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Detection of changes of high-frequency activity by statistical time-frequency analysis in epileptic spikes

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ABSTRACT

Objective: A novel type of statistical time-frequency analysis was developed to elucidate changes of high-frequency EEG activity associated with epileptic spikes.
Methods: The method uses the Gabor Transform and detects changes of power in comparison to background activity using t-statistics that are controlled by the false discovery rate (FDR) to correct type I error of multiple testing. The analysis was applied to EEGs recorded at 2000 Hz from three patients with mesial temporal lobe epilepsy.
Results: Spike-related increase of high-frequency oscillations (HFOs) was clearly shown in the FDR-controlled *t*-spectra: it was most dramatic in spikes recorded from the hippocampus when the hippocampus was the seizure onset zone (SOZ). Depression of fast activity was observed immediately after the spikes, especially consistently in the discharges from the hippocampal SOZ. It corresponded to the slow wave part in case of spike-and-slow-wave complexes, but it was noted even in spikes without apparent slow waves. In one patient, a gradual increase of power above 200 Hz preceded spikes.
Conclusions: FDR-controlled *t*-spectra clearly detected the spike-related changes of HFOs that were unclear in standard power spectra.
Significance: We developed a promising tool to study the HFOs that may be closely linked to the pathophysiology of epileptogenesis.

1. Introduction

Recent development of digital EEG recording with high sampling frequency rates (1000–2000 Hz) has facilitated observation of high-frequency activity of up to 600 Hz (Le Van Quyen et al., 2006). High-frequency oscillations (HFOs) ranging from 80 to 250 Hz (ripples) can be recorded from the hippocampus and entorhinal cortex of normal rodents (Buzsáki et al., 1992; Chrobak and Buzsáki, 1996) and also from human hippocampus (Bragin et al., 1999a). In kainic acid-treated rats and patients with mesial temporal lobe epilepsy, even faster HFOs of 250–500 Hz (fast ripples) have been detected using microelectrodes or microwires from regions close to the epileptogenic lesion, and are suggested to reflect pathological hypersynchronous events crucially associated with seizure generation (Bragin et al., 1999a,b; Staba et al., 2002; Rampp and Stefan, 2006). Jirsch et al. (2006) demonstrated for the first time that HFOs in the range of 100–500 Hz can be recorded from human epileptic patients during focal seizures using depth macroelectrodes: they made an important advance for the study of HFOs that had been limited by the mandatory usage of microelectrodes or microwires to record fast ripples.

The interictal epileptic spikes on EEG are traditional indications of epileptic irritability of the brain. An epileptic spike sometimes occurs together with a slow wave immediately following the spike and then is referred to as a spike-and-slow-wave complex. Urrestarazu et al. (2006) found using depth macroelectrodes that the power of high-frequency activity above 100 Hz is decreased during the period immediately following spikes, and that this decrease is prominent in the hippocampus but less consistent in amygdala and neocortex. It was indicated that the reduction in fast activity could reflect a depression in neuronal activity during post-spike slow waves. Experimental studies have shown an inhibitory action of neuronal hyperpolarization caused by both intrinsic and synaptic mechanisms in the slow wave phase following the paroxysmal depolarization shift (PDS) that corresponds to spikes (Ayala et al., 1973; Neckelmann et al., 2000). Given a hypothesis that reduction of the inhibitory action, especially altered balance between excitation and inhibition, is involved in epileptogenesis (Ayala et al., 1973), further analysis with respect to the changes of

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high-frequency activity associated with epileptic spikes might lead to a better understanding of the mechanisms of seizure generation.

We have developed a novel type of statistical time-frequency analysis in order to elucidate such spike-related changes of high-frequency activity in more detail regarding their frequency characteristics and temporal sequence. We performed a preliminary evaluation of this analysis with clinical data in the present study.

2. Materials and methods

2.1. Patients and EEG recording

Between 2005 and 2007, 47 patients with medically intractable epilepsy were recorded with intracranial electrodes and a high sampling rate at the Montreal Neurological Institute. The first three patients with bi-temporal implantations and mesial temporal lobe epilepsy were selected for this study. No other selection criteria were used. The Montreal Neurological Institute and Hospital Research Ethics Committee approved this study and informed consent was obtained from each patient.

