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Beamforming applied to surface EEG improves ripple visibility

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HIGHLIGHTS

- Beamformer-based virtual electrodes showed more ripples than physical EEG electrodes.
- Virtual electrodes had a better SNR than physical electrodes.
- Virtual ripples predicted the ROI better than physical ripples, but sensitivity was still poor.

ABSTRACT

Objective: Surface EEG can show epileptiform ripples in people with focal epilepsy, but identification is impeded by the low signal-to-noise ratio of the electrode recordings. We used beamformer-based virtual electrodes to improve ripple identification.

Methods: We analyzed ten minutes of interictal EEG of nine patients with refractory focal epilepsy. EEGs with more than 60 channels and 20 spikes were included. We computed ~79 virtual electrodes using a scalar beamformer and marked ripples (80–250 Hz) co-occurring with spikes in physical and virtual electrodes. Ripple numbers in physical and virtual electrodes were compared, and sensitivity and specificity of ripples for the region of interest (ROI; based on clinical information) were determined.

Results: Five patients had ripples in the physical electrodes and eight in the virtual electrodes, with more ripples in virtual than in physical electrodes (101 vs. 57, $p = .007$). Ripples in virtual electrodes predicted the ROI better than physical electrodes (AUC 0.65 vs. 0.56, $p = .03$).

Conclusions: Beamforming increased ripple visibility in surface EEG. Virtual ripples predicted the ROI better than physical ripples, although sensitivity was still poor.

Significance: Beamforming can facilitate ripple identification in EEG. Ripple localization needs to be improved to enable its use for presurgical evaluation in people with epilepsy.

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1. Introduction

Epilepsy surgery is a treatment option that can be considered in patients with refractory focal epilepsy. Presurgical identification of the epileptogenic zone, defined as the minimum area of cortex that has to be resected to achieve seizure freedom (Lüders et al., 2006), is essential for a good surgery outcome. Currently 52–62% of patients are reported to be seizure free five years after surgery

(de Tisi et al., 2011; Hauptman et al., 2012; Jobst and Cascino, 2015), suggesting limitations in the presurgical identification of the epileptogenic zone.

High frequency oscillations (HFOs: ripples 80–250 Hz and fast ripples 250–500 Hz) are new markers for epileptic tissue, mostly investigated in invasive electroencephalography (EEG). HFOs are often spatially and temporally correlated with epileptic spikes (Urrestarazu et al., 2007; Jacobs et al., 2008) and several studies have shown that ripples and fast ripples occur more often within the seizure onset zone than outside (Staba et al., 2004; Urrestarazu et al., 2006; Malinowska et al., 2015). Surgical resection of HFO-generating tissue is associated with seizure freedom (Urrestarazu et al., 2007; Jacobs et al., 2010; Akiyama et al.,

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2011; Haegelen et al., 2013). Invasive EEG electrodes are close to the neuronal generators and therefore have high signal-to-noise ratios (SNRs). Identification of ripples in non-invasive EEG is impeded by the distance between the generators and the electrodes, volume conduction, and reduction in SNR due to patient and environmental noise, such as muscle artifacts (Muthukumaraswamy, 2013). Some studies have reported ripples in surface EEG in focal epilepsy (Melani et al., 2013; Andrade-Valenca et al., 2011; van Klink et al., 2016b) and in generalized or idiopathic epilepsy (Kobayashi et al., 2010, 2011, 2015; van Klink et al., 2016c; Chaitanya et al., 2015). However, the number of detected ripples is usually low compared to invasive recordings, 0.5 ripples/minute compared to 12.9/min (Andrade-Valenca et al., 2011), and low signal quality deems about one third of the clinical EEGs of insufficient quality for ripple analysis.

Increasing the SNR of the EEG signal might increase the yield of ripples in surface EEG recordings. Beamforming is a source reconstruction technique that acts as a spatial filter and estimates location-specific brain activity by selectively weighting the signals measured by the electrodes (Van Veen et al., 1997). It has been shown that beamformer analysis increases the SNR in magnetoencephalography (MEG), and even enables detection of spikes (Hillebrand et al., 2016) and ripples (van Klink et al., 2016a) in patients with epilepsy without identifiable events in the raw signals.

