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High-Frequency Oscillations Recorded on the Scalp of Patients With Epilepsy Using Tripolar Concentric Ring Electrodes

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ABSTRACT Epilepsy is the second most prevalent neurological disorder (∼1% prevalence) affecting ∼67 million people worldwide with up to 75% from developing countries. The conventional electroencephalogram is plagued with artifacts from movements, muscles, and other sources. Tripolar concentric ring electrodes automatically attenuate muscle artifacts and provide improved signal quality. We performed basic experiments in healthy humans to show that tripolar concentric ring electrodes can indeed record the physiological alpha waves while eyes are closed. We then conducted concurrent recordings with conventional disc electrodes and tripolar concentric ring electrodes from patients with epilepsy. We found that we could detect high frequency oscillations, a marker for early seizure development and epileptogenic zone, on the scalp surface that appeared to become more narrow-band just prior to seizures. High frequency oscillations preceding seizures were present in an average of 35.5% of tripolar concentric ring electrode data channels for all the patients with epilepsy whose seizures were recorded and absent in the corresponding conventional disc electrode data. An average of 78.2% of channels that contained high frequency oscillations were within the seizure onset or irritative zones determined independently by three epileptologists based on conventional disc electrode data and videos.

INDEX TERMS Electroencephalography, epilepsy, high-frequency oscillations, tripolar concentric ring electrode sensors, Laplacian.

I. INTRODUCTION

Epilepsy is the second most prevalent neurological disorder (∼1% prevalence) [1] affecting approximately 67 million people worldwide with up to 75% from developing countries [2]. EEG is important in developing countries for various clinical uses, including evaluation of suitability for epilepsy surgery [3] and treatment of status epilepticus [4].

Epilepsy diagnosis is complicated by the fact that electrical potentials recorded from scalp electroencephalogram (EEG) have poor sensitivity to localized epileptiform activity, especially high frequency oscillations (HFOs) which now attract a lot of attention as a promising marker of epileptogenesis and ictogenesis [5]–[8]. Misdiagnosis of epilepsy is very common in patients of all ages and occurs in up to 50% of the patients [9], [10].

The HFOs occupy the gamma (30-100 Hz), ripple (100-200 Hz) and fast ripple (200-500 Hz) bands along with delta, theta, alpha and beta bands making up the remainder of the spectral content of EEG. Appearance of fast EEG rhythms at the onset of seizures in humans and animal models of epilepsy has been described in many studies and first reported in humans by Fisher et al. [11] and Allen et al. [12].

Fast rhythms are especially evident in intracranial recordings in patients considered for surgical treatment of their drug-resistant epilepsy. In recent years, there has been a surge in the number of publications on HFOs and their role in epilepsy (for reviews, see [8], [13]–[16]. Numerous studies on animal models and epilepsy patients have revealed that: 1) HFOs are one of the most common early manifestations of seizures recorded within minutes before seizure onset; 2) HFOs appear to be the most likely EEG correlate of a seizure onset zone (SOZ); and 3) the removal of HFO-generating areas correlates with good surgical outcome [5]–[7], [11], [12], [17]–[29]. Thus, HFOs appear to be an excellent marker for the epileptogenic zone [8] but their recording from scalp with conventional disc electrodes is difficult.

EEG has been a very useful research and clinical instrument for almost a century since its first human use by Hans Berger in 1920s [31]. However, it has significant limitations as a tool to measure brain activity. The distance to the brain and the relatively large electrical impedance of the skull significantly reduce small electrical signals generated by individual neurons. To be detectable at the scalp, the signal should be produced by a relatively large population of neurons acting more or less synchronously at scales of at least several centimeters [32]. Only in this case does the sum of individual neuronal signals become large enough to be detected at the scalp. Synchronous activity within neuronal assemblies is now considered an important mechanism of information processing, and this synchrony is expressed through neuronal oscillations occurring at different frequencies spanning several orders of magnitude from infraslow ($\sim$0.01 Hz) up to ultrafast ($\sim$1000 Hz) (for a comprehensive review of brain oscillations, see [33]. There is an intricate relationship between temporal and spatial scales of brain oscillations in that higher frequency oscillations (e.g., high gamma band $>$60 Hz) usually occur at smaller distances between sources and involve smaller neuronal populations. This is because more precise synchronization dictated by shorter oscillatory periods can be achieved only through shorter neuronal connections with shorter propagation times or non-synaptic communication such as ephaptic interactions and gap junctions. Long distance connections have longer propagation times and therefore synchronization at larger distances is less precise and preferentially occurs at lower frequencies (e.g., within delta, theta, alpha and beta bands). As a result, high frequency oscillations $>$60 Hz usually reflect activity within well localized neuronal assemblies at spatial scales of a few mm, which are not typically ''visible'' from the scalp. Thus, conventional EEG has lower sensitivity to high frequency components of brain activity [34], [35].

