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Evidence that juvenile myoclonic epilepsy is a disorder of frontotemporal corticothalamic networks

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ABSTRACT

The purpose of this study is to determine regions of cerebral cortex activated during the onset and propagation of dense array electroencephalographic (dEEG) epileptiform discharges in patients with juvenile myoclonic epilepsy (JME), through the use of 256 channel, dense array scalp EEG recordings. Ten patients (16–58 years old) with the clinical diagnosis of JME comprised the study group. In all cases the MRI and neurological exams were normal, while standard EEG recordings documented typical "generalized" 4–6 Hz epileptiform patterns. Outpatient dEEG recordings captured epileptiform discharges in each patient. Localization of onset and spread of discharges in relation to a standard MRI model was accomplished by applying dipole fits and a distributed linear inverse method of cortically constrained source analysis. All patients showed epileptiform discharges that localized to sources that included orbitofrontal/medial frontopolar cortex, while basal–medial temporal lobe sources were observed in 5/10 subjects. In many ways similar to discharges of typical absence, epileptiform patterns in JME are usually irregular and frequently include temporal lobe structures as the dominant contributors to the discharges. We find that epileptiform discharges in patients with JME are not "generalized" in the sense of bilaterally synchronous diffuse onset. Rather, discharges have both localized onsets and a restricted cortical network during propagation that includes regions of frontal and temporal cortex.

Introduction

Juvenile myoclonic epilepsy (JME) is a common, genetically heterogeneous, idiopathic generalized epilepsy syndrome characterized by age-related onset of seizures, and by variable seizure types that may include myoclonus, generalized tonic-clonic convulsions, and absence (Zifkin et al., 2005). The clinical examination reveals no focal neurological signs, and standard magnetic resonance imaging (MRI) studies reveal no characteristic structural lesions. Electroencephalographic (EEG) studies disclose that interictal epileptiform discharges are typically diffuse, with bilateral spikes or multiple spikes, and 4–6 Hz spike–wave or multiple spike–slow-wave complexes. By definition, and consistent with other idiopathic generalized epilepsy syndromes, ictal EEG patterns on standard EEG recordings appear to show simultaneous involvement of both cerebral hemispheres at the beginning of seizures (Nordli, 2005).

Supported by experimental evidence, the pathophysiology of JME and other idiopathic epilepsies, such as typical childhood absence, has been postulated to be linked to thalamic and corticothalamic mechanisms, which, in turn have provided an explanation for the apparently "generalized" nature of the seizures (McCormick, 2002; Slaght et al., 2002). Recent findings that disclose thalamic magnetic resonance spectroscopic abnormalities in JME (Mory et al., 2003), and atrophy in the thalamus in childhood absence, provide additional evidence implicating thalamic involvement in these syndromes (Chan et al., 2006).

Regardless of the role of subcortical mechanisms in generalized epilepsy syndromes, it is also clear from experimental evidence that focal cortical regions, particularly in frontal lobe structures, modulate corticothalamic circuitry, and that these selective cortical regions are likely of fundamental importance in the pathophysiology of generalized seizures. Investigators in the 1940s found that regions of orbitofrontal cortex regulated corticothalamic augmenting and recruiting responses in animals (Morrison and Dempsey, 1942; Morrison and Dempsey, 1943). More recently, studies have shown that some corticothalamic circuits, mediated by nucleus reticularis thalami and controlled by orbitofrontal cortex (Yingling and Skinner et, 1976, 1977), are normally related to sleep spindle generation and become pathological in spike–wave complexes (Steriade, 2003; Steriade and Amzica, 2003). Spike–wave discharges in animal studies that show activity in medial frontal cortex during sleep onset is further evidence establishing the restricted cortical distribution of the

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discharges and the importance of corticothalamic networks in the genesis of both spike–wave discharges and sleep patterns (Steriade and Amzica, 2003). In a model of absence where high-density, simultaneous cortical and subcortical EEG electrodes were employed, a frontal cortical focus was shown to drive the spike–wave discharges, implying that the factors responsible for initiation of seizures are found in the cortex, rather than in the thalamus (Meeren et al., 2002).

The apparent "generalized" nature of typical childhood absence, JME, and other generalized epilepsies may be related more to convenience of interpretation than to a detailed examination of the electrographic evidence. It has long been recognized that spike–wave discharges in absence are not diffuse, but are typically frontally preponderant (Niedermeyer, 2000). Other investigators point out that epileptiform discharges in absence may be fragmented, especially during sleep, with focal spikes often observed over centrotemporal and occipital regions, and over the midline in conjunction with K-complexes (Niedermeyer, 2000; Panayiotopoulos, 1994). In JME, epileptiform discharges are also frontally preponderant and may show lateralization to one side or the other (Lancman et al., 1994). The not infrequent occurrence of focal epileptiform discharges on EEG, as well as focal semiological features of the clinical seizures, has been well documented in patients with JME (Usui et al., 2005).