Simulated surface EEG studies have shown that beamforming can be used to accurately estimate the sources in the brain (Van Hoey et al., 1999; Murzin et al., 2011, 2013; Mohamadi et al., 2012). Beamforming in EEG has mainly been used to localize task-related activity (e.g. Grosse-Wentrup et al., 2009; Cohen and Ridderinkhof, 2013; Hipp and Siegel, 2013; Schepers et al., 2013; Muthuraman et al., 2014; Smith et al., 2014; Knyazev et al., 2016; Van Vliet et al., 2016). Another application of beamforming is the rejection of artefacts and reconstruction of sources in EEG-fMRI (Brookes et al., 2008, 2009) and in MEG (Adjamian et al., 2009; Hillebrand et al., 2013). It has been shown that beamforming can also be used to localize epileptic spikes (Van Drongelen et al., 1996), and to localize ictal EEG activity (Gritsch et al., 2011), although dipole models or other distributed source models are more commonly used to localize spike activity (Plummer et al., 2008). One study used beamforming to reconstruct EEG signals, so-called *virtual electrodes*, at the same position as the actual electrodes, and showed an increased SNR and enhanced spike visibility in the virtual electrodes (Ward et al., 1999). In this study we performed reconstruction of electrodes at cortical locations to investigate if the increased SNR aided the identification of ripples in patients with focal epilepsy, similar to what we see in MEG (van Klink et al., 2016a). We compared the ripples in the physical EEG electrodes with ripples in virtual electrodes placed across the cortex, and their relation to the suspected epileptogenic area.

2. Methods

2.1. Patients

We retrospectively selected data from patients with refractory focal epilepsy, who underwent a 64- or 85-electrode cap EEG recording between 2007 and 2014 at the University Medical Center Utrecht. These EEGs were performed because localization of the epileptogenic area was difficult with standard MRI, video-EEG and other presurgical diagnostics. We included patients if the following data were available: (1) EEG recording with at least 60 electrodes and a sample frequency of at least 1024 Hz; (2) coregistered to a 3D T1 anatomical MRI, either 1.5 T or 3 T, with cubic voxels of 0.6 mm (patients 1 and 5) or 1 mm. All patients or

caretakers gave written informed consent to use the data for research.

2.2. EEG recording

The EEG was recorded with a 64-electrode EEG cap, using a Micromed 64-channel SD amplifier, or an 85-electrode EEG cap, using a Micromed Long Term Monitoring (LTM) Express amplifier (Micromed, Treviso, Italy), both with 1024 Hz sampling frequency. The EEG was recorded according to the clinical protocol, which was approximately 45 min of EEG in most cases. EEG channels with extensive artifacts were discarded for further analysis after visual inspection. A continuous epoch of ten minutes eyes closed resting-state EEG with good signal quality was selected for analysis in each patient. If available, NREM2 or NREM3 sleep was included in this epoch, as ripples occur more often during sleep (Staba et al., 2004; Bagshaw et al., 2009) and muscle artifacts occur less often during sleep (Andrade-Valenca et al., 2011).

2.3. Lead field calculation

EEG requires a more sophisticated forward model than MEG, particularly since beamformers are sensitive to modelling errors (e.g. (Hillebrand and Barnes, 2003)). A multi-layer realistic head model is preferred (Murzin et al., 2011; Staljanse et al., 2013). We calculated the lead field using a boundary element model (BEM) based realistically shaped head model. The 3D T1 MRI was segmented to construct a model that contained layers for the brain, skull and scalp of the patient (Fuchs et al., 2002), with conductivities of 0.3300, 0.0042 and 0.3300 S/m, respectively (Gabriel et al., 1996). The positions of the EEG electrodes were estimated according to the 10–10 system, because the Polhemus files for some patients were unreliable, because electrodes were missing, were localized at an unreliable position (i.e. compared to the approximate expected position as based on the 10–10 system), or were in unclear order. Our study group contained some small children, who did not always cooperate and made sudden movements that made the Polhemus files unreliable. The lead fields were computed for virtual electrodes on two surfaces oriented parallel to, and at a distance of approximately 2 and 4 cm from the skull. These surfaces were aimed to include the gyral and sulcal cortex. Virtual electrodes were spaced 3.5 cm apart in each surface, which resulted in an average of 79 virtual electrodes per patient (range: 68–103). The number of virtual electrodes was comparable to the number of physical electrodes in most patients (range: 49–89), and made it feasible to perform visual ripple marking. The lead fields were normalized per virtual electrode to correct for undesired depth dependent amplification of white noise (Fuchs et al., 1999). The normalization parameter was 1.5. Lead field computation and MRI segmentation were performed in Curry Neuroimaging Suite 7.0.9 (Compumedics Neuroscan, Victoria, Australia).