Conventional scalp EEG is also contaminated by noise represented by non-brain electrical activity such as ocular artifacts, scalp muscle potentials, and the electrocardiogram [36]. Additional noise is occasionally produced by abnormally large electrode impedance, electrode movement, amplifier drifts, etc. The noise can be as large as, or even larger than, the brain potential of interest and represents a significant problem for electroencephalographers and neurologists. This noise shows high spatial coherence due to smearing effects of the head volume conductor [37]–[39]. Conventional disc EEG recordings also have reference electrode problems. A common average reference and concentric electrodes have been proposed to resolve the reference electrode problems [40]. However, in the common average reference recordings, it is possible that components present in most of the electrodes but absent or minimal in the electrode of interest may appear as ''ghost potentials'' [41]. Thus, there is a strong need to develop new types of electrodes beyond conventional disc electrodes.

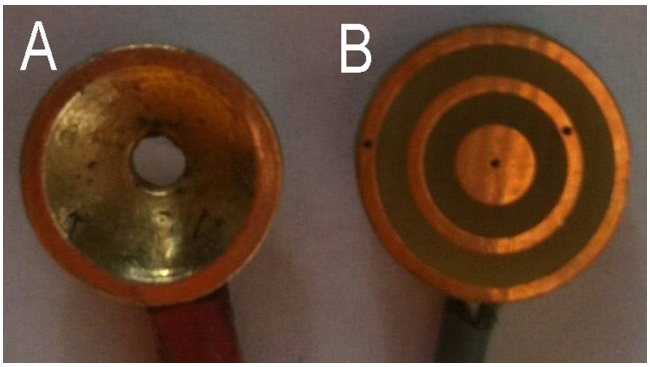

FIGURE 1. Conventional disc electrode (A) and tripolar concentric ring electrode (B).

To overcome the poor signal-to-noise ratio and reference problems of the disc electrodes Besio et al. have developed the tripolar concentric ring electrode (TCRE), a transformative electrode configuration [42]. The TCRE consists of three electrode elements - outer ring, middle ring, and the central disc (Fig. 1, B). It is distinctively different from the disc electrode which has a single element (Fig. 1, A). The novelty of the TCRE lies in a new principle of recording electrical activity of the brain from the scalp through its three closely spaced elements. It can provide three separate signals from the three electrode elements used to record two bipolar differential signals for the tripolar Laplacian derivation first described in [42] as a weighted sum {16*(M-D)-(O-D)} where O, M, and D are the potentials on the outer ring, middle ring, and central disc, respectively. The tripolar signal is a 'hardware realization' of the Laplacian i.e., the second spatial derivative of the scalp signal [43]. Unlike other software methods ('Laplacian montages' in conventional EEG systems) which approximate the Laplacian by taking differences between disc electrodes placed, at best, $>$1 cm apart, the TCRE performs the Laplacian automatically and takes bipolar differences of the surface potentials from closely spaced ($\sim$1 mm) concentric electrode elements with our custom preamplifier. With the electrode elements so close to each other, globally originating sources such as eye blinks, muscle or motion-related artifacts contribute nearly equally and are attenuated sharply when bipolar differences are performed by the preamplifier [42]. Compared with disc signals, EEG recorded with

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the TCRE (tEEG as described by [42]) has about a 4-fold (374%) increase in signal-to-noise ratio (SNR) and less than one-tenth (8.27%) the mutual information between signals recorded from two adjacent TCREs (which suggests a significant attenuation of volume conductance effects and, as a result, higher spatial resolution) [42], [44]. The TCRE also has strong attenuation of various artifacts, −100 dB at one radius from the electrode [42].

The current study presents preliminary data from patients with epilepsy in whom tEEG was recorded in parallel with clinical conventional scalp EEG. The goal is to demonstrate that tripolar electrodes may provide a unique opportunity to record HFOs from scalp and thus improve diagnosis of epilepsy and localization of the seizure onset and the irritative zones. Their implementation into clinical practice may eventually help determine where to place and reduce the number of intracranial grids and depth electrodes to be implanted during presurgical evaluation of patients.

II. METHODS

A. EPILEPSY PATIENT RECRUITMENT

Patients for this study were recruited from the National Institute of Neurology and Neurosurgery (NINN; ten patients) and Rhode Island Hospital (RIH; two patients). Patients were referred by the epilepsy clinic in each institution with the diagnosis of drug resistant epilepsy using the International League Against Epilepsy criteria [45]. Diagnosis of epilepsy and epileptic seizures was based on the international classification of seizures 1981 [46] and epileptic syndromes 1989 [47]. The recording protocols were approved by the institutional review boards at each hospital.

