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Non-harmonicity in high-frequency components of the intra-operative corticogram to delineate epileptogenic tissue during surgery

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HIGHLIGHTS

- An auto-regressive model residual modulation (ARRm) delineates epileptic tissue based on the non-harmonicity of the signal.
- Tissue with high ARRm corresponds to fast ripples and removal of this tissue relates to outcome.
- The ARRm can be used as real-time analysis tool during epilepsy surgery as it is fast and insensitive to subtle artefacts.

ABSTRACT

Objective: We aimed to test the potential of auto-regressive model residual modulation (ARRm), an artefact-insensitive method based on non-harmonicity of the high-frequency signal, to identify epileptogenic tissue during surgery.
Methods: Intra-operative electrocorticography (ECoG) of 54 patients with refractory focal epilepsy were recorded pre- and post-resection at 2048 Hz. The ARRm was calculated in one-minute epochs in which high-frequency oscillations (HFOs; fast ripples, 250–500 Hz; ripples, 80–250 Hz) and spikes were marked. We investigated the pre-resection fraction of HFOs and spikes explained by the ARRm (h^2-index). A general ARRm threshold was set and used to compare the ARRm to surgical outcome in post-resection ECoG (Pearson X^2).
Results: ARRm was associated strongest with the number of fast ripples in pre-resection ECoG ($h^2 = 0.80$, $P < 0.01$), but also with ripples and spikes. An ARRm threshold of 0.47 yielded high specificity (95%) with 52% sensitivity for channels with fast ripples. ARRm values >0.47 were associated with poor outcome at channel and patient level (both $P < 0.01$) in post-resection ECoG.
Conclusions: The ARRm algorithm might enable intra-operative delineation of epileptogenic tissue.
Significance: ARRm is the first unsupervised real-time analysis that could provide an intra-operative, 'on demand' interpretation per electrode about the need to remove underlying tissue to optimize the chance of seizure freedom.

1. Introduction

Epilepsy is a dynamic condition as seizures occur intermittently and in most cases unexpectedly. This suggests that the underlying processes responsible for the generation and cessation of seizures are non-harmonic, i.e. non-linear and non-stationary. A high level of non-linearity in the system is needed to initiate seizures (Helling et al., 2015). The epileptiform EEG contains several

Abbreviations: ARRm, autoregressive model residual modulation (novel algorithm); $ARRm_{orig}$, autoregressive model residual modulation (original algorithm); ECoG, electrocorticogram; FR, fast ripples; HFO, high-frequency oscillation; R, ripples; r_n, residual signal variance, after modelling using an autoregressive model with order n; S, spikes.

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biomarkers which all have a strong non-linear component (Elger et al., 2000; Andrzejak et al., 2012). This holds true for epileptiform inter-ictal spikes, for the recently discovered high-frequency oscillations (HFOs; >80 Hz) and for seizures themselves. All these events appear without notice (Jacobs et al., 2008; Staba et al., 2014; Staba and Worrell, 2014).

During epilepsy surgery there is need for biomarkers to delineate the epileptogenic tissue that should be resected to assure seizure freedom after surgery. Even in the presence of an epileptogenic lesion on MRI the resection boundaries are not always clear, e.g. in cases of neuronal tumours, in which the epileptogenic zone may extend beyond the lesion, or when the hippocampus is secondarily affected (Gallentine and Mikati, 2009). Epilepsy surgery can be tailored by identifying spikes in the intra-operative electrocorticogram (ECoG), but this method is controversial (Kuruvilla and Flink, 2003; van 't Klooster et al., 2015). Surgical removal of cortex showing fast ripples, between 250 and 500 Hz, has been associated with post-operative seizure freedom (Wu et al., 2010; van 't Klooster et al., 2015). HFOs probably result from hyper synchronous, out-of-phase firing of groups of principal neurons (Jefferys et al., 2012), and might be more local to the epileptogenic tissue than spikes (Crépon et al., 2010; Jefferys et al., 2012). It may thus be better for the tailoring of epilepsy surgery with ECoG to rely on HFOs, especially fast ripples, rather than on the currently used spikes (van 't Klooster et al., 2015).

Visual analysis of HFOs is time consuming and requires the presence of expert reviewers during surgery (Zelmann et al., 2009). The time available to record and analyse HFOs is limited, and HFO occurrence is infrequent, so they can easily be missed (van Klink et al., 2014; van 't Klooster et al., 2015). Automatic detectors have been developed, but most still require extensive computing time (Blanco et al., 2010; Crépon et al., 2010; Zelmann et al., 2010, 2012; Dumpelmann et al., 2012; von Ellenrieder et al., 2012; Worrell et al., 2012; Burnos et al., 2014), making these techniques unsuitable for use in the time frame of surgery. Additionally, it can be difficult to distinguish pathological HFOs from physiological high frequency activity. High frequent physiological activity probably shows a harmonic pattern (Kerber et al., 2014). It can also be difficult to distinguish HFOs from artefacts, while artefact sources, such as the diathermy and the surgical microscope, are ubiquitous in the surgical theatre (Zijlmans et al., 2012b). Analysis of non-harmonicity in high-frequency components of the EEG signal, recorded at a high sampling rate >2000 Hz, may provide an automated and objective solution that bypasses these issues.