2.4. Beamforming

Beamformer weights for each virtual electrode were calculated using a scalar beamformer similar to Synthetic Aperture Magnetometry (SAM; (Robinson and Vrba, 1999)), where the optimum current orientation was found using the approach proposed by Sekihara and colleagues (Sekihara et al., 2004). The data covariance matrix was based on 80 Hz high-pass finite impulse response (FIR) filtered EEG segments of good signal quality. Regularization was applied to limit the sensor noise projected by the beamformer (Robinson and Vrba, 1999). A regularization parameter of 15% was used, because this resulted in the least noisy signals at visual inspection in the time and frequency domain. The signals at virtual electrode positions were computed using Fieldtrip (Oostenveld

et al., 2011, version September 2015) and Matlab (The Mathworks Inc., Natick, Massachusetts, USA, version R2015b) and saved in EDF format, allowing analysis in EEG software.

2.5. Event marking

Physical and virtual channels were reviewed using the Harmonie Reviewer software (Stellate, Montréal, Canada). Physical channels were reviewed in a longitudinal bipolar montage. All instances with spikes (spike-times) were marked in physical and virtual channels, displayed at 10 s/page and 20–30 $\mu\text{V}/\text{mm}$. Spike-times were marked by a first reviewer (AM) and checked by a second reviewer (NvK). The reviewers were blind for the physical channel spike-times when marking virtual channel spike-times and vice versa. Spike-like events with an unusual sharpness or amplitude in either physical or virtual channels were considered as artifacts. Patients were excluded from further analysis if less than 20 spike-times were marked in the physical and virtual electrodes together.

Ripples in physical and virtual electrodes were marked by using a split screen, with 80 Hz high pass FIR filtered channels on the left hand side, and the unfiltered signal on the right hand side. The filtered screen showed 0.5 s/page and 1–1.5 $\mu\text{V}/\text{mm}$. Only ripples co-occurring with spikes in a physical or virtual channels were marked by one reviewer (AM) and then checked by a second reviewer (NvK or MZ). The reviewers were blind for the ripples in the physical channels when marking ripples in the virtual channels and vice versa. Ripples were defined as at least four consecutive oscillations with an amplitude clearly standing out from the background. Ripple-like events with irregular morphology or very high amplitude compared to the background were considered artifacts.

2.6. Definition of the region of interest

All patient records were screened for information about the surgical resection area, surgery outcome, irritative zone, MRI-lesions, PET, MEG and SPECT abnormalities. Based on all available information, a region of interest (ROI) was determined by two researchers (AM and NvK) and a clinical neurophysiologist (CF). The ROI was defined as the smallest volume containing the clinically most relevant regions, thus representing the suspected epileptogenic zone. We chose this method of ROI selection instead of comparing to all separate clinical presurgical tests, because different information was available for each patient and because presurgical tests could be contradicting. The ROI was defined through the following protocol, depending on the available information: (1) the ROI was the resected brain area in patients with good surgical outcome; (2) in patients with poor surgical outcome the ROI was the resected brain area when the resection was assumed incomplete and other investigations were converging; (3) if (1) and (2) were not applicable, the ROI was the most convincing common denominator of the available EEG, MRI, PET, MEG and SPECT information; (4) if no common denominator could be found, no ROI was defined. The ROI was delineated in the MRI and visualized together with the physical and virtual electrodes. The ROI was marked with a margin of approximately 2 cm, to increase the sensitivity. Each physical and virtual electrode was marked as being inside or outside the ROI. Locations of the bipolar physical electrodes were defined as halfway between the two electrodes from which they were derived.