Ictal and non-ictal recordings were obtained; for non-ictal recordings lateralization and localization of the irritative zone (IZ) was determined whereas in ictal recordings the SOZ or IZ was identified with the appearance of behavioral changes associated with focal low voltage, fast activity, flattening or slow wave interruption [48].

B. HEALTHY SUBJECT EEG AND tEEG RECORDINGS

To verify that TCREs can be used to record physiological signals we recorded from three healthy subjects, one at Stanford School of Medicine and two at the University of Rhode Island (URI) placing conventional disc electrodes over the occipital lobe (at the O1 and O2 locations of the 10-20 International Electrode System with reference at A1 and ground electrode placed on the right collar bone). Two TCREs were placed right next to the conventional electrodes at the O1 and O2 locations (O1' and O2' positions, respectively). The TCRE EEG signals (tEEG) were first preconditioned with our custom made preamplifiers (gain = 20) and then passed to the bipolar inputs of the (Stanford - EEG-1200, Nihon Kohden Corporation, Tokyo, Japan; URI – Grass Technologies Aura LTM-64, Grass Technologies, West Warwick, RI) clinical EEG recording system. All signals were recorded with 1 to 120 Hz band-width at 500 S/s and stored to the hard drive for post processing. The subjects were asked to close and open their eyes repeatedly to record the presence or absence of alpha rhythms, respectively.

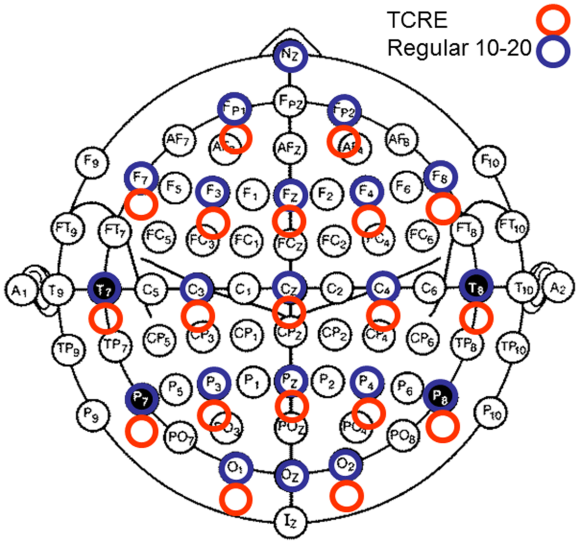

FIGURE 2. The 10-5 montage with TCREs (red) placed near the 10-20 locations. Note: T7/P7 and T8/P8 are the same as T3/T5 and T4/T6 in 10-20 nomenclature. The blue rings are for standard 10-20 electrode locations.

C. PATIENTS WITH EPILEPSY EEG AND tEEG RECORDINGS

The study's recording protocol was designed in such a way as to avoid any interference with clinical EEG recording and evaluation. At both the NINN and RIH during the attachment of clinical conventional disc electrodes (referred to as 'EEG electrodes' or 'EEG signals' in the subsequent text), the patient's scalp was cleaned with Nuprep and then EEG electrodes were placed at the 10-20 International Electrode System locations using Ten-20 paste. Collodion was also used to help hold all electrodes in place at the NINN. To obtain tEEG recordings in parallel to the clinical EEG, the TCREs were placed just behind the disc electrodes in locations close to the 10-10 sites and attached to the scalp with Ten-20 paste (Fig. 2). The ground was placed on the forehead (RIH, NINN) and the reference electrode was placed on the forehead at RIH and on the Oz location at NINN. Clinical EEG was recorded with the Comet AS40 system (Grass Technologies, West Warwick, RI) and stored separately for further clinical evaluation. The EEG sampling rate was 200 samples per second (S/s) and the low-pass filter was 70 Hz (NINN and RIH). The tEEG data were pre-amplified with the gain equal to either 6 (for eight patients) or 100 (for four patients) and amplified and digitized with an Aura LTM-64 system (Grass Technologies, West Warwick, RI) at different sampling frequencies for different patients. For four patients the data were filtered 1-100 Hz and digitized at 200 S/s, another six were filtered 1-200 Hz and digitized at 400 S/s and for the remaining two patients the data were filtered 1-250 Hz and 1-500 Hz respectively and digitized at 1600 S/s.

