High-frequency oscillations during human focal seizures

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Discrete high-frequency oscillations (HFOs) in the range of 100–500 Hz have previously been recorded in human epileptic brains using depth microelectrodes. We describe for the first time similar oscillations in a cohort of unselected focal epileptic patients implanted with EEG macroelectrodes. Spectral analysis and visual inspection techniques were used to study seizures from 10 consecutive patients undergoing presurgical evaluation for medically refractory focal epilepsy. Four of these patients had focal seizure onset in the mesial temporal lobe, and in all 12 of their seizures, well-localized, segmental, very high frequency band (VHF: 250–500 Hz) oscillations were visually identified near the time of seizure onset from contacts in this zone. Increased high-frequency band (HF: 100–200 Hz) activity compared with the background was distinguished both visually and with spectral analysis later in the seizures of 3/4 mesial temporal patients, involving contacts in the generator region and, in one patient, areas of contralateral peri-hippocampal propagation. Three patients with well-defined neocortical seizure-onset areas also demonstrated focal HF or VHF oscillations confined to the seizure-onset channels during their eight seizures. No discrete HF or VHF activity was present in the poorly localized seizures from the remaining three patients. These results show that discrete HFOs can be recorded from human focal epileptic brain using depth macroelectrodes, and that they occur mostly in regions of primary epileptogenesis and rarely in regions of secondary spread. Absent high-frequency activity seems to indicate poor localization, whereas the presence of focal HFOs near the time of seizure onset may signify proximity to the epileptogenic focus in mesial temporal lobe and neocortical seizures. We postulate that focal HFOs recorded with depth macroelectrodes reflect the partial synchronization of very local oscillations such as those previously studied using microelectrodes, and result from interconnected small neuronal ensembles. Our finding that localized HFOs occur in varying anatomical structures and pathological conditions perhaps indicates commonality to diverse epileptogenic aetiologies.

Keywords: EEG; epilepsy; high-frequency oscillations; ripples; fast ripples

Abbreviations: HF = high-frequency band; HFO = high-frequency oscillation; VHF = very high frequency band

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Introduction

Traditionally, the range of EEG oscillation frequencies believed to be clinically relevant has been limited to the gamma band (~40–100 Hz) and below. This is reflected by the commonly used low-pass filtering of the EEG signal around 70 Hz and the concomitant 200 Hz sampling rate, thereby restraining identifiable signal frequencies to <100 Hz. Studies using higher sampling rates (1000–2000 Hz) have demonstrated that higher-frequency EEG oscillations can have physiological and pathological relevance in humans. Wavelet bursts up to 600 Hz are seen superimposed on the primary cortical evoked response in human EEG and magnetoencephalography, and may reflect very early sensory processing (Curio, 2000). Discrete bursting oscillations between 100 and 500 Hz have been identified in mesial temporal structures of human epileptic patients and, through analogy with rodent models, these appear to represent normal memory processing in some instances but may indicate epileptogenesis in others (Bragin et al., 1999a, c).

It has been hypothesized that high-frequency oscillations (HFOs) represent localized networks of mutually activating
neuronal ensembles. Bragin et al. (1999a, b, c) used medial temporal implanted depth microelectrodes to measure local field oscillations in kindled rat brains as well as in epileptic patients. Discrete oscillations between 100 and 200 Hz were termed ripples, and are found in rodent as well as in human non-epileptic hippocampi and entorhinal cortices. Ripples occur most prominently during non-REM sleep, and it was proposed that they have a functional role whereby episodic memories are consolidated by phase synchronization (Draguhn et al., 2000). In contrast, there are discretely localized, visually identifiable oscillations present at higher frequencies in the limbic structures of kindled rats and in epileptic mesial temporal lobes of humans. These oscillations occur between 250 and 500 Hz and are probably pathological. So-called fast ripples were only identified in epilepticogenic areas with microelectrodes, and investigators propose that they represent the hypersynchronous discharging of locally interconnected principal neurons capable of generating spontaneous seizures (Staba et al., 2002).

HFOs > 100 Hz have rarely been studied during ictal activity in humans. Fisher et al. (1992) looked at seizures exhibiting electrodecremental EEG onset patterns using subdural grid recordings from five patients with neocortical epilepsies. The spectral power was calculated during the initial ictal activity and peaks were present from 80 to 120 Hz in contacts close to the seizure focus. Also, using subdural grids, Traub et al. (2001) analysed seizures from 11 children with cortical malformations, and were able to visually identify restricted areas of HFOs up to 130 Hz preceding the seizure onset, superimposed on ictal and interictal burst activity. Finally, Allen et al. (1992) used depth macroelectrodes to record frontal lobe seizures in a patient with cortical dysplasia, and visually and spectrally identified 105–115 Hz sustained oscillations in the channel closest to the neuronal migration lesion at the time of clinical seizure onset.

We hypothesize that 100–500 Hz HFOs may be recorded during seizures using depth macroelectrodes, and that these high frequencies are located near epileptogenic regions. Ictal activity was prospectively recorded from patients with intractable temporal and extra-temporal lobe epilepsies, and we used visual assessment as well as spectral analysis techniques to identify HFOs. We have found distinct HFOs localized to areas of seizure onset and propagation in a variety of patients in this study.

Methods

The Montreal Neurological Institute and Hospital Research Ethics Committee approved this study and informed consent was obtained from all participants.

Patient selection and recording methods

Patients with medically refractory focal seizures undergoing investigation for their epilepsies with intracranial electrode implantation were enrolled prospectively and consecutively in the study between September 2004 and July 2005. The sites for electrode placement were individualized according to the clinical history, seizure semiology, neuroimaging and previous electrophysiological investigations. The implantation consisted of a combination of depth electrodes and epidural electrodes according to the method of Olivier et al. (1994). Electrodes were implanted stereotactically using an image-guidance system (SSN Neuronavigation System, Mississauga, Ontario, Canada) through percutaneous twist drill holes in the skull.