2.7. Analysis

The SNR was determined in patients with ripples in both physical and virtual electrodes. The SNR was calculated by the average

power in the HFO band (80–500 Hz) for the marked ripples, divided by the average power in the same frequency band for event-free epochs of signal with the same length as the ripples. The difference in SNR between physical and virtual channels was determined with a linear mixed model, to account for between-patient differences. We assumed an unstructured covariance structure with patients as random effect and the type of channel as fixed effect. We counted the number of spike-times and ripple-times in physical and virtual electrodes and determined how many times a ripple was marked in the physical and virtual electrodes at the same time. We compared the overall number of spike-times and ripple-times in the physical and virtual electrodes using a Wilcoxon Signed Rank Test.

2.8. Location of electrodes with ripples

All physical and virtual electrodes for each patient were categorized into one of four groups: (a) inside ROI, with ripples, (b) inside ROI, without ripples, (c) outside ROI, with ripples and (d) outside ROI, without ripples. These groups were used to determine the performance of the ripples in the physical electrodes and the virtual electrodes as a predictor for the ROI. Sensitivity was defined as the number of channels with ripples inside the ROI, divided by the total number of channels with ripples, and specificity was defined as the number of channels without ripples outside the ROI, divided by the total number of channels without ripples. We calculated the area under the receiver operator curves (ROC) and the 95% confidence intervals (CI), and compared the performance for the physical and virtual channels with each other and with chance using the DeLong test (DeLong et al., 1988). The cutoff value, as number of ripples per channel, with the best performance was determined by the highest sum of sensitivity and specificity. Statistical analyses were performed in RStudio (version 0.98.1060, RStudio Inc, Boston, MA, USA), using an α of 0.05.

3. Results

3.1. Patients

We included nine patients, of whom six were males and seven were children (Table 1). Five of them had tuberous sclerosis. Eight patients underwent surgery, five of whom were seizure free afterwards. A ROI could be determined for all patients except for patient 3, in whom, based on the available clinical information, many parts of the brain were considered to be involved in the epilepsy. The first six patients had a 85-channel EEG, of which on average 74 channels were clean from artifacts and used for the analysis. Patients 7 to 9 had a 64-channel EEG, of which on average 53 channels could be used. We placed on average 79 virtual electrodes in each patient (range 68–103). Patients 1 and 8 were asleep during the recording (NREM2–3), the other patients were awake.

3.2. Spike and ripple events in physical and virtual electrodes

The physical electrodes showed 616 spikes and the virtual electrodes showed 688 spikes (Table 2). Eight patients showed ripples, four of whom showed ripples only in the virtual electrodes and one showed only 1 ripple only in the physical electrodes. Seven patients had more ripples in the virtual electrodes than in the physical electrodes. We computed the SNR for three patients who had ripples in both physical and virtual electrodes (patients 1, 6, and 7), and found a significantly higher SNR for virtual electrodes than for physical electrodes (9.2 vs. 6.0, $F(133.0) = 13.7$, $p < .001$, SNR was normally distributed for both physical (Kolmogorov-Smirnov $p = .2$) and virtual channels (Kolmogorov-Smirnov

Table 1

Patient characteristics; epilepsy etiology; age at first seizure; the number of physical and virtual electrodes; the number of spike-times and ripple-times visible in the physical electrodes, the virtual electrodes and how many were co-occurring in both types of electrodes; and the maximum number of ripples in the physical and virtual channels. M: male; F: female; TSC: tuberous sclerosis complex; FCD: focal cortical dysplasia; MCD: malformation of cortical development; MTS: mesial temporal sclerosis; ILAE: International League Against Epilepsy qualification for Focal Cortical Dysplasias.