The auto-regressive model residual modulation (ARRm) can be used to predict which intracranial EEG channels are within the presumed epileptogenic area (Geertsema et al., 2015). We developed the ARRm algorithm to identify 'bad' channels. The ARRm reflects the amount of non-harmonicity in the high-frequency components of the signal, in terms of high residual signal variation after autoregressive modelling. The ARRm can be computed rapidly and only requires short epochs of EEG and thereby seems to lend itself to online analysis during surgery (Geertsema et al., 2015). We adjusted the ARRm algorithm to reduce the influence of typical intra-operative ECoG artefacts; artefacts may produce spuriously large residual signal variations, resulting in false positive high ARRm values unrelated to the epileptic tissue. We focused on the rejection of subtle short-lasting electrode and movement artefacts, as these are the most difficult to identify.

We aimed to test the potential of the new ARRm algorithm to identify epileptogenic tissue during surgery. Therefore we compared the ARRm to the occurrence of fast ripples, ripples and spikes in pre-resection intra-operative ECoG, and studied the relationship between ARRm results in post-resection ECoG and post- surgical outcome.

2. Methods

2.1. ECoG database

2.1.1. Patients

The database consisted of intra-operative ECoG recordings sampled at 2048 Hz, before and after resection, of patients with refractory focal epilepsy who underwent tailored epilepsy surgery between 2008 and 2012 at the UMC Utrecht. General anaesthesia was induced using a combination of propofol and a synthetic opioid and maintained using a target-controlled propofol infusion pump. The surgical strategy was based on the results of presurgical diagnostics (e.g. MRI, PET, MEG, video-EEG) together with intra-operative tailoring based on inter-ictal spikes and spike patterns, using conventional EEG settings (70 Hz low pass filter, 10 s/-page) in a common average reference montage. HFOs were never analysed during surgery. The database was collected according to the guidelines of the institutional ethical committee of the UMC Utrecht, The Netherlands. The institutional ethical committee approved the study and waived the need for written informed consent because of the retrospective character, provided that data were coded and handled anonymously.

The database was constructed based on the inclusion and exclusion criteria as described in a previous study (van 't Klooster et al., 2015). We included 54 patients (median age 15.5 years, 29 male, 30 right-sided surgeries) with a median follow-up after surgery of 25 months (range 17.0–35.8 months). The resection area was temporal in thirty-three patients, frontal in twelve, peri-central in seven, and parietal and occipital each in one patient. Pathology was classified in four groups; mesial temporal sclerosis (MTS, $N = 8$), tumours with glial components (including gangliomas and dysembryoplastic neuroepithelial tumours (DNET); $N = 23$), malformations of cortical development (e.g. focal cortical dysplasia (FCD) and tuberous sclerosis; $N = 15$) and other pathologies (e.g. cavernomas and gliosis; $N = 8$). Thirty patients (56%) became seizure free after surgery (Engel 1A) (Engel et al., 1993). This post-surgical outcome was determined for the most recent follow-up with a minimum of one year.

2.1.2. ECoG recordings

Intra-operative ECoG recordings were made with a 64-channel EEG system (MicroMed, Veneto, Italy) at 2048 Hz sampling rate using an anti-aliasing filter at 538 Hz. We used 4×5 or 4×8 electrode grids and 1×6 or 1×8 electrode strips (Ad-Tech, Racine, WI). The platinum electrodes are embedded in silicone with a 4.2 mm^2 contact surface and 1 cm inter-electrode distance. Grids and strips were placed in multiple configurations before (pre-resection ECoG), during extension of the resection, and after resection (post-resection ECoG). Propofol anaesthesia was stopped during ECoG registration until a continuous ECoG background pattern was achieved. The anaesthesiologist monitors the patient's heart rate and blood pressure closely, restarting the propofol before the patient starts to wake up. To minimize propofol effects we selected the last minute of each pre- and post-resection recording for analysis; on average this was 11 min after propofol was stopped. Analysis was performed on bipolar electrode pairs lengthwise on the grids. Bipolar channels with continuous artefacts that were visible in the raw ECoG signal were excluded.

2.2. Marking of HFOs and spikes

We used an automated detector previously developed, adapted for our intra-operative ECoG, to detect HFOs (Zelmann et al., 2010). The detector uses a high pass finite impulse response (FIR) filter >80 Hz for ripples and >250 Hz for fast ripples (Zelmann et al.,