Intracranial depth electrodes were manufactured on site by wrapping 3/1000 in. (0.076 mm) stainless steel wire around a 10/1000 in. (0.254 mm) stainless steel central core. These wires were coated with Teflon except for regions where the insulation was stripped to form electrode contacts. In total, there were nine contacts on each depth electrode that were spaced along the length of the core wire at 5 mm intervals. The deepest contact (contact 1) was made from the tip of the core wire and had an uninsulated length of 1 mm, while more superficial contacts (contacts 2–9) were formed from stripped sections of the marginal wire that was tightly wound to make 0.5 mm long coils. The effective surface area for each of the eight superficial contacts was 0.80 mm², and was 0.85 mm² for the single deep contact. The locations of electrodes are listed for the 10 patients in this study in Table 1. Typically, depth electrodes in the temporal lobe were directed orthogonally through the middle temporal gyrus in anterior, mid and posterior locations such that the deepest contacts became situated in the amygdala/uncus (LA/RA: left/right amygdala), anterior hippocampus (LHA/RHA) or the middle hippocampus/parahippocampal gyrus (LMH/RMH), respectively. Rarely, a depth electrode was in the temporal pole (LTP/RTP) or was directed at insular cortex (LI/RI). Frontal lobe electrodes were implanted through the lateral frontal convexity with deepest contacts located at the mesial frontal cortical surface: anterior and middle cingulate cortex locations, respectively (LAC/RAC; LMC/RMC), orbitofrontal cortex (LOF/ROF). Depth electrodes were at times targeted at discrete lesions (4 patients); for patient 5, a cortical dysplasia in the left opercular (LOP) and middle frontal gyrus (LMF); for patient 6, an anterior insular dysplastic lesion (RI); for patient 7, the borders of a large ponscencephalic cyst in the LOP, premotor (LPM) and parieto-occipital areas (LPO); for patient 8, residual low-grade tumour and glial tissue in the left mid-temporal lobe (LMT). In addition, epidural electrodes were situated commonly overlying peri-sylvian or peri-rolandic areas, and in some cases were placed surrounding MRI-identified lesions.

Patients’ antiepileptic drugs were reduced and the intracranial EEG was monitored continuously for spontaneous seizures during the typical 2-week implantation period. The EEG telemetry signal was digitally recorded with a 128-channel Harmonic system for long-term monitoring (Stellate, Montreal, QC) with filter settings of 0.1 and 500 Hz and a sampling frequency of 2000 Hz for continuous periods lasting 24–96 h, while at other times the digitization occurred with standard settings of 200 Hz sampling and 0.1 and 70 Hz filter frequencies.

Selection of seizures and characteristic sections

A neurologist from the Montreal Neurological Hospital Epilepsy Unit analysed all spontaneous seizures—regardless of sampling frequency—that were recorded during the implantation period. If possible, the neurologist attempted to identify (one or more) locations of seizure onset and propagation for each event. Only seizures recorded at 2000 Hz sampling frequency were selected for further
Table 1 Demographic, neuroimaging and electrophysiological data of 10 patients undergoing implantation studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Neuroimaging</th>
<th>Implanted electrode locations*</th>
<th>Interictal epileptic discharge locations</th>
<th>Seizure-onset location/pattern</th>
<th>Seizure propagation locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 M</td>
<td>MRI—Bil. MT atrophy, R &gt; L</td>
<td>Depth (6)—LA, LAH, RA, RAH, RMH, RI</td>
<td>Bil. MT independently</td>
<td>R mid. hippocampus/ low-frequency rhythmic spikes</td>
<td>R T neocortex, L MT and ant. T neocortex</td>
</tr>
<tr>
<td>2</td>
<td>45 M</td>
<td>MRI—Hypertrophic L T pole</td>
<td>Depth (5)—LTP, LA, LAH, LMH, LOF</td>
<td>L MT lobe and L T pole neocortex independently</td>
<td>L MT lobe/ low-frequency rhythmic spikes</td>
<td>L ant. T neocortex</td>
</tr>
<tr>
<td>3</td>
<td>34 F</td>
<td>MRI—Normal PET—Normal</td>
<td>Depth (5)—RA, RAH, RMH, RAC, ROF</td>
<td>R MT lobe ± involving R T and Fr. neocortex</td>
<td>R MT lobe/low-voltage fast activity</td>
<td>R T and Fr neocortex</td>
</tr>
<tr>
<td>4</td>
<td>42 F</td>
<td>MRI—R MT atrophy, R centrum semi- oval small white matter lesions, L T arachnoid cyst</td>
<td>Depth (6)—LA, LAH, LMH, RA, RAH, RMH</td>
<td>Bil. MT independently</td>
<td>R MT lobe and very infrequently L MT lobe/ low-frequency rhythmic spikes</td>
<td>R T neocortex</td>
</tr>
<tr>
<td>5</td>
<td>36 M</td>
<td>MRI—Cortical dysplasia in L OP and mid Fr gyrus (confirmed on pathology)</td>
<td>Depth (6)—LAC, LOF, LOP, LMF, RAC, ROF Epidural (6)—L peri-central</td>
<td>L inf Fr convexity</td>
<td>L inf Fr convexity/rhythmic 4–13 Hz spikes</td>
<td>Bil. Fr neocortex</td>
</tr>
<tr>
<td>6</td>
<td>28 F</td>
<td>MRI—Suspected cortical dysplasia in R ant. insula lctal SPECT—R Fr pole perfusion abnormality</td>
<td>Depth (7)—LAC, LMC, LOF, RAC, RMC, ROF, RI</td>
<td>R pars orbitalis ± R lat Fr convexity and L med Fr neocortex</td>
<td>R pars orbitalis/rhythmic 4–13 spikes</td>
<td>Bil. med and lat Fr neocortex</td>
</tr>
<tr>
<td>7</td>
<td>36 M</td>
<td>MRI—Large L CP porencephalic cyst with surrounding gliosis</td>
<td>Depth (7)—LTP, LA, LOF, LOP, LAC, LPM, LPO Epidural (3)—L peri-central, L SPL, L PO</td>
<td>L ant lat Fr convexity, L SMG and L T pole independently</td>
<td>L MFG and ant. Ci/low-voltage fast activity</td>
<td>L Fr neocortex</td>
</tr>
<tr>
<td>8</td>
<td>40 F</td>
<td>MRI—L ant. T cavity (post-lobectomy) with gliosis</td>
<td>Depth (1)—LMT Epidural (7)—L T, L SMG, L AG</td>
<td>Multifocal independent involving L middle and post. T neocortex and L insula</td>
<td>L T neocortex</td>
<td>L MT lobe</td>
</tr>
<tr>
<td>9</td>
<td>22 F</td>
<td>MRI—L Par and ant. T surgical cavities with gliosis; L atrium cavernous angioma</td>
<td>Depth (2)—LAH, LMH Epidural (8)—L C, L SMG, L AG, L SPL, L IPL</td>
<td>Multifocal independent involving L middle and post. T neocortex and L MT lobe</td>
<td>No electrographic changes associated with clinical seizure onset</td>
<td>L MT and post. T neocortex</td>
</tr>
<tr>
<td>10</td>
<td>49 F</td>
<td>MRI—R MT atrophy</td>
<td>Depth (6)—LA, LAH, LMH, RA, RAH, RMH Epidural (8)—Bil. T</td>
<td>Bil. MT independent</td>
<td>Multifocal independent involving L middle and post. T neocortex and L MT lobe</td>
<td>Diffuse bil. MT and T neocortex</td>
</tr>
</tbody>
</table>