The 60 Hz notch filter was used for all patients. The recording sessions at the NINN usually lasted for six hours, from around 7am to 1pm. For the two patients at RIH, the recording was stopped shortly after the patient had a seizure (130 minutes total) and for the other the recording lasted 66 minutes. The NINN recording protocol included requests to patients to be sleep deprived the night before coming for a video-EEG monitoring and all patients signed an additional consent form as antiepileptic drugs dosage was reduced by half the previous day of the recording. Recorded data were reviewed by board certified neurologists and seizure onset time and duration were determined for each seizure. Seizure onset time was defined as the beginning of the first observable seizure pattern in either EEG or tEEG.

D. SIGNAL PROCESSING

The data were stored on the hard drive and exported from Twin (Grass Technologies, West Warwick, RI) into ASCII text files that were then imported to Matlab (Mathworks, Natick, MA) and converted to .mat files. For the tEEG, two bipolar pairs were recorded for each TCRE. Then the data were preprocessed with the tripolar Laplacian algorithm [42]. Next we used a modified version of the algorithm reported by Gardner et al. for detection of HFOs combined with the visual inspection to rule out high frequency artifacts [25]. The algorithm performed a continuous short-time Fourier transform to calculate the power within a particular frequency band over consecutive and half-overlapping one-second epochs using a Hamming tapering window. As a result, the time course of power modulations was obtained. Then we used visual inspection to determine where the HFOs were. Simple thresholding was also used to find events which had power significantly higher than the interictal background EEG. The average power and its standard deviation over the interictal period were calculated first. Then the time periods when the HFO power was exceeding its average plus two standard deviations were found. Frequency bands starting at high gamma band ($\sim$60 Hz) and up to the upper bound of the band-pass filter that varied for individual patients were searched for HFOs. We selected segments up to an hour prior to the onset of the seizures and generated spectrograms to follow the temporal dynamics of pre-seizure HFOs. For the patients who had epileptiform activity only but no seizures we calculated spectrograms on 10 minute long segments centered on the periods of epileptiform activity. For the patients who did not have either epileptiform activity or seizures we performed spectral analysis on multiple 10 minute long segments at various times during the recording.

E. HFO/SOZ CORRELATION

To assess the relationship between tEEG channels containing HFOs preceding seizures and the SOZ the ratio between the number of tEEG channels with HFOs in the SOZ and the total number of tEEG channels with HFOs was calculated for each patient whose seizure was recorded. We also calculated the ratio between the total number of tEEG channels with HFOs and the total number of tEEG channels to assess how widespread the HFOs were for each patient. Both ratios were averaged for the five patients with seizures included in this study. Only the channels containing HFOs preceding the seizures were assessed. SOZ or IZ was determined for each patient independently by three epileptologists (IEMJ, JNG, and RSF) based on EEG data and videos only. The epileptologists did not have access to tEEG data and were not aware of the HFO detection results. In one patient the third SOZ was determined by the location of resection by the surgeon. A disjunctive (logical OR) fusion rule was used to combine the SOZ determinations by the three epileptologists. That is all channels determined as part of the SOZ (IZ) by either one of the epileptologists were considered to be a part of the SOZ (IZ).

III. RESULTS

A. HEALTHY SUBJECT tEEG TESTING

First, we demonstrate the suitability of TCREs to provide a sound EEG signal sensitive to physiological rhythms such as alpha activity as well as their insensitivity to myogenic activity which often corrupts scalp EEG recordings especially in the high frequency range $>$30 Hz. If the TCRE attenuates volume conductance effects and has a greater sensitivity to local sources, how good is it for recording global brain rhythms such as alpha activity? Figure 3, (A/C) shows the signals that were recorded with eyes closed/open and their corresponding power spectral densities are presented in Fig. 3, (B/D). The alpha waves were present in tEEG (top trace, blue) coinciding with the corresponding alpha rhythm recorded by conventional disc electrodes (middle and bottom traces, red and green respectively) (Fig. 3, A, B). The alpha waves were blocked in both tEEG and EEG when the eyes were open (Fig. 3, C, D). Thus, this result demonstrates the ability of TCREs to record physiological rhythms.

A relative insensitivity of TCREs to myogenic activity is demonstrated by tEEG and EEG records obtained from the same subject during head movements (Fig. 4). In the middle trace (red) and the bottom trace (green) it is evident that from about 3 to 6 seconds there is a high-frequency contamination in the bipolar disc recordings that is significantly attenuated in the tEEG (top trace, blue). This high-frequency interference coincided with head movements and is most likely caused by muscle artifacts. Panel B of Fig. 4 shows the power spectral densities for the traces in panel A. The tEEG power (blue) has the lowest power in the higher frequencies range where the muscle artifact is prominent in the records from the conventional bipolar disc signals. From our experience, such attenuation of myogenic artifacts is observed consistently with tEEG records.