#	Gender/age	Epilepsy etiology	Age at first seizure	# Physical/virtual electrodes	# Spike-times			# Ripple-times			Maximum # ripples per channel (physical/virtual)
					Physical	Virtual	Both	Physical	Virtual	Both	
1	M/3	TSC (TSC2-mutation)	7 weeks	64/68	198	156	119	42	53	25	27/25
2	M/10	FCD, ILAE type 1B	5 years	89/68	50	59	33	0	8	0	0/3
3	F/12	TSC (TSC2-mutation)	10 weeks	76/95	104	124	97	1	0	0	1/0
4	F/9	TSC	4 months	67/77	5	33	5	0	0	0	0/0
5	M/5	TSC (TSC2-mutation)	3 months	77/77	27	29	15	0	2	0	0/2
6	M/3	TSC (TSC1-mutation)	10 months	69/74	35	31	24	3	9	2	2/5
7	M/30	Unknown	12 years	49/70	124	218	98	11	21	3	7/14
8	F/15	FCD, ILAE type 2B	3 years	54/78	9	14	1	0	4	0	0/2
9	M/42	MTS, Wyler grade 4	13 years	57/103	64	24	8	0	4	0	0/3
Totals					616	688	400	57	101	30	

Table 2

Epilepsy location: surgical resection area, surgical outcome at # years after surgery, ictal and interictal EEG/MEG abnormalities, MRI lesions, PET- and SPECT abnormalities and the ROI. L: left; R: right; NA: not available; MTS: mesial temporal sclerosis; VNS: vagal nerve stimulator; SISCOM: subtraction ictal SPECT co-registered to MRI; ROI: region of interest.

#	Surgery	Seizure onset zone	Interictal EEG abnormalities	MEG	MRI	PET/SPECT	ROI
1	Parasagittal tuber L parietal. Engel 1B (3 years)	L parietal parasagittal	L parietocentral parasagittal	NA	Multiple subependymal nodules and subcortical tubers	NA	L central and parietal parasagittal
2	R face area. Engel 4B, subtotal resection (1 year)	R central parasagittal	R central parasagittal and frontotemporal	NA	Gray matter loss and hyperintensity R frontolateral	NA	R frontocentral and central
3	Two tubers in L prefrontal lobe. Engel 1C (5 years, no seizures after VNS)	L precentral	R (fronto)-temporal L frontopolar	R (mid)-frontal, centro-temporal L occipital	Fontal, occipital, periventricular, cortical and subcortical tubers	PET: L fronto-polar, fronto-central and frontolateral R parietal	none
4	Parasagittal tuber L parietal behind postcentral gyrus. Engel 1A (3 years)	L central	L central, centroparietal, frontotemporal R frontotemporal	NA	Multiple Subependymal nodules and subcortical tubers	NA	L central, centroparietal
5	NA	NA	R midfrontal, frontotemporal, temporal, temporo-occipital, L temporal	R temporal, frontal	Multiple tubers, R frontal, temporal	Ictal SPECT: bilateral abnormalities, multiple foci SISCOM: R frontal, temporoparietooccipital	R frontal, temporal
6	Parasagittal tuber R parietal. Engel 2A (1 year)	NA	Centroparietal midline L parieto-occipital L and R central R frontocentral	NA	Multiple subependymal nodules and subcortical tubers, R parietal focal cortical dysplasia	NA	R centroparietal
7	L posterior superior temporal gyrus. Engel 1A (1.5 year)	L posterior superior temporal gyrus	L posterior temporal	NA	Abnormal cortical area in L posterior superior temporal gyrus	NA	L posterior superior temporal gyrus
8	L mesoparietal, behind postcentral gyrus. Engel 4B, probably subtotal resection (6 years)	L posterior cingulate gyrus. L frontal, frontolateral	L frontal, temporal, parietal	L parietal	Subcortical abnormality L parietal	NA	L parietal incl. part of posterior cingulate gyrus
9	L temporal lobe and hippocampus. Engel 1A (2 years)	NA	L temporal, frontal, central	NA	Cavernoma R cingulate gyrus, MTS L	PET: abnormality L frontal and temporal	L temporal

$p = .06$), and there was no multicollinearity (variance inflation factor (VIF) = 1.11)). We found more instances with ripples (ripple-times) in virtual electrodes than in physical electrodes (101 vs. 57 respectively; $Z = 2.38$, $p = .02$). The number of spike-times was not significantly different (688 vs. 616 respectively; $Z = 0.65$, $p = .52$). Examples of marked ripples in physical and virtual electrodes are shown in Fig. 1.