Abbreviations: M = male; F = female; Fr = frontal; T = temporal; MT = mesial temporal; Par = parietal; CP = centroparietal; PO = parieto-occipital; OF = orbito-frontal; CI = cingular; SMG = supra-marginal gyrus; C = central; OP = operculum; AG = angular gyrus; SPL = superior parietal lobule; IPL = inferior parietal lobule; ant. = anterior; post. = posterior; sup = superior; inf. = inferior; med. = medial; lat. = lateral; bil. = bilateral; mid. = middle; *Description of depth electrode abbreviations is provided in the Methods section.
analysis. Ictal events were excluded if they were not associated with clinical manifestations or if the electrodes became disconnected from the amplifier during the seizure. Characteristic seizure sections were chosen visually from the unfiltered EEG viewed at 10 s/page (33 mm/s) in bipolar montage wherein consecutive contacts on each depth electrode are compared (for instance, for electrode LA, we examined channels LA1-LA2, LA2-LA3...LA8-LA9). Sections were 3–10 s in duration and included pre-ictal background as well as 3–6 ictal portions. The background section was marked at least 5 s before the seizure onset, and all following ictal portions were selected to reflect seizure onset, evolution, propagation and termination. Attempts were made to maintain consistency in the chosen sections among seizures in the same patient in order to allow comparison of individual sections. This consistency included sections that had similar ictal localization, rhythmic frequency and morphology. For each patient, all seizures studied had similar onset patterns, similar ictal localization, rhythmic frequency and morphology. Further, when comparing background and ictal sections for each channel of the bipolar montage, there was a parallel increase in the number of channels involved to different extents or at different stages of the ictal process. When the evolution of seizures was vastly different, sections were occasionally not marked so as to not equate different propagation patterns during the comparison of seizure sections.

Channels exhibiting artefacts around the time of seizures were eliminated from the analysis. This was determined visually from the unfiltered EEG viewed at 10 s/page. Typically, the most superficial channels were contaminated with artefact because the ultimate and penultimate superficial contacts (contacts 8 and 9) were often located out of the skull vault and consequently contaminated by muscle artefact. A summary of the channels and seizure sections analysed is shown in Table 2.

### Quantification of HFOs in seizure sections by spectral analysis

Frequency spectra were obtained by fast Fourier transformation of the background and ictal sections for each channel of the bipolar montage, using non-overlapping epochs of 0.512 s that were averaged over the course of each section. Initially, spectral power was plotted for all channels and sections in order to identify frequency peaks in the EEG. The frequency spectra almost always displayed smooth quasi-exponential decays at gamma frequencies and beyond, with the exception of occasional 60 Hz artefact peaks. Highest energies were present at very low frequencies (0.1–10 Hz) followed by progressively lower spectral powers at higher frequencies. Further, when comparing background and ictal sections for channels involved in seizure activity, there was a parallel increase in spectral power across all frequencies with the increased amplitude of the EEG (Fig. 1).

