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.

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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) 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 focial 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...
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 centropetalal
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 MIR
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 the inferior head surface, the average reference allows the
modeling of dynamic scalp potentials (Grave de Peralta Menendez et al., 2004). 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
topographies (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.

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

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 convolution.
EEG source analysis

In analyzing each epileptiform burst, we examined the onset and the characteristic features (for example, waves and spikes) with both scalp topographies and linear inverse source estimation. The electrodes were positioned in relation to skull landmarks in accordance with the standard 10–20 EEG system (nasion, periauricular points), and registered with the head conductivity model used for source analysis. We applied the linear inverse method of local autoregressive average (LAURA) in order to weight the solution distribution (Grave de Peralta Menendez et al., 2004). Because the vector fields of electrical sources fall off with the cube of distance (and the potential fields with the square of distance), the LAURA method constrains the solution with a weighting function that assumes the result will have a spatial smoothness with this physical property. The LAURA inverse solutions were implemented within the GeoSource software package (http://www.egi.com), using the probabilistic cortical gray matter locations from the Montreal Neurological Institute probabilistic atlas (www.bic.mni.mcgill.ca). For EEG selections with low noise we used a realistic finite difference model created from the MRI of an adult who closely fits the MNI average MRI (e.g. Figs. 3, 4). For EEG selections with higher noise we used a spherical head conductivity model (e.g. Figs. 8–10).

Results

The epileptiform discharges demonstrated some variability in morphology and in source analysis from one burst to another in the same subject and also between subjects. The onset of an epileptiform discharge, defined as the first large-voltage transition of a spike–wave burst, consisted typically of a surface negative slow wave (often overlaid with one or two positive spikes) or surface negative spike, similar to that observed in typical absence seizures (Holmes et al., 2004; Tucker et al., 2007). The initial slow wave is typically found to relate to sources in midline frontal regions, while the midline positive spikes typically reflect propagation of surface-negative discharges along orbitofrontal cortex, with the depth-positive component of the discharge dipole manifesting itself as a positive spike at the top of the head. Sampling at multiple time points at the beginning and during the recorded epileptiform bursts revealed some consistent patterns in source localization, common to discharges found in individual patients, as well as between subjects. The common denominator in all 10 cases included sources that localized epileptiform components to discrete, unilateral regions of orbitofrontal/frontopolar cortex, with secondary sources in two subjects that involved more posterior medial frontal or posterior frontal–parietal regions. Detailed examination of the dominant sources at variable time points within discharges revealed cyclic oscillation between those sources (e.g. medial frontal to orbitofrontal/frontopolar cortex and back again). A pattern observed in 5/10 subjects was localization of sources that include medial temporal structures, in addition to the frontal regions. In these cases the frontal sources appear to precede the first temporal activation, implying propagation from midline frontal/orbitofrontal cortex to medial temporal cortex. However, observing temporal sources that appear later in the same discharge suggests that temporal structures form part of the cyclic epileptiform neuronal circuit for that individual.

The figures serve to illustrate the patterns that we observe. Figs. 1–4 (patient 7) feature an individual where the dominant sources of discharges are largely confined to midline frontal and orbitofrontal/frontopolar regions. Fig. 1 shows a standard 10–20 EEG recording of an epileptiform burst in patient 7, with the initial component of the discharge being a surface negative slow wave. Fig. 2 is a topographic display of all 256 channels at the same point (red synch line) of the onset of the same discharge that demonstrates the characteristic anterior frontal-midline preponderance. Application of source analysis at the point of the maximal amplitude of this initial slow wave form, as displayed on a standard MRI model that also includes a cortical “flatmap” reveals localization of the slow wave to medial frontal cortex (Fig. 3). Fig. 4 displays source analysis results determined 150 ms after the time measured for the results shown in Figs. 1–3, at the peak of the first surface positive spike, and reveals a prominent frontopolar source.

Figs. 5–10 (Patient 9) demonstrate a pattern that includes temporal lobe structures as components of the epileptiform network. Fig. 5 shows that the first spike that precedes the “main body” of the epileptiform burst in this example is localized mainly to left midline frontal central regions, while first large discharge in that segment shows localization to orbitofrontal/frontopolar cortex (Fig. 6). In another series of discharges, the topographic display reveals that the first component of the burst is a typical surface negative slow wave (Fig. 7), with the dominant source in medial frontal regions (Fig. 8), while less than 200 ms later, near the end of that same slow wave, the sources implicate left orbitofrontal and temporal regions (Fig. 9). Finally, 8 ms after the time point shown in Fig. 9, left medial temporal sources predominate (Fig. 10), suggesting propagation from frontal to temporal regions during the sequence displayed in Figs. 7–10. The Table 1 includes details on the most important localization of cortical sources of epileptiform discharges for each subject.