3.3. Location of electrodes with ripples

The physical and virtual electrodes with ripples and the ROI in each patient are shown in Fig. 2. Four patients had ripples in physical electrodes: these electrodes were all over the ROI in patient 6, partly over the ROI in patient 1 and not over the ROI in patient 7. These three patients showed ripples in virtual electrodes as well

Fig. 1. Example of ripples in physical channels and virtual channels in two patients. Unfiltered EEG is shown on the left. The grey marked epoch is 80 Hz high pass filtered and shown on the right. In patient 1 ripples are found in the physical channels as well as in the virtual channels (underlined), and the background noise is lower in the virtual channels than in the physical channels. In patient 8 physical channels did not show a ripple, whereas the virtual channels at the same time, located in the same area, did show ripples on multiple channels (underlined).

(see below). Patient 3 had one ripple in one physical channel, which was not found in the virtual electrodes, and a ROI could not be defined.

Seven patients showed ripples in virtual electrodes. In patient 8 most of these electrodes, in patients 1, 2, 6 and 7 part of them and

in patient 5 and 9 none of them were located inside or nearby the ROI. In other words, physical electrodes outperformed virtual electrodes in one patient (6), while virtual electrodes outperformed physical electrodes in three patients (2, 7, 8) in terms of spatial congruency with the ROI.

Fig. 2. Ripples in physical (blue) and virtual (red) electrodes. R = right, L = left. The ROI is plotted in green (if available). Filled circle markers indicate electrodes with ripples. Open square markers indicate electrodes without ripples. Marker size corresponds to the number of ripples found in the electrode. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 2 (continued)

Only three patients (patients 1, 6, and 7) showed ripples in both the physical and the virtual electrodes. All three showed more ripples in the virtual than in the physical electrodes, with 60%, 66% and 27% of the physical ripple-times also being a virtual ripple-time. In patient 1 both the physical and virtual electrodes with ripples were dispersed throughout the brain. In patient 6 and 7 the physical electrodes with ripples seemed to be more clustered than the virtual electrodes with ripples, with partly overlapping locations.

The ROC curve (Fig. 3A) shows that ripples in virtual electrodes were a significant predictor of the ROI (AUC 0.65, 95% CI: 0.57–0.74, $p < .001$), while ripples in physical electrodes were not (AUC 0.56, 95% CI: 0.47–0.70, $p = .16$). The performance of the virtual electrodes was also significantly better than the physical electrodes ($D(905.3) = 2.2$, $p = .03$). There was no difference in the AUC value for virtual ripples for patients with good outcome compared to patients with poor outcome ($D(523.8) = 0.05$, $p = .96$, Fig. 3B). The AUC of 0.65 for the virtual ripples, however, indicates a poor predictive value, as the cutoff value with the best performance has a sensitivity of 55.4% and a specificity of 72.2%, and discriminated channels without ripples from channels with one or more ripples (cutoff ≥ 1).

4. Discussion

We showed the feasibility of beamforming applied to surface EEG. We demonstrated a positive effect on ripple visibility in the recordings and on the ripple's predictive value for the suspected epileptogenic area. We found significantly more ripples in the virtual electrodes than in the physical electrodes, and in four patients ripples were found in virtual electrodes, but not in physical electrodes. On patient level, ripples in virtual channels better predicted the suspected epileptogenic area than ripples in physical channels in three patients, although the sensitivity was poor. These findings suggest that beamforming might be used in clinical EEG to improve the SNR and thereby increase ripple visibility.

Ripples in surface EEG are found in 60–80% of patients with focal epilepsy (van Klink et al., 2016c; Andrade-Valenca et al., 2011), which is higher than the 4 out of 9 (44%) patients who show ripples in physical electrodes in the current study. In the virtual electrodes we found ripples in 7/9 patients (78%). The SNR of the virtual channels was higher than the physical channels in all patients, which made marking of ripples easier and more reliable.