A second more detailed analysis of seizure spectra involved comparing background and ictal sections using recognized EEG bands. The spectral power was calculated in the following bands: 'sub-gamma', 0–40 Hz; gamma, 40–58 and 62–100 Hz; 'high frequency (HF)', 100–200 Hz; 'very high frequency (VHF)', 250–500 Hz. The 58–62 Hz band was excluded from the gamma band because of filter algorithm. The computer screen was split in order to inspect the expanded EEG at each of these two filter settings simultaneously with identical gains. Distinct HFOs were defined as events (i) containing at least four consecutive peaks with similar inter-peak intervals; (ii) appearing on several occasions at a similar frequency in the same channel, in the same seizure section; (iii) able to be easily separated at both the 50 and 100 Hz high-pass filter settings from the predominant activity. For short segments of <100 ms, HFOs were discriminated from the surrounding EEG, and for longer events, they were identified by comparison with the background sections. We did not consider events to be present if the same high-frequency rhythm was unchanged through all seizure and background sections. This identification of HFOs will be illustrated in the Results section below. Frequency calculations were performed manually from the computer display by peak counting. When a high-frequency event was identified using this method, we later applied a notch filter at 60 Hz to ensure that this was not caused by artefact from the power source.

### Table 2 Summary of depth electrode recordings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total no. of clinical seizures</th>
<th>No. of seizures analysed</th>
<th>No. of sections (including background)*</th>
<th>Channels recorded</th>
<th>Channels analysed after exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>40</td>
<td>33</td>
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<tr>
<td>3</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>40</td>
<td>29</td>
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<tr>
<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>48</td>
<td>42</td>
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<tr>
<td>5</td>
<td>16</td>
<td>5</td>
<td>5</td>
<td>48</td>
<td>33</td>
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<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>56</td>
<td>49</td>
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<tr>
<td>7</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>56</td>
<td>26</td>
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<td>8</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>7</td>
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<tr>
<td>9</td>
<td>19</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>14</td>
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<tr>
<td>10</td>
<td>13</td>
<td>1</td>
<td>5</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Total (average)</td>
<td>93 (9.3)</td>
<td>25 (2.5)</td>
<td>50 (5.0)</td>
<td>408 (40.1)</td>
<td>304 (30.0)</td>
</tr>
</tbody>
</table>

*Total number of sections selected in each of the patient’s seizures.

**Detection of distinct HFOs in seizure sections by visual inspection**

The pre-ictal background and ictal sections were analysed visually for the presence of distinct oscillations with frequencies >100 Hz. As described below, seizures most often resulted in increased power of all frequencies over the background, with slower oscillations (i.e. <50 Hz) comprising the bulk of the change in spectral power (Fig. 1).

To visualize distinct HFOs, the bipolar EEG described above was expanded to 0.62 s/page (530 mm/s) and digitally high-pass filtered at 50 Hz as well as 100 Hz using an FIR (finite impulse response) expanded to 0.62 s/page (530 mm/s) and digitally high-pass filtered.
possible contamination by the main power source. Spectral band power was then used to determine relative band power changes in seizure sections as compared with each seizure’s background. Calculations were as follows: relative VHF = (VHFsection – VHFbackground)/VHFbackground; relative HF = (HFsection – HFbackground)/HFbackground; relative gamma = (gammasection – gammabackground)/gammabackground; relative sub-gamma = (sub-gammasection – sub-gammabackground)/sub-gammabackground.

However, as shown in Fig. 1, all band powers tended to increase during ictal activity concomitant with the visible increase in EEG amplitude. In order to identify specific increases in high-frequency band powers beyond these more generalized increases, we used the sub-gamma band as a measure of the widespread spectral changes related to EEG amplitude and calculated the differences between high-frequency and sub-gamma results (i.e. relative VHF or HF or gamma minus relative sub-gamma). We therefore measured the increase in high frequencies beyond the ‘expected’ increase similar to that in sub-gamma. For example, if the sub-gamma band increased by 2-fold, and the VHF band increased by 5-fold, we considered that the VHF band increased by 3-fold over its expected rise.

Statistical analysis was performed using the channels and ictal sections in which distinct, visually identifiable HFOs were seen. Spectral band values from the individual 0.512 s ictal epochs included in an ictal section were compared with averaged background values for each seizure in order to calculate relative VHF, HF and sub-gamma as detailed above. If the patient had multiple seizures, the relative VHF, HF and sub-gamma results from ictal epochs were concatenated for statistical analysis. We applied a transformation of the relative band values using the formula Log (X + 1) in order to have an approximate Gaussian distribution for each measure. A one-way analysis of variance (ANOVA) was performed comparing the sub-gamma, HF and VHF bands. If the F-test was significant (P < 0.01), a post hoc Tukey test compared HF with sub-gamma and VHF with sub-gamma. Significance is reported for relative HF or VHF means that are greater than relative sub-gamma at P < 0.01.

**Results**

Ten consecutive patients (4 males, mean age: 36 years) were enrolled in the study (Table 1). This cohort included a variety of temporal and extra-temporal cases, with the great majority showing abnormalities on MRI. The most frequent sites for placement of depth electrodes were in the temporal and frontal lobes. Implantations were unilateral in five patients and bilateral in five. Seizure onsets were well defined and focal in seven patients (patients 1–7, Table 1). In patient 8 the onset was unilateral neocortical temporal; in patient 9, the onset was in a region without electrodes; in patient 10,
the onset was bilateral temporal. We will refer to patients 8–10 as patients with regional-onset seizures. Depth electrodes (each containing nine contacts) were more numerous in the former group as compared with the latter (6.0 ± 0.8 versus 3.0 ± 2.6), whereas there was no corresponding significant difference in the number of epidural electrodes (5.0 ± 5.9 versus 7.7 ± 0.6). Among the patients with focal seizure onset, four had seizures starting in mesial temporal areas and the remaining three had extra-temporal neocortical foci.

