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High frequency oscillations in intra-operative electrocorticography before and after epilepsy surgery

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HIGHLIGHTS

- Ripple, spike and fast ripple rates in intra-operative electrocorticography decreased after surgical resection of epileptogenic tissue in epileptic patients.
- Resection of areas showing fast ripples seems related to good surgical outcome.
- Ripples not associated with a spike increased after resection in sensorimotor areas.

ABSTRACT

Objective: Removal of brain tissue showing high frequency oscillations (HFOs; ripples: 80–250 Hz and fast ripples: 250–500 Hz) in preresection electrocorticography (preECoG) in epilepsy patients seems a predictor of good surgical outcome. We analyzed occurrence and localization of HFOs in intra-operative preECoG and postresection electrocorticography (postECoG).
Methods: HFOs were automatically detected in one-minute epochs of intra-operative ECoG sampled at 2048 Hz of fourteen patients. Ripple, fast ripple, spike, ripples on a spike (RoS) and not on a spike (RnoS) rates were analyzed in pre- and postECoG for resected and nonresected electrodes.
Results: Ripple, spike and fast ripple rates decreased after resection. RnoS decreased less than RoS (74% vs. 83%; $p = 0.01$). Most fast ripples in preECoG were located in resected tissue. PostECoG fast ripples occurred in one patient with poor outcome. Patients with good outcome had relatively high postECoG RnoS rates, specifically in the sensorimotor cortex.
Conclusions: Our observations show that fast ripples in intra-operative ECoG, compared to ripples, may be a better biomarker for epileptogenicity. Further studies have to determine the relation between resection of epileptogenic tissue and physiological ripples generated by the sensorimotor cortex.
Significance: Fast ripples in intra-operative ECoG can help identify the epileptogenic zone, while ripples might also be physiological.

1. Introduction

Epilepsy surgery aims at the removal of epileptic brain tissue to achieve seizure freedom. In 60–70% of the patients who undergo epilepsy surgery, long-term seizure freedom is achieved (de Tisi et al., 2011; Hauptman et al., 2012). Successful surgery may lead to improved cognitive outcome and better cognitive and social development in children (Van Schooneveld and Braun, 2013). Intra-operative electrocorticography (ECoG) can be used during surgery to delineate the epileptogenic area. Removal of areas showing interictal epileptiform discharges, especially spikes, in the preresection ECoG (preECoG) has been associated with increased seizure freedom (Kuruvilla and Flink, 2003; Stefan et al., 2008). After the

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resection, ECoG can be performed again (postECoG) to check for the presence of remaining spikes. The use of intra-operative ECoG to tailor surgery is disputed. Some studies showed that the presence of remaining spikes was correlated with seizure recurrence and removal led to improved outcome (Stefan et al., 2008; Tripathi et al., 2010) while others showed no correlation (Schramm, 2008; Wray et al., 2012). PostECoG spikes might arise from surgical manipulation of the neocortex, especially at the edge of the resection (Schwartz et al., 2000).

Spontaneous high frequency oscillations (HFOs: ripples 80–250 Hz and fast ripples 250–500 Hz) are proposed as new biomarkers for the epileptogenic zone. HFOs, especially fast ripples, have shown to be more correlated with the seizure onset zone (SOZ) than interictal epileptiform discharges such as spikes (Bragin et al., 2002; Urrestarazu et al., 2007; Jacobs et al., 2008; Wu et al., 2010; Zijlmans et al., 2012b). Most previous studies concentrated on HFOs in ECoG and depth EEG recordings obtained before resection, showing increased seizure freedom when more electrodes with ictal HFOs (Fujiwara et al., 2012) or interictal HFOs were removed (Jacobs et al., 2010; Akiyama et al., 2011; Haegelen et al., 2013). One study in intra-operative preECoG found a correlation between removal of areas showing fast ripples and seizure freedom (Wu et al., 2010).

Ripples are not necessarily pathological, as physiological ripples occur in the mesiotemporal, occipital, and sensorimotor area (Nagasawa et al., 2012) and have been related to cognitive functions like memory (Axmacher et al., 2008). It seems difficult to distinguish physiological from pathological ripples (Engel et al., 2009), but the co-occurrence with spikes might be an indicator of pathology (Wang et al., 2013). Fast ripples in healthy tissue were only found after stimulation; spontaneous fast ripples have not been described (Curio et al., 1994; Staba et al., 2004).