B. DATA FROM tEEG RECORDINGS IN PATIENTS WITH EPILEPSY

Video-EEGs and tEEGs were performed in 12 patients. We separated the patients into 3 groups: (1) Patients who had clin-

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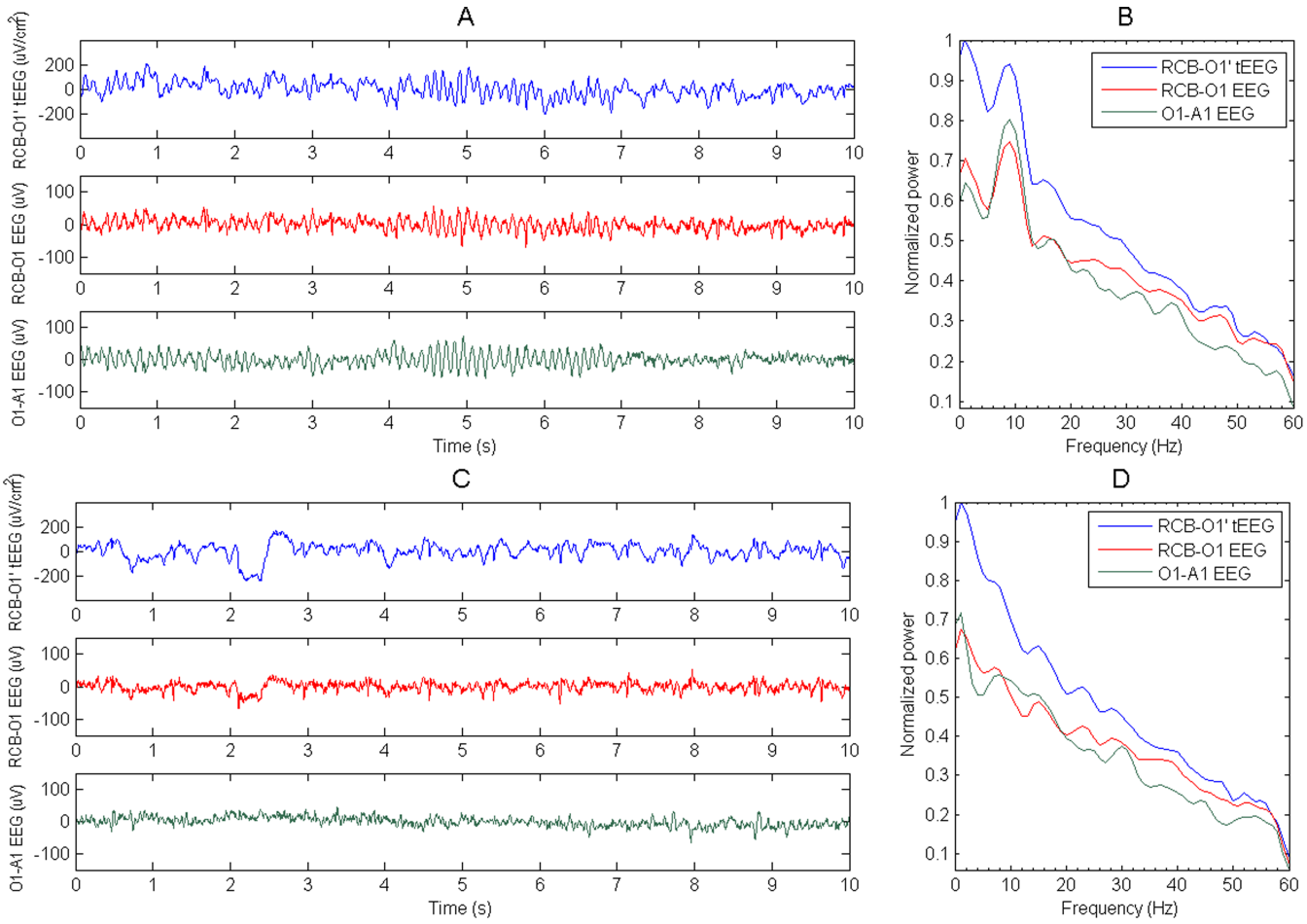