**Effect of high-pass filtering on visually identifiable EEG oscillations**

The standard EEG sampling rate is 200 Hz and with low-pass filtering of this signal; frequencies > 100 Hz are not detectable. Very sharp or fast components of the EEG are therefore best resolved with high sampling frequencies. Also, high-frequency signals are best discerned by expanding the horizontal (time) axis of the EEG as the signal visualized at standard time-scales (e.g. 7.5–10 s/page) allows discrimination of oscillations from 0.5 to 30 Hz, but faster frequencies quickly surpass the resolution of computer screens that typically have 1000–1200 vertical columns per page. The effects of sampling frequency and time-scale expansion on the electroencephalographer’s ability to identify sharp or fast components of the EEG are shown in Fig. 2.

As illustrated previously, the depth EEG displays a predominantly exponential decay in its spectral array in all channels during both pre-ictal and ictal periods (Fig. 1), although peaks were often present below 25 Hz at the predominant

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**Fig. 2** High frequencies may be visualized with expanded time-scales and with high-pass filtering. (A) Seizure activity in three channels is shown from patient 2 at a standard time-scale of 7.5 s/page. A short, highlighted sample is shown for further visualization. (B) Highlighted sample shown at an expanded time-scale with improved visualization of higher-frequency components. (C) Highlighted sample displayed with low-pass 65 Hz filtering to simulate a recording at 200 Hz digitizing frequency. The high-frequency sharp components are blunted in comparison with B. (D) Highlighted sample with expanded time-scale and high-pass filtering of 50 Hz. Note that the gain has been increased. The predominant rhythm seen with this filtering is between 50 and 75 Hz. (E) Highlighted sample with high-pass filtering of 100 Hz. The predominant rhythm is now between 100 and 150 Hz.
frequency of the seizure discharge. As a result, high-pass filtering this signal very often results in a visually identifiable oscillation slightly superior to the cut-off frequency. This is seen in Fig. 2 with high-pass filters at 50 and 100 Hz, wherein, with different gains, oscillations of 50–75 and 100–150 Hz are recognized, respectively. However, intermixed within these predominant rhythms, there are occasional relatively higher amplitude very fast components with frequencies > 100 Hz that are identifiable at both filter settings (Fig. 2D and E).

**HFOs identified through visual inspection**

We examined seizures and their pre-ictal backgrounds using expanded time-scales with simultaneous 50 Hz as well as 100 Hz high-pass filtering. High-frequency events were identified according to the criteria outlined previously (see methods section). Chiefly, HFOs were deemed significant if they were almost identical at both filter settings and at the same gain, if they occurred repetitively in a paroxysmal or sustained fashion, and if the periodicity of the oscillations in these segments was relatively stable. Such events were distinguished in 7 of the 10 patients, and occurred at frequencies in the HF and VHF bands (shown in the final Results section).

Most commonly, HFOs were segmental, lasting 10–50 ms either in the HF or in the VHF band (heretofore called HF or VHF segmental oscillations, Figs 3–5), or, less commonly, they were prolonged and lasting 50 ms to a few seconds (heretofore called HF or VHF prolonged oscillations, Figs 6

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**Fig. 3** Discrete HFOs are identified in the EEG through visual inspection of the digitally filtered signal. (A) Unfiltered ictal EEG at standard time-scale (patient 4). Highlighted sample for further visual analysis in (B) and (C). Ictal EEG is shown at an expanded time-scale and increased vertical gain with high-pass filtering at 50 and 100 Hz in B and C. A brief 160–210 Hz (HF band) segmental oscillation is well visualized in the RAH1-2 channel at both filter settings. (D) Unfiltered ictal EEG at standard time-scale (patient 1). A highlighted sample is shown at increased vertical and horizontal gain in parts E and F with filtering. A discrete 285–375 Hz (VHF band) segmental oscillation is clearly visualized in RMH2-3 and, to a lesser extent, RMH3-4 at both filter settings.
HFOs of all types were present in very limited distributions with HF events confined to 1–3 channels and VHF to 1–2 channels of the same depth electrode. Although these events were most often localized in deep mesial temporal structures, neocortical localizations were also seen (described later). There was a wide variation in the amplitude of HFOs but generally events with frequencies from 100 to 200 Hz were of higher amplitude than those from 250 to 500 Hz, commonly ranging between 40 and 200 μV and 5–30 μV, respectively. In an exceptional case (patient 1), we found HF activity up to 1000 μV (Fig. 4).

**HFOs identified through spectral analysis**

Characteristic seizure sections were marked before the detailed visual analysis described above. These sections were compared with the pre-ictal background for gamma, HF and VHF bands. A similar comparison using the sub-gamma band was used as an internal reference to help identify channels in which prominent high-frequency activities were located. The differences in relative band power between high-frequency and sub-gamma activity were graphed for all channels. In most channels, the activity in the HF and VHF bands decreased in relative importance compared with the sub-gamma band (Fig. 8). In other words, whereas sub-gamma most often increased at seizure onset (reflecting the visually observable changes), activity in HF and VHF bands increased less or decreased at seizure onset. There were exceptions, however; few channels showed increases in HF or VHF larger than those in sub-gamma (Fig. 8), and when positive peaks were prominent, they corresponded on visual analysis to discrete or continuous HF or VHF oscillations. Table 3 shows the statistically significant increases in high-frequency spectral power in channels and sections containing visually identifiable HFOs.

Spectral analysis was generally less proficient than visual analysis in identifying VHF than HF segmental oscillations. This could be explained by the fact that VHF segmental
oscillations typically contained only small fractions of the energy in the VHF band of an ictal section because these events were of restricted frequency, had a low amplitude and often a short duration (i.e. 10–30 ms) (Fig. 3). Even when VHF oscillations were longer than 50 ms, this spectral analysis method was inconsistently able to detect these events. Figures 6 and 7 demonstrate well-localized VHF oscillations near the time of seizure onset from patients 3 and 7, respectively. Despite the VHF segmental oscillations lasting 50–100 ms in patient 3, there was no detectable spectral difference peak. In patient 7, a positive spectral difference peak was seen with VHF oscillations lasting > 1 s, yet it did not reach statistical significance.