Stereoelectroencephalography (SEEG) was performed by implanting depth electrodes orthogonally through the middle temporal gyrus in anterior, mid and posterior locations so that the deepest contacts were situated in the amygdala, hippocampus and parahippocampus. The implantation method is described by Olivier et al. (1994). Electrode bundles were implanted stereotactically using an image-guidance system (SSN Neuronavigation System, Mississauga, Ontario, Canada) through percutaneous holes drilled in the skull.

Intracranial depth electrodes (electrode bundles) 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 electrode bundle 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 mm^2, and was 0.85 mm^2 for the single deep contact. Impedances were measured once immediately after implantation; they varied between 1 and 20 kΩ (Urrestarazu et al., 2006).

The EEG telemetry signal was digitally recorded with a 128-channel Harmonie system for long-term monitoring (Stellate, Montreal, Canada) with filter settings of 0.1 and 500 Hz and a sampling frequency of 2000 Hz in conformity to Jirsch et al. (2006) and Urrestarazu et al. (2006). The analysis was performed using a bipolar montage. Each channel compared two adjacent contacts of the same electrode bundle. (Table 1) shows the information about the implanted electrodes and the finding of the seizure onset zone (SOZ) of each patient. The SOZ was defined as the set of contacts that showed the earliest ictal activity during the intracranial investigation.

2.2. Spectral analysis

SEEG recordings were visually reviewed to identify the interictal epileptiform discharges. The discharges were categorized according to spatial distribution and morphology. The polarity of spike peak was negative in some discharges and positive in others depending on the relation between the generator and the electrode locations, but the identified spike types had a consistent polarity. In each patient, four different types of discharges were classified and marked in the interictal SEEG data: (1) a spike-and-slow-wave complex recorded from the SOZ (SW_{SOZ}), (2) a spike without slow wave recorded from the SOZ (S_{SOZ}), (3) a spike-and-slow-wave complex recorded from outside the SOZ (NSOZ)(SW_{NSOZ}), and (4) a spike without slow wave recorded from outside the SOZ (S_{NSOZ}).

With respect to each spike type, 50 EEG segments lasting 2000 ms (comprising 4000 data-points) and non-overlapping were sampled for analysis, each segment including a marked spike and surrounding background activity. The spike segments were selected not to include any other spike or artifact in the channel of the marked spikes, and the minimal interval between the selected spikes was 2.5 s. A time-frequency power spectrum was built for each spike segment of bipolar EEG data by using the Gabor (Windowed Fourier) Transform (Kobayashi et al., 2004) with a sliding Gaussian window of 50 ms FWHM (full width half maximum) (the spike-related spectral data). The frequency range was 50–500 Hz. The Fourier Transform was performed on 512 data-points (256 ms; frequency resolution 3.9 Hz) of the window at each time-step, and the step of the sliding window was 2 ms. The signal power was converted to logarithmic scale to obtain a more Gaussian distribution (Gasser et al., 1982). The average spike-related spectra were obtained by averaging the 50 data segments regarding each spike type.

For statistical comparison of the power of fast activity between the spikes and the background, 300 EEG segments lasting 256 ms and non-overlapping were selected in the background, and the Fourier Transform was similarly applied to each background

Table 1
Summary of the results of analysis.

Patient	Spike type	Electrode location	Relation to seizure origin	Fast activity in spike	Post-spike depression of fast activity
1	SW	Left hippocampus	SOZ	+++	+++
	S	Left hippocampus	SOZ	+++	++
	SW	Left temporal neocortical region	NSOZ	+	No
	S	Right temporal neocortical region	NSOZ	No	No
2	SW	Right hippocampus	SOZ	+++	+++
	S	Right hippocampus	SOZ	+	++
	SW	Left amygdala	NSOZ	++	No
	S	Left amygdala	NSOZ	++	No
3	SW	Right hippocampus	SOZ	+++	+
	S	Right hippocampus	SOZ	+	No
	SW	Left hippocampus	NSOZ	+	no
	S	Left hippocampus	NSOZ	+	no

SW, spike slow wave; S, spike without slow wave.
SOZ, seizure onset zone; NSOZ, non-seizure onset zone.
Fast activity in spike and the post-spike depression of fast activity were rated as +++ when they involved the whole frequency band of 50–500 Hz, as ++ when they extended beyond 200 Hz but did not involve the whole frequency band of 50–500 Hz, and as + when they did not extend beyond 200 Hz.