Previous surface EEG studies showed a good specificity (83–89%) and poor sensitivity (48%) for identification of the seizure onset zone by ripples (Andrade-Valenca et al., 2011; Melani et al., 2013). We found similar sensitivity (55%), and somewhat lower, but still relatively high specificity (72%) for the suspected epileptogenic zone. The poor sensitivity for ripples indicates that they are not suitable to determine the full extent of the epileptogenic region. This is in line with the fact that ripples in virtual channels showed similar sensitivity and specificity in patients with good and poor outcome, and indicates that this technique is not ready for clinical application. When higher sensitivities can be reached by improving the technique, the difference between good and poor outcome patients might become clearer. The good specificity, indicates that when a ripple is found, it is very likely to be in the epileptogenic region. Since the sensitivity and specificity for ripples in the physical channels reported in previous studies is comparable to our sensitivity and specificity obtained with virtual channels, it might not be necessary to calculate beamformer virtual electrodes for patients with ripples in the physical electrodes. However, for patients without discernable ripples in the physical electrodes, virtual electrodes might provide new information. In the latter case it may be that a beamformer calculated on the basis

of a more simple volume conductor model would still do an equally good job.

Beamforming acts as a spatial filter and therefore improves the SNR of the signals (Vrba and Robinson, 2001). Reconstruction of virtual electrodes at locations of interest can result in enhanced spike visibility in MEG (Hillebrand et al., 2016) and in EEG (Ward et al., 1999), and enhanced ripple visibility in MEG (van Klink et al., 2016a) and in EEG, as we show in this study. Virtual electrodes can theoretically be placed in each voxel of the MRI, which would result in too many channels to visually mark spikes or ripples, and go beyond the spatial resolution of the beamformer. If the moments of interest, the time points of ripples, are known, then source reconstruction can be used to generate a 3D representation of brain activity at these moments of interest. Lu et al. (2014) used such an approach to localize >30 Hz gamma band activity in patients with focal epilepsy, using SWARM, and determined the eventual surgical location in all 5 patients. Papadelis et al. (2016) used the wavelet Maximum Entropy on the Mean to localize ripples in EEG and MEG in two patients. These studies suggest that if the ripple-times are known, source reconstruction could aid to accurate localization of the ripple generating area.

Fast ripples (250–500 Hz) in invasive EEG have been described as a better marker for the epileptogenic zone than ripples (Jacobs et al., 2010; Wu et al., 2010; van 't Klooster et al., 2015). Fast ripples in surface EEG are rare, and their relation with the epileptogenic zone has not been confirmed (Pizzo et al., 2016). The sample frequency of our data was not high enough to allow identification of fast ripples. However, future studies should investigate whether reconstruction of virtual electrodes from surface EEG with an adequate sampling frequency can result in an increase in fast ripple visibility, similar to the increase in ripple visibility seen in this study.

EEG source analysis is usually performed with high density EEG recordings. The performance of source reconstruction increases with increasing number of electrodes (Lantz et al., 2003). 128-channel EEG is often used (Brodbeck et al., 2011; Knyazev et al., 2016), and systems with more than 200 electrodes are available. However, use of such a high number of electrodes is not common in clinical practice. In this study, we used our clinical 60- to 85-channel EEG recordings. The low density may have influenced the accuracy of the virtual electrode signals and the estimated ripple locations. Similarly, the estimated EEG electrode positions could have influenced the results, as electrode position errors could displace the sources after beamforming. E.g. Dalal et al. (2014) show that an average displacement of electrodes of ~7 mm can result in localization errors of the order of 5 mm. We considered such displacements to be of minor consequence for our proof-of-principle study, as the definition of our ROIs was wide as well.

In seven patients the epochs did not contain sleep, resulting in more muscle and movement artifacts. This can explain the low number of ripple-times in physical and virtual electrodes. Also, our selection of patients included people who often could not undergo MEG, mostly because they could not sit still for a long time. High-density EEG was only performed in patients with an unclear epileptic focus, i.e. complex patients, which impeded a clear interpretation of ripple localization. We expect better performance in data from patients with unifocal and clearly localized epilepsy and who are able to sit still or sleep during the recording.