**Localization of high-frequency events**

We analysed 12 seizures from the four patients with mesial temporal foci, and in all of these we identified VHF events ranging in frequency from 285 to 400 Hz in onset as well as propagation sections of the seizure (Table 3). Events
were segmental in all sections except for patient 3, in whom prolonged VHF oscillations were seen early during the seizures concomitant with the low-voltage fast onset pattern seen more grossly. In four patients, VHF events were always localized to channels within the seizure-onset zone determined by the clinician. Such events involved disparate mesial temporal structures including the amygdala, anterior and middle hippocampi among our four patients. In one case (patient 2), we found asynchronous VHF segmental oscillations in two different areas of the mesial temporal lobe within each of the patient’s seizures during the propagation section (Fig. 4). Discrete VHF events were not seen in the background sections of our mesial temporal lobe cases except for patient 4 in whom this was present but was far less frequent as compared with ictal sections. Analysis of spectral data of the EEG sections in which HFOs were visually identified revealed significant VHF changes in patient 1 only. As discussed above, this is caused by the difficulty of

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**Fig. 6** Prolonged HF and VHF oscillations at the time of seizure onset in a case of mesial temporal lobe epilepsy. (A) Unfiltered low-voltage fast seizure-onset pattern for patient 3 starting from the right mesial temporal region. First highlighted sample (1) represents pre-ictal background followed by three ictal onset samples (2–4). (B) Expanded and 50 Hz high-pass filtered background (1: middle left) and ictal (2: middle right; 3,4: lower) samples. Initial prolonged (>50 ms) 300–375 Hz (VHF) oscillations are indicated (2, arrows) and followed by mixed HF and VHF (3) and then 120–190 Hz (HF) oscillations (4) in the RAH1-2 channel, which are not seen in the background. Lower-amplitude 120–190 Hz prolonged oscillations are also present in RMH1-2 simultaneously with the RAH1-2 HF oscillations. The increased HF but not VHF oscillations were also identified using spectral analysis of the corresponding 3–5 s long seizure-onset sections for this patient’s four seizures (not shown).
the spectral analysis method to capture the brief VHF oscillations.

A second consistent finding among our four mesial temporal lobe cases was the presence of HF events ranging from 120 to 200 Hz. Aside from patient 3, these events were always segmental and, in contrast to VHF events, occurred exclusively during ictal propagation sections (Table 3). Similar to the VHF HFOs, however, they were always located in only a few channels within the different mesial temporal lobe structures, but HF HFOs differed in that they could also be seen in an area of contralateral propagation to the initial seizure-onset zone (patient 1, Fig. 4). HFOs were again

Fig. 7 VHF activity at the time of seizure onset in a case of neocortical epilepsy. Patient 7 had a frontal neocortical porencephalic cyst and seizure onset occurred first in contacts close to the border of the cyst. (A) Unfiltered low-voltage fast-activity seizure-onset pattern at standard time-scale. (B) Filtered highlighted samples from background and seizure-onset sections at expanded time-scale and gain. Sustained 330–400 Hz VHF activity is seen at the time of seizure onset in channels LAC2-3 and LAC3-4. (C) Spectral analysis of the seizure-onset section from A reveals an ‘excess’ increase (compared with sub-gamma) in the VHF band of channel LAC3-4 and to a lesser extent in the gamma band of channel LAC4-5, whereas other channels showed less marked or negative changes.
distinctive for patient 3 in that the HF events were also seen during onset ictal sections, were prolonged (lasting 300–1200 ms) and immediately followed the VHF prolonged oscillations. The spectral analysis method confirmed statistically significant HF HFOs in either onset or propagation sections in three of the four patients.

In the neocortical seizure-onset group (eight seizures analysed in three patients), HFOs were once again identified solely in regions located within the seizure-onset zone determined by the clinician (Table 3). Unlike the mesial temporal seizures, however, the patterns of HFOs appeared more varied. One patient with a focal cortical dysplasia (patient 5) showed mixed HF and VHF oscillations that were initially discontinuous (150–300 ms duration) in the background and later became largely continuous in the ictal sections (not shown). In contrast, there were no HFOs identified in the other dysplastic case (patient 6) either in the background or at seizure onset, and these were only seen later in the patient’s seizures as segmental HF oscillations in the frontal neocortical onset zone. Yet another pattern of HFOs was seen in our third patient with neocortical seizures, where patient 7 who had a porencephalic cyst demonstrated de novo prolonged

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**Fig. 8** Summary spectral analysis data among patients with localized seizure onsets demonstrating focal HF or VHF activity. Top left graph is a key to read the patient graphs. For patients 1–7, the graphs represent in each channel means with standard errors for all seizures of relative band power differences (or ‘excess’ power) for HF (left) and VHF (right) bands at seizure onset (unshaded) and during propagation (shaded). Band power differences were mostly negative in onset and propagation sections, indicating that the relative importance of HF and VHF activity had most often decreased during seizures compared with their importance in the background. Less-frequent positive peaks were seen exclusively in patients 1 and 3–7. Discrete channels with visualized HFOs often had associated positive peaks that reached statistical significance and are marked in Table 3.
Table 3 Locations of visually identified HFOs and statistically significant spectral peaks in seizures