Discussion

A concept has arisen in recent years that thalamocortical circuits are involved in both normal and abnormal cerebral rhythmicity (McCormick, 2002) and that the same circuits that modulate physiologic patterns (such as sleep spindles) are also implicated in the generation of spike–wave discharges observed in the generalized epilepsy syndromes (Steriade, 2003; Steriade and Amzica, 2003). Support of this hypothesis was provided in a recent study of a depressed patient without epilepsy, in demonstrating that electrical stimulation of the inferior thalamic peduncle and nucleus reticularis thalami produced thalamocortical recruiting responses in frontal cortex that are similar to the wave–spike discharges of absence (Velasco et al., 2006).

Although much of the early research on the generalized epilepsies has emphasized the importance of subcortical mechanisms to explain apparently widespread and synchronous discharges (Gloor, 1978), both recent and early evidence also suggests that the cerebral cortex plays a critical role in the initiation of generalized seizures. Focal cortical regions are found to drive the thalamocortical circuits during spontaneous seizures in an animal model of absence (Meeren et al., 2002), while other investigators find that cortical excitability is enhanced in patients with some forms of primary generalized epilepsy (Brodmann et al., 1999). In animals, experiments demonstrate that the antiabseence effect of ethosuximide resides primarily, if not exclusively, in the cortex (Richards et al., 2003).

The present study provides evidence that juvenile myoclonic epilepsy is not truly “generalized” in the sense of global activation of the cortex at the onset and propagation of epileptiform discharges. Rather, restricted networks of cortex are involved in the discharges.

Fig. 1. Wave–spike discharges for patient 7. This is an absence-like wave–spike seizure for this patient, beginning with the typical pattern of a brief oscillation, then the anterior-negative slow wave shown here. This is a chart view of the standard 10–20 EEG montage. The time between heavy green lines is 1 s. At the upper right is the 256-channel topographic voltage map (average reference; red = positive, blue = negative, white = zero; electrode locations as black dots). The red vertical (synchronization) line in the chart shows the time point for the potentials shown in the map. This is also the red synchronization line shown in Fig. 2 and time point for the source model in Fig. 3.
Topographic waveform plot for patient 7. This plot shows a 1100-ms epoch for each of the 256 channels, arrayed in their approximate positions on the head surface. The view is looking down on the top of the head, left at left, nose at top, with the inferior head sites unfolded and extended to the edges of the chart. The red line marks the time point marked in Fig. 1 and shown for Fig. 3.
most typically in regions of medial orbitofrontal, and anterior, basal–medial temporal lobe. The focal cortical involvement of JME and other generalized epilepsy syndromes may well have an anatomic basis. Focal cortical microdysgenesis has been found in postmortem studies of individuals who had primary generalized epilepsy in life (Meencke and Janz, 1984). Although standard clinical MRIs are “normal” in JME, detailed quantitative voxel-based MRI studies document widespread structural changes in the cortex, particularly in medial frontal areas (Woermann et al., 1999). Proton MRS studies disclose regions metabolic abnormalities, including reduced concentrations of N-acetyl aspartate in frontal lobe (Sinister et al., 2003a; Savic et al., 2000, 2004 and occipital lobe (Sinister et al., 2003b) in patients with JME and other generalized epilepsy syndromes. Neuropsychological studies further document frontal lobe dysfunction in JME (Devinsky et al., 1997; Pascalicchio et al., 2007), while reduced dopamine transporter binding is found in the frontal cortex of JME subjects, a finding that possibly relates to the neuropsychological findings (Cuimas et al., 2008). In studies of patients undergoing electroconvulsive therapy, under conditions whereby iatrogenic generalized tonic-clonic convulsions can be well documented and the timing

![Source localization model for the time point shown in Figs. 1 and 2. This is a linear inverse model, computed with realistic head shape and conductivity (finite difference model) with the LAURA (local autoregressive average) constraint on smoothness. The black lines are source orientation vectors, pointing in the positive direction from each voxel center. The crosshairs denote point of maximal source. Consistent with the topographies shown in the map in Fig. 1 and the 256 plot in Fig. 2, the source model for this slow wave suggests the surface-negative slow wave is generated in midline frontocentral cortex. A “flatmap” of the cortical surface of the standard MRI model is shown in the bottom half of the figure.](image-url)
controlled, use of single photon emission computed tomography documents that only selective cortical areas are involved (Blumenfeld et al., 2003).