Remaining HFOs in intra-operative postECoG have not been studied before and the influence of resection on HFO occurrence is unknown. This information can establish the clinical usefulness of HFOs during surgery and improve the understanding of their pathophysiology. We focused on intra-operative ripples, fast ripples and spikes in preECoG, their difference in rate between pre- and postECoG and their relation to surgical outcome. Further, we studied occurrence of HFOs and spikes at the edge of the resected area.

2. Methods

2.1. Patients

Patients with refractory epilepsy who underwent tailored surgery with intra-operative ECoG between 2008 and 2012 at our center and for whom one year postsurgical outcome was available were retrospectively selected. Only spikes were used in clinical decision making. Patients were excluded if they had recurrent tumor growth, had disconnection surgery, had chronic ECoG registration before surgery, did not have both pre- or postECoG, or if their data had been used in optimizing the automatic HFO detector, which will be discussed later. Recordings with numerous artifacts or a burst suppression pattern were excluded. Postsurgical outcome was classified using the Engel classification, dichotomized into good (Engel 1) and poor (Engel $\geqslant$2) outcome. Patients who met the inclusion criteria were divided into four groups: (1) patients with temporal lobe epilepsy (TLE) and good outcome, (2) patients with TLE and poor outcome, (3) patients with extratemporal lobe epilepsy (ETLE) and good outcome and (4) patients with ETLE and poor outcome. We randomly selected as many patients as possible from each group, while maintaining equal numbers in the groups. (Table 1).

2.2. Intra-operative ECoG

A 4×5 electrode grid and sometimes 1×8 electrode strips (Ad-Tech, Racine, WI, USA) were placed on the cortex during surgery. ECoG was registered with a 128-channel EEG system (MicroMed, Veneto, Italy), at 2048 Hz sampling rate with an anti-aliasing filter at 538 Hz. Electrode grids and strips were placed, and preECoG was recorded for three to four minutes. Then the grid and strips were replaced into different positions, to make sure the suspected epileptogenic cortex and surrounding areas were covered. After initial resection, electrode grids and strips were again placed on the cortex, around the resected area, and ECoG was again measured. If needed, resection was extended and ECoG recording repeated. The last recorded ECoG was defined as the postECoG. The grid and strips were placed in at least one and maximum five positions in pre- and postECoG. ECoG during propofol anesthesia shows a burst suppression pattern, which is not appropriate for clinical decision making. Propofol was therefore interrupted typically 5–10 minutes until the signal showed a continuous background pattern with conventional EEG settings (1.6–70 Hz, 10 s/page, 100 μV/mm) in which spikes can be found (Zijlmans et al., 2012a). Patients did not wake up.

2.3. Data selection

ECoG was visually assessed in a bipolar montage along the length of the electrode grid or strip. One-minute epochs of ECoG were selected from each electrode position pre- and postECoG, near the end of each recording.

2.4. Detection of HFOs

Ripples and fast ripples were detected retrospectively by an automatic detection algorithm, adapted from the Montreal Neurological Institute (MNI) HFO detector (Zelmann et al., 2010). Identified ripples and fast ripples were visually checked using Stellate Harmonie Reviewer (Montreal, QC, Canada), and artifacts identified as HFOs were removed.

The MNI detector was designed to identify HFOs in depth EEG recordings and was adapted and optimized for intra-operative ECoG recordings. Optimization of the detection parameters was performed on 103 pre- and postECoG channels from recordings from six patients, randomly selected from our database, different from the patients selected for this study (Table 2). Ripples and fast ripples in one minute epochs were visually scored in each bipolar channel by two reviewers (NvK, MvtK or MZ) in Stellate Harmonie Reviewer. Inter-rater variability was determined and channels were discussed until kappa was at least 0.5 (Zelmann et al., 2009). Visual analysis was performed as described earlier (Zelmann et al., 2009), but amplitude sensitivity for ripples was set at 5 μV/mm because intra-operative ECoG baseline amplitude was too high for evaluation at 1 μV/mm. HFOs in consensus of both reviewers were used as gold standard reference for optimization of the parameters. Two new steps were added to the detection algorithm to limit the number of falsely detected events. These were restrictions on the amplitude and on the number of cycles of each HFO. The optimized detector was validated on 377 other pre- and postECoG channels of the same six patients. Comparing HFOs identified by reviewers and by the detector resulted in a sensitivity of 93.6% and specificity of 84.6% for ripples and 94.2% sensitivity and 93.4% specificity for fast ripples. Sensitivity and specificity were defined as in (Zelmann et al., 2010). Visual post processing of the automatically detected HFOs was still required.