<table>
<thead>
<tr>
<th>Patient (total no. of seizures)</th>
<th>Seizure-onset zone location (no. of seizures/total)</th>
<th>Pre-ictal background section(s) Visualized HFOs (no. of seizures with events/total)</th>
<th>Seizure-onset section(s) Visualized HFOs (no. of seizures with events/total)</th>
<th>Seizure propagation section(s) Visualized HFOs (no. of seizures with events/total)</th>
<th>Spectral band statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (2) R pars orbitalis (2/2) None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>–</td>
<td>None identified</td>
<td>–</td>
</tr>
<tr>
<td>7 (1) L mid. frontal gyrus and ant. cingulum (1/1) None identified</td>
<td>L ant. cingulum (1/1): 330–400 Hz</td>
<td>L ant. cingulum (1/1): 330–400 Hz</td>
<td>–</td>
<td>L ant. cingulum (1/1): 330–400 Hz</td>
<td>–</td>
</tr>
<tr>
<td>Regional-onset seizures</td>
<td>8 (2) Diffuse (2/2) None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>N/A</td>
</tr>
<tr>
<td>9 (2) Diffuse (2/2) None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>N/A</td>
</tr>
<tr>
<td>10 (1) Diffuse (1/1) None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>None identified</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: R, right; L, left; mid., middle; ant., anterior; inf., inferior; \( ^2 \)HF band oscillations occurred immediately following VHF oscillations (Fig. 6); \( ^2 \)Segmental VHF oscillations were infrequent as compared with ictal sections (see text); \( ^2 \) Mixed frequency oscillations in HF and VHF bands were discontinuous in background and more continuous in ictal sections (see text).
VHF oscillations at seizure onset that later became segmental. Positive spectral peaks were present in channels containing HFOs in these three patients, and were statistically significant except for patient 7 for whom only one seizure was available for analysis (Fig. 8, Table 3).

We analysed five seizures among three patients with poorly localized ictal onset zones for the presence of HFOs. As mentioned above, these patients averaged fewer depth electrodes as compared with the other two groups. They also differed from the mesial temporal and neocortical onset cases in that no HFOs were visually identified either in background or ictal sections. Moreover, no important maxima were seen in the spectral band value differences of seizure sections.

**Discussion**

The important finding of this study is that distinct, focal HFOs in the range of 100–500 Hz can be identified in human focal epilepsy patients using depth macroelectrodes. Moreover, we found that when present in the VHF band (250–500 Hz) near the time of seizure onset, the distribution of these oscillations correlates well with the seizure-onset zone determined by the clinician. Focal HFOs are seen not only in mesial temporal but also in extra-temporal cases, and HFOs were notably absent in patients who had regional seizure-onset zones (patients in whom no focal onset was recorded). The recording of HFOs with macroelectrodes implies that they occur over a much wider volume than that had been observed with microelectrodes. Our macroelectrodes have a surface ∼1000 times larger than typical microelectrodes. We speculate that these HFOs result from the summation of very local oscillations partially synchronized over a relatively large volume, local oscillations that have been reported using microelectrodes (Bragin et al., 1999a, 2002).

**HFOs in mesial temporal-onset seizures**

Previously, HFOs in human mesial temporal epilepsy patients have been recorded using microelectrodes only. This method involves platinum–iridium microwires measuring 40 μm in diameter being inserted through the lumen of a multi-contact clinical depth electrode and extending a few millimetres beyond its tip. Microelectrodes record the field potential from a very small volume and dipole models can be calculated within mesial structures from the multiple closely spaced wires. Using microelectrodes, fast ripples (250–500 Hz) were first identified in the intrahippocampal kainate rat model of mesial temporal lobe epilepsy, and in this model as well as in humans, they are often associated with interictal and ictal spikes in tissue capable of generating spontaneous seizures (Bragin et al., 1999c). Fast ripples demonstrate a reversal of polarity across middle layers of entorhinal cortex, and the cellular networks underlying their generation appear to be more localized than the slower ripples (Chrobak and Buzsaki, 1996; Bragin et al., 2002). Until recently, only fast ripples have been ascribed pathological significance and are considered surrogate markers of epileptogenicity (Bragin et al., 2000). In contrast, ripples are equally present in epileptogenic and non-epileptogenic temporal lobe, and are suppressed by the desynchronizing effects of wakefulness and REM sleep, thereby suggesting that they are a normal feature of the hippocampal EEG (Staba et al., 2004), perhaps involved in physiological memory function (Buzsaki et al., 1992; Klausberger et al., 2003). However, this initial characterization of physiological ripples has been questioned and it appears that, particularly in the dentate gyrus, these may be pathological and epileptogenic (Bragin et al., 2004; D’Antuono et al., 2005).

The localized fast activities observed in this study at the time of seizures have several characteristics similar to HFOs recorded in mesial temporal structures using microelectrodes. Like ripples and fast ripples, the discrete fast activities presented here were recorded stably in the same electrode contacts over several days, whereas contacts that initially failed to exhibit HFOs never did so in subsequent seizures. The HFOs occurred usually in short segments ranging from 10 to 50 ms (the notable exception being patient 3) and were frequently, but not always, associated with ictal spikes. Lastly, we found that VHF oscillations, like fast ripples, were located primarily in channels near the epileptic generator.

Despite these similarities, we have noted two important differences between the HFOs described to date and those presented here. Although ripples and fast ripples have been extensively characterized in the hippocampus and entorhinal cortices of rats and patients, only ripple-like oscillations have been described in the rat amygdala (Ponomarenko et al., 2003), and neither of these HFOs have yet been reported in the human amygdala as was seen in one of our patients (patient 4). Secondly, we found that HFOs, particularly in the VHF band, were more prominent at seizure onset than in the background or later in the seizure, whereas ripples and fast ripples have not been studied during human seizures.