Which montage is best to use for HFO analysis is disputable. An average reference montage often distributes noise, and a bipolar montage could give different results depending on the direction of the montage. A Laplacian montage in our data showed lower background noise than the bipolar montage, but also showed fewer ripples. The bipolar montage is most often used in literature (Andrade-Valenca et al., 2011; Kobayashi et al., 2015). In contrast,

Fig. 3. (A) Receiver operating curve (ROC) for physical (blue) and virtual (green) electrodes of all seven patients with ripples and a well-defined region of interest. Vertical lined and horizontal lined areas, bordered by black lines, show the 95% confidence interval of the ROCs of physical and virtual electrodes respectively. Crossed line filled areas these confidence intervals overlap. The light grey line indicates the ROC that represents a non-predictive measure, acting as good as chance. The area under the curve for the virtual electrodes (AUC 0.65) was significantly larger than the AUC for an uninformative test ($p < .001$) and for the physical electrodes (AUC 0.56, $p = .03$). The best performance for virtual electrodes showed a sensitivity of 55.4% and a specificity of 72.2% for a cutoff value of >1 ripple per channel. However, an AUC of 0.65 indicates a poor predictor. (B) ROC for virtual electrodes for patients with good (green) and with poor (red) outcome. Horizontal lined and vertical lined areas, bordered by black lines, show the 95% confidence interval of the ROCs of good and bad outcome patients respectively. Crossed line filled areas these confidence intervals overlap. The light grey line indicates the ROC that represents a non-predictive measure, acting as good as chance. There was no significant difference in the AUC value for virtual ripples for patients with good outcome compared to patients with poor outcome ($D(523.8) = 0.05$, $p = .96$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the virtual channels contain reference-free estimates of neuronal activity, hence a choice for a particular montage is not required.

Whether ripples in virtual electrodes in patients without ripples in physical electrodes are true reflections of epileptogenicity can only be examined by comparing them with a confirmed epileptogenic zone (i.e. resection resulting in seizure freedom). To assure that the ripples we marked in both the virtual and physical electrodes are of epileptogenic origin, we only marked ripples at the time of an epileptic spike, and discarded ripples with irregular morphology or extremely high amplitude compared to the background. Interestingly, one patient showed one ripple in the physical electrodes, which was not reproduced in the virtual electrodes. This might indicate that the coverage of the virtual electrodes was not sufficient to catch all ripples.

We determined the ROI using the most evident clinical information available. The gold standard is seizure freedom after resective surgery, but this was available in only four of our patients. In the other patients, less evident information, such as the location of MRI lesions, was used to determine the ROI. This was the best way we could determine the ROI for these patients, given the information that was available. In some patients, a large proportion of the virtual electrodes with ripples were located outside the ROI, but near to it, thus lowering the sensitivity and specificity. Ripples in these electrodes may reflect epileptogenicity as well. Their position close to the ROI might be caused by the variable spatial resolution of the virtual electrodes (Barnes et al., 2004), inaccuracy of the estimation of physical electrode positions (Dalal et al., 2014) or head model imperfections (Lanfer et al., 2012; Montes-Restrepo et al., 2014). However, it could also be the case that the ROIs were imperfect indicators of the epileptogenic zone. A larger study with successfully operated patients would be required to obtain spatially more accurate ROIs.

This is a first proof-of-principle study to show the feasibility of ripple analysis in beamformer reconstructed virtual electrodes in surface EEG. Future research should determine the additional effect of higher density EEG, higher density virtual electrodes, com-

bination with source reconstruction, and sleep epochs on the ripple visibility. The predictive value of the identified ripples for the epileptogenic zone should be assessed by including patients with a clear focus and seizure freedom after surgery.

5. Conclusion

Beamforming in surface EEG can improve ripple visibility, as virtual electrodes showed more ripples than physical electrodes, and the SNR was improved. Beamformer virtual electrodes with ripples predicted the clinically suspected epileptogenic zone better than physical electrodes with ripples in some patients, although the sensitivity of these virtual ripples was still poor. Good prediction of the epileptogenic zone and a sufficient number of events are necessary to use surface EEG ripples for decision-making in epilepsy surgery. Further studies with higher electrode density and better data quality are necessary to investigate the clinical value of ripple identification in surface EEG by beamforming.

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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