FIGURE 3. **Global physiological rhythms such as alpha activity observable with eyes closed can be recorded by TCREs. Panel A: the top trace (blue) is tEEG from a TCRE placed next to the conventional disc electrode at O1. The middle trace (red) is from the conventional disc electrode at O1. Both the top and middle traces are recorded with respect to the reference on the right collar bone (RCB). The bottom trace (green) is from the O1 electrode with respect to the A1 reference electrode. Panel B: the power spectral densities for the signals of panel A. Panels C and D are the signals and power spectral densities when the eyes are open. It is evident that the alpha waves are present in both tEEG and EEG records, specifically between 4 and 5 seconds (panel A), which is confirmed by the spectra displaying a peak just below 10 Hz (panel B) but are not seen in panels C and D.**

ical seizures (n=5), (2) patients with epileptiform activity but no seizures (n=3), and (3) patients with neither epileptiform activity nor seizures (n=4). Simultaneously recorded EEG and tEEG and the corresponding spectrograms from representative patients are shown in Figs. 5 and 6. For Fig. 5 the patient was a 42-year-old woman with seizure onset at 9 years. Seizures were simple and complex partial. She had been diagnosed with right temporal lobe epilepsy and had undergone a right temporal lobectomy but seizures persisted. She was on clonazepam (CNZ), lamotrigine (LTG) and phenytoin (PHT) at the time of the study. In Figure 5 conventional EEG data are on panels A, B, E, F, and I and tEEG data are on panels C, D, G, H, and J. The conventional EEG data were obtained from the bipolar montage (channel F8-F4). The tEEG signals are from a TCRE placed directly behind the F8 electrode. This patient had a generalized seizure (onset at approximately 610 seconds in the time scale of panels A-D in Fig. 5). The seizure activity is evident by large increases in signal amplitude and power at all frequencies. Panels E, F, G, and H are eleven-second EEG and tEEG segments (marked by the black line in panel C) shown at higher sequential resolution. Note the series of high gamma-band HFOs between approximately 60 to 80 Hz (highlighted by ellipse in panel C) occurring about every two seconds which are clearly evident in the tEEG but not EEG, starting approximately 10 min prior to the generalized seizure activity (compare panels A and C as well as E and G). With further zoom in panels I and J showing two-second segments, one can see a high frequency burst in the tEEG (black horizontal line in the panel J) which is not present in the EEG (panel I).

Figure 6 portrays the data from a second patient that also had a seizure. This patient was a 45 year old male, with onset of epilepsy at 22 years. His seizures consisted of simple partial seizures followed by complex partial with or without secondarily generalization. He was on carbamazepine (CBZ) and LTG at the time of the recording. His magnetic resonance imaging showed left mesial temporal sclerosis and a right frontal venous angioma. Panel B shows bipolar EEG (Fp2-F4). Panel D shows tEEG recorded from location Fp2' directly behind the Fp2 disc electrode. Panels A and C are the

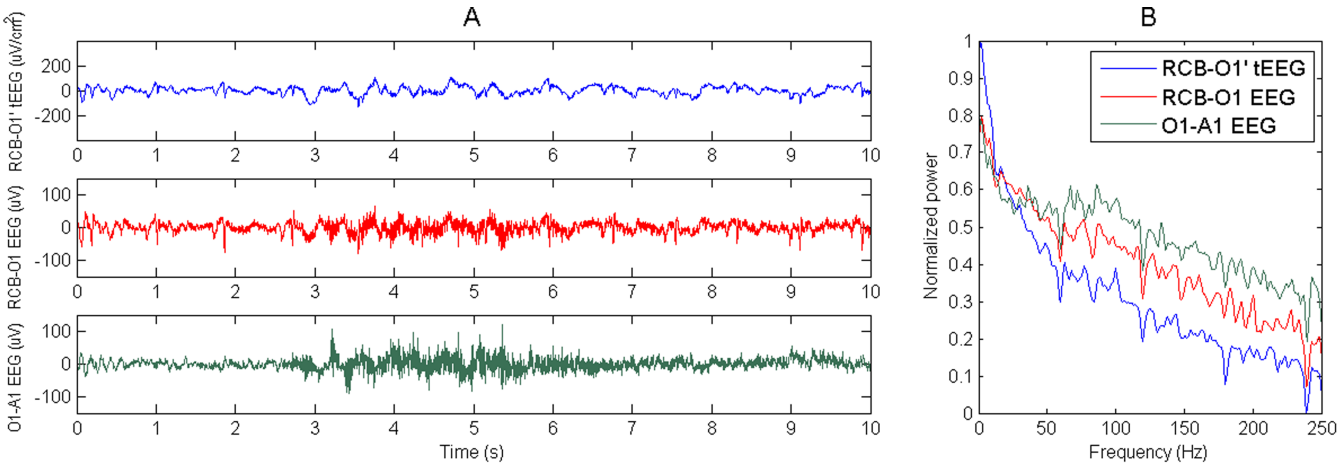

FIGURE 4. TCREs are relatively immune to myogenic activity. Panel A: the top trace (blue) is tEEG from a TCRE placed next to the conventional disc electrode at O1. The middle trace (red) is from the conventional disc electrode at O1. Both the top and middle traces are recorded with respect to the reference on the right collar bone (RCB). The bottom trace (green) is from the O1 disc electrode with respect to the A1 reference electrode. Conventional EEG is heavily corrupted by muscle artifacts which are evident from approximately 3 to 6 seconds of the record (middle [red] and bottom [green] traces) coinciding with head movements by the subject. These artifacts are nearly unnoticeable in the tEEG (top trace [blue]). Panel B: the power spectral densities for the signals shown in panel A. The power spectrum for the tEEG (blue) has much less high frequency power (>30 Hz) due to myogenic activity.