In the last two decades, advances in physical models of neural sources of EEG activity has led to the possibility of relating the distribution of diffuse spike–wave patterns to electrical sources in specific regions of cerebral cortex. An early study that applied equivalent dipole analysis to spike–wave complexes suggested that the most common source was in basal midline frontal lobe (Rodin et al., 1994), with further research using conventional recordings in children with absence again emphasizing the importance of inferior frontal generators (Rodin, 1999). More recently, investigations that utilized scalp EEG recordings with a high degree of spatiotemporal resolution, in combination with source analysis and a realistic MRI model, were employed in studies of absence seizures (Holmes et al., 2004; Tucker et al., 2007). These studies demonstrated that localized orbitofrontal and medial frontal, and occasionally temporal, regions were most commonly involved at the onset and in the propagation of ictal discharges in absence.

With this background in mind, we undertook the present study to investigate whether specific, as opposed to diffuse, cortical regions are involved in JME at the onset and during propagation of epileptiform discharges. The investigation utilized 256-channel dense array (dEEG) recordings to improve the degree of spatial information that can be extracted from scalp (i.e. maximize the "spatial Nyquist"), and included coverage of face and neck in order to electrically sample inferior brain regions as much as possible (Lantz et al., 2003). By digitizing the dEEG recordings at 1000 Hz, we improved the temporal stability of the signal to closely examine scalp potential distributions and the rapid transitions of the spike and wave complexes. With enhanced spatiotemporal resolution of the electrographic data, we then applied a linear inverse method of source analysis, in conjunction with a realistic brain model, to discern the neural sources of scalp potentials (Grave de Peralta Menendez et al., 2004).

Methods

Patients

Ten patients with the clinical diagnosis of juvenile myoclonic epilepsy (JME) were included in this study. The diagnosis was established on the basis of the history, age of onset of seizures, seizure types, clinical findings, standard international 10-20 EEG, and neuroimaging. All patients underwent standard 10-20 EEG recordings that documented the characteristic 4–6 Hz spike–wave or multiple spike epileptiform discharges found in JME (Nordli, 2005). The group was composed of five women and five men between 16 and 58 years of age. Neurological exam and brain MRI studies were normal in every patient. Four subjects had family histories of epilepsy. Two subjects had generalized tonic-clonic, myoclonic, and absence seizures, seven had generalized tonic-clonic and myoclonic seizures, and one had absence and myoclonic seizures. The age of onset of seizures was between 12 and 19 years (Table 1).

256 channel dEEG scalp recordings

After approval by the University of Washington Human Subjects Review Committee, informed consent was obtained from each subject for less than 60 min of outpatient recordings with dense-array scalp EEG techniques. The 256-channel Geodesic Sensor Net was applied to each person during the recording, requiring about 30 min for application and adjustment. The dEEG-amplifier characteristic included a bandpass of 0.1 to 400 Hz and sampling rate of 1000 Hz. No effort was made to reduce or alter, for purposes of this study, any of the antiepileptic medications that each patient was routinely prescribed. Epileptiform discharges were recorded in all cases.

EEG referencing and mapping

The 256-channel dEEG was recorded with a common vertex reference, and re-referenced digitally to various montages for inspection, including the average reference. Because of the improved coverage of the inferior head surface, the average reference allows the potential at each index electrode to be examined with reference to an estimate of the zero potential of the head (Bertrand et al., 1985; Dien, 1998; Junghofer et al., 1999). The average-referenced dEEG waveforms were examined with topographic waveform plots, a technique that allows inspection of geometric distribution of the potential fields. In addition, topographic maps were created with spherical spline interpolation (Perrin et al., 1987). We examined dynamic scalp topography of spike–wave discharges with animations created at each 1-ms interval (Tucker et al., 1994).

Table 1
Summary of clinical data and cerebral localization on standard MRI of main components from source analysis of epileptiform discharges.

Patient	Age (years)	Sex	Onset (years)	Risk factors	Seizure types	Cortical localization of discharges: Major sources
1	33	M	13	Family Hx	GTC myoclonic absence	Orbitofrontal frontopolar anterior-medial temporal
2	31	F	16	None	GTC myoclonic	Orbitofrontal frontopolar anterior-medial temporal
3	25	F	14	None	GTC myoclonic	Orbitofrontal frontopolar anterior-medial temporal
4	16	M	16	None	GTC myoclonic	Orbitofrontal frontopolar
5	24	M	12	Family Hx	GTC myoclonic	Orbitofrontal frontopolar posterior-medial frontal
6	28	M	13	None	GTC myoclonic absence	Orbitofrontal frontopolar anterior-medial Temporal temporal
7	27	F	13	None	GTC myoclonic	Orbitofrontal frontopolar posterior-medial frontal
8	33	M	17	Family Hx	GTC myoclonic	Orbitofrontal frontopolar anterior-medial temporal
9	20	F	19	None	Myoclonic absence	Orbitofrontal frontopolar anterior-medial temporal
10	58	F	12	Family Hx	GTC myoclonic	Orbitofrontal frontopolar

The clinical examination and standard MRI studies were normal in all cases.
M = male; F = female; family Hx = family history of epilepsy; GTC = generalized tonic-clonic convulsion.