). Inclusion criteria were as follows: (1) a typical clinical history of JME with onset of myoclonic jerks and generalized seizures in adolescence; (2) no evidence of neurological abnormality and intellectual decline; (3) apparent spike or polyspike and wave discharges on normal background rhythm on previous standard international 10—20 EEG; and (4) normal MRI finding by visual inspection. The study protocol was approved by the Institutional Review Board of Korea University Medical Center. Clinical data of the included patients are summarized in Table 1.

EEG recording

A 64-channel EEG signal and two electrooculogram channels were recorded at a sampling rate of 1600 samples/s using an EEG recording system (Grass Technologies, Quincy, MA, USA). An electrode cap with sintered Ag/AgCl electrodes was