corresponding time-frequency spectrograms. In this patient, we also found gamma band bursts (∼70 Hz) in the tEEG, approximately three minutes before the seizures. The black ellipse in Fig. 6(C) highlights the high gamma-band burst HFOs in the tEEG at location Fp2' approximately 4 min prior to the partial seizure. The HFOs are present throughout the pre-seizure spectrogram but became more consolidated around 70 Hz about 3 min prior to the seizure. In contrast, HFOs were not found in the EEG. It is also important that the tEEG during the tonic seizure was less contaminated with muscle and movement artifacts than the EEG (compare panels E and F). Also note the higher power in EEG (compare panels A and C) from approx. 400 to 650 s when the patient was still anxious/disoriented and moving while recovering from the seizure. During that same period the movement-related artifact power was much lower in tEEG (Fig. 6, C).

C. HFO/SOZ CORRELATION

Overall, HFOs preceding seizures were present in tEEG data from all five patients whose seizures were recorded. For these five patients, out of all the tEEG channels that contained HFOs an average of 78.2% were also in the SOZ (IZ) (patient minimum: 42.9%; maximum: 100%). The average percentage of the total number of tEEG channels recorded that contained HFOs is equal to 35.5% (patient minimum: 5.3%; maximum: 73.7%).

Figure 7 portrays the relationship between the clinical SOZ (IZ) and HFO-containing channels for two patients that we present the spectrograms for in Fig. 5 (panel A) and Fig. 6 (panel B) respectively.

IV. DISCUSSION

It has been shown that EEG is frequently contaminated by artifacts originating from various sources such as scalp muscles, eye blinks, eye movements, or patient movement [49]. LeVan et al. [50] state what is intuitively obvious; artifacts obscuring the EEG at the time of seizure onset can greatly hinder the interpretation of the recorded seizures.

During a tonic or tonic-clonic seizure, muscle activity is very prominent and is reflected in the EEG by random, high frequency signals [51]. Hallez et al. [52] showed that when EEGs were moderately contaminated with muscle artifacts blind source separation techniques based on canonical correlation provides signals that are more reliable for source estimation than raw EEG. They also found that in cases of severe muscle contamination of the EEG or when the muscle artifact had different spatial information than the spatial information of the epileptiform event, the blind source separation techniques based on canonical correlation did not work well. In general, a major reason why EEG has not reached its full potential in epilepsy diagnosis is due to artifact contamination.

We have found that the TCRE and the tEEG automatically attenuate myogenic activity and movement artifacts. In contrast to the typical examples of artifact contaminated conventional bipolar EEG, the tEEG is much less contaminated by the muscle activity. It should be noted that conventional approaches to remove muscle artifacts by digital signal processing (such as filtering) lead to significant loss of information since the gamma band activity and HFOs in general are within the bandwidth of the electromyogram (EMG). In other words, removing the EMG will inevitably remove high frequency components of the brain activity, which is not a desirable result. The tEEG, although not as obvious, may also be contaminated with EMG (Fig. 4, A, top blue trace) but from a much more local source. The EMG from more distant sources have nearly equal contributions on the elements of the TCRE and are cancelled out when the potentials on the elements are subtracted from each other with bipolar differences.