In addition, the amplitudes of VHF oscillations (250–500 Hz) recorded in our subjects were much smaller than human fast ripples (5–30 versus 100–1250 μV, respectively) (Bragin et al., 2002). In part, the explanation for the difference in amplitudes is that the recorded field potentials from locally generated fast ripples are averaged across the much larger surface area of the macroelectrode and therefore result in smaller oscillation amplitudes as compared with recordings from smaller microelectrodes. In keeping with this explanation is our finding of little difference in the amplitudes of HF oscillations (100–200 Hz) as compared with human ripples (40–1000 versus 120–1050 μV, respectively), and the wider field potentials from a broader network of neurons seen in ripples (Chrobak and Buzsaki, 1996; Bragin et al., 2002). Another reason for smaller amplitudes in our results is the probable relative lack of synchrony between the locally generated HFOs seen with microelectrodes.
HFOs in neocortical-onset seizures

In this study, macroelectrode contacts were also able to record stable HFOs in seizure-onset areas of three patients with neocortical-onset seizures. We found focal high frequencies during seizures to be consistently present despite the varying epileptic aetiologies that included cortical dysplastic and porencephalic cyst lesions. This finding is in keeping with previous neocortical recordings in cats during seizures (Grenier et al., 2003). In humans, Worrell et al. (2004) described focal ictal activity in the high gamma range in a series of neocortical seizures, and others have reported localized ictal high frequencies up to 130 Hz in a few seizures associated with cortical dysplastic lesions (Allen et al., 1992; Traub et al., 2001). While we and others have observed that localized high frequencies appear in seizure-onset zones, it remains unclear as to whether in all cases these zones also have represented the ‘true’ epileptic generator areas. In our series, we found differing patterns of HFO onset, duration and oscillatory frequency among the three patients with neocortical epilepsy, and it remains unclear as to whether these variables provide important information reflecting proximity to the site of epileptogenesis.

HFOs in regional-onset seizures

We have postulated that focal high frequencies recorded using depth macroelectrodes could provide important information about the localization of epileptic generators in a variety of seizure types. This hypothesis may be supported by our findings in patients with regional-onset events. In the three patients comprising this group, intracranial investigations were unable to delineate a seizure focus, and, notably, these same patients were solely devoid of HFOs. While fewer depth electrodes were used in this group as compared with the two others, we might expect that this more limited depth EEG coverage would negatively but similarly affect sampling for focal high frequencies and for epileptogenic areas in these patients. The absence of focal HFOs on the depth EEG may indicate poor localization in cases of focal epilepsy but future studies with more patients are needed to strongly assert this position.

Mechanistic implications

Patients with mesial temporal lobe epilepsy demonstrated discrete fast oscillations consistently in areas of seizure onset, and we postulate that when HFOs occur early during ictal activity (perhaps more prominently in the VHF band), their presence may help delineate areas of epileptic generation. We found the duration of VHF HFOs at the time of ictal onset to be varied and shorter in seizures characterized by a rhythmic spike-onset pattern, and prolonged (>50 ms) in the seizures with low-voltage fast onset. Interestingly, Bragin et al. (2005a) studied seizures from kindled rats and also found very different HFO characteristics depending on the gross ictal onset pattern. Whereas focal HFOs (fast ripples) appeared prominently at the time of seizure onset in rhythmic spike events, as they did in our patients, HFOs were rarely seen in low-voltage fast seizures, unlike what we found in our patients. Several authors assert that these two different gross temporal lobe ictal onset patterns indicate differing regions of origin (Spencer et al., 1992; King and Spencer, 1995; Velasco et al., 2000; Bragin et al., 2005b).

The low-voltage fast ictal onset pattern is often associated with neocortical foci, whereas, the rhythmic spike pattern is more common with hippocampal seizure generation. One of our patients with low-voltage fast ictal pattern had a mesial temporal lobe onset (patient 3, Fig. 6) and the other a neocortical onset (patient 7, Fig. 7). As both patients showed prolonged VHF oscillations, a pattern-specific rather than region-specific pathophysiological mechanism may be hypothesized, if indeed fast oscillations reflect phenomena closely linked to the generation of seizures. HFO variables such as amplitude, duration or frequency may provide insight into the involved neuronal circuits, and be affected by factors such as neuronal loss or mossy fibre sprouting in areas of pathologically interconnected neuron clusters.

Neocortical epilepsy patients also demonstrated localized high frequencies in the same bands and in seizure-onset areas, analogous to the findings in mesial temporal epilepsy patients. These similarities suggest commonality to diverse epileptogenic origins. Little is known about the pathogenic epileptic circuitry associated with the gliotic tissue of porencephalic cysts, but cortical dysplastic tissue has an intrinsic ability to develop seizure-like discharges (Palmini et al., 1995; Dubeau et al., 1998; Avoli et al., 1999; Turkdogan et al., 2005) and has multiple alterations in excitatory and inhibitory receptors that influence epileptic activity (Ferrer et al., 1992; Alonso-Nanclares et al., 2005). These alterations may be important in the generation of the apparently pathological HFOs that we found during the seizures of two patients with neuronal migration lesions.

Future directions

This was a study designed to explore the hypothesis that focal HFOs were recordable using macroelectrodes in the depth EEG of focal epilepsy patients. It is unknown whether the discrete oscillations we have described fall into well-defined bands, and the development of automatic detection methods to pool high-frequency events either ictally or interictally would be helpful. Lastly, we have postulated that the presence or absence of HFOs in the depth EEG could have diagnostic implications in the evaluation of epilepsy patients. However, we have used the EEG seizure onset as a surrogate for the epileptogenic area in our discussions regarding the potential relevance of HFOs in localization, and 1–2 year surgical outcome results would be useful in strengthening these assertions.

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