Our results are also convergent with neuroimaging studies that implicate specific structural abnormalities in JME. Investigators have found regions of decreased cortical thickness in both frontal and temporal cortical gyri (Tae et al., 2008; Koepp, 2005; Kim et al., 2007) and atrophy in the thalamus (Kim et al., 2007), when compared to controls, in JME patients. Diffusion tensor MRI studies document white matter reductions in anterior thalamus and prefrontal cortex in individuals with JME, and provide further evidence of the abnormal corticothalamic neural circuitry operative in this syndrome (Deppe et al., 2008).

Our results emphasize the particular importance of orbitofrontal cortex as part of the network activated during the epileptiform discharges in JME. Although the seizures in this series of JME patients were not as stereotyped and consistent as those in pure absence, they often showed the characteristic “absence-like” wave–spike seizure pattern of a slow surface-negative wave over orbitofrontal cortex, interrupted by surface-positive spikes down the frontal midline,
Fig. 5. Discharges in patient 9. In this segment using the standard 10-20 montage, the vertical synch line (here colored brown) marks a spike before a series of epileptiform discharges. The topographic voltage map (blue = negative, red = positive, white = zero potential) shows the distribution over left central regions. The source model and corresponding flatmap suggest broadly distributed brain activity, dominated by mid-cingulate and left lateral temporal sources.
Fig. 6. The first large epileptiform discharge in this segment from patient 9 (3 s later in the segment in Fig. 5) shows a frontopolar surface topography and source model.
The first in this series of discharges from Patient 9 is a surface-negative wave over midline frontal sites. The dense array topographic waveform plot shows a typical feature for this patient, a run of fast activity on the positive-going downslope of this negative wave.
apparently superposed on the frontal negative wave (Holmes et al., 2004; Tucker et al., 2007). This pattern cannot be visualized with conventional EEG. Such data may be convergent with animal studies that document the important role of orbitofrontal cortex in modulating the nucleus reticularis thalami, and thus thalamocortical projections. Consistent with the putative role of orbitofrontal cortex in this circuitry are studies that demonstrate not only that stimulation of this region elicits recruiting responses, but also that ablation of orbitofrontal cortex, and not other regions of frontal lobe, will abolish the thalamocortical recruiting response (Morrison and Dempsey, 1942; Morrison and Dempsey, 1943). Pathology of the circuit that includes orbitofrontal cortex, corticothalamic neurons, inferior thalamic peduncle, and nucleus reticularis thalami may be responsible for the generation of wave–spike discharges in absence and JME (Velasco et al., 2006). Furthermore, derangement of physiologic slow oscillations in neocortex, likely responsible for the temporal coordination of self-
organized oscillations in neocortex, entorhinal cortex, subiculum, and hippocampus, that permit transfer of information among these structures, may explain the co-occurrence of orbitofrontal and medial temporal involvement in JME (Sirota and Buzsakì, 2005). Additional evidence of linkage between hippocampus and orbitofrontal, cingulate, and retrosplenial cortex (and the mechanisms affecting consciousness), is provided by studies in rat that demonstrate that slow waves in these structures may be remote effects elicited by focal hippocampal seizures (Englot et al., 2008). The remote influence on frontothalamic slowing in this animal model seems to reflect the reverse sequence of what we believe may occur in JME, in which absence-like frontothalamic seizures may often engage the fronto-temporal circuitry as well.

An important limitation of the present study was the reliance on registration with an atlas for anatomical source imaging. Future research will involve the use of an individual subject’s own MRI.
rather than a standard model, to improve spatial resolution of electrophyslogic sources, and will employ more advanced source analysis techniques and estimates of time delays between relevant sources, to achieve an even greater insight into underlying processes and propagation pathways.

This study provides evidence that epileptiform patterns in JME are highly localized to specific cortical regions, both at the onset and during propagation of discharges, rather involving the cortex diffusely. Research of this nature, which takes advantage of new technology that improves the spatiotemporal resolution of scalp EEG, should enhance an understanding of the abnormal neurophysiology of human epilepsy by identifying the specific abnormal circuits. When this knowledge is applied in conjunction with advances in genetic and molecular neuroscience, novel diagnostic and
therapeutic measures may become available in the future for persons with difficult epilepsy.

References