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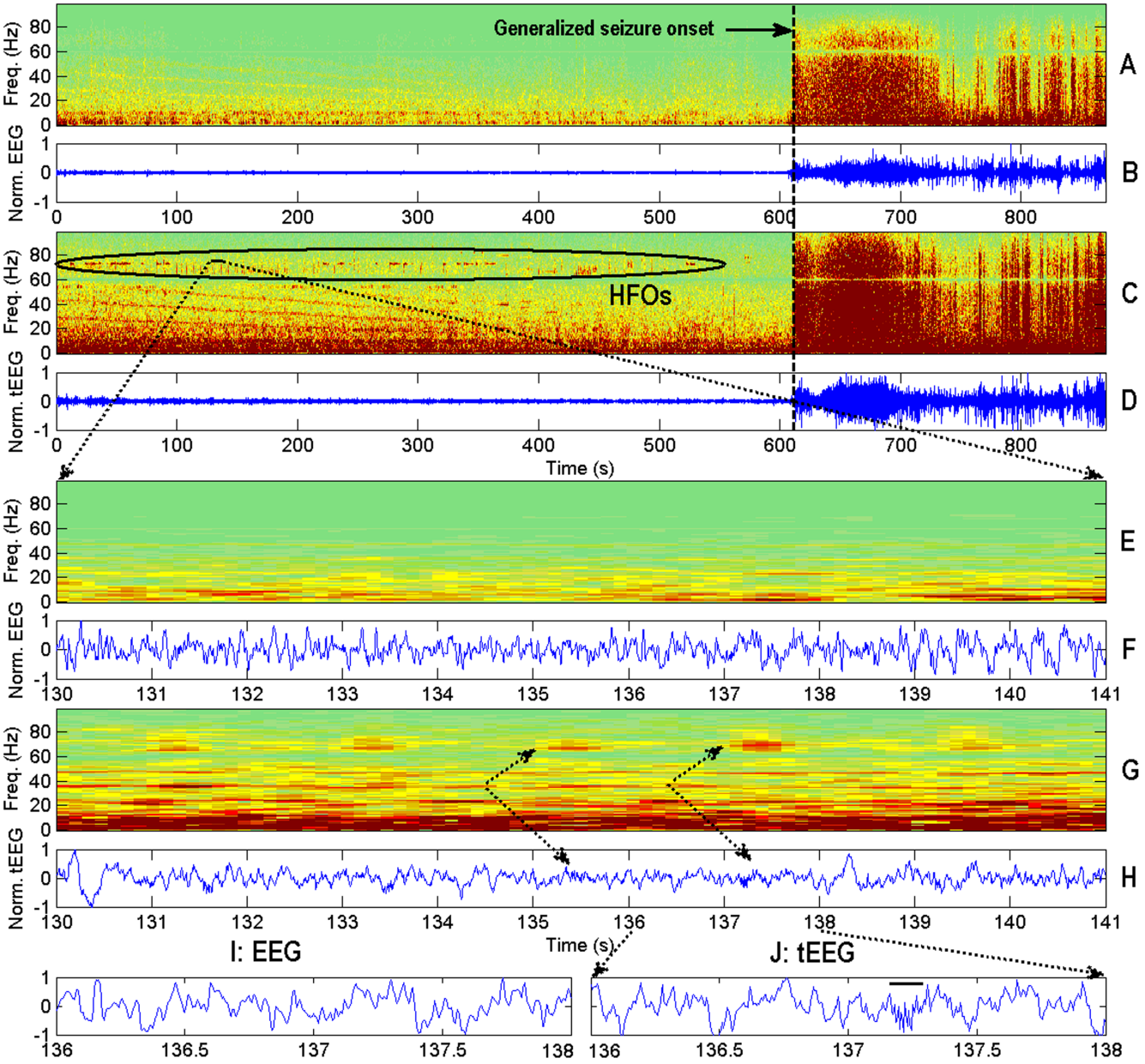

FIGURE 5. **A representative example of simultaneously recorded EEG and tEEG from one patient. Conventional EEG (bipolar montage, channel F8-F4, panels B, F and I, 1-70 Hz, 200 S/s), tEEG (from a tripolar electrode placed right behind the F8 position (F8′), panels D, H and J, 1-100 Hz, 200 S/s,) and their spectrograms (panels A, E and panels C, G for EEG and tEEG, respectively) starting ∼10 min before and continuing during a generalized seizure with onset marked with the dashed vertical black line. Seizures is identified by marked increases in signal amplitude and power at all frequencies. Panels E-H: eleven-second EEG and tEEG segments (marked by the black line in panel C) are shown at higher temporal resolution. Note a series of high gamma-band bursts HFOs at 60-80 Hz (highlighted by ellipse in C) occurring about every 2 s, which are clearly seen in the tEEG spectrogram only. Panels I, J: Further zoom-in of two-second segment shows one HFO in tEEG (black horizontal line in the panel J) while this HFO is absent in EEG (panel I).**

In this study, we show, in a limited number of patients, that high-power HFO activity is detected at specific locations on the scalp surface in the tEEG records of patients with epilepsy. This HFO activity was apparent prior to seizures. Although there may have been HFO activity at various times in the tEEG during the recordings the bandwidth of the HFO activity narrowed sharply and the power increased just prior to the seizure. We did not see the HFO activity in the conventional EEG, even when using bipolar montages which somewhat attenuates global artifacts. In some instances this may partially be due to the low-pass filter used to record the EEG. The EEG low-pass filter was set to 70 Hz and this cutoff frequency may have partially filtered out gamma band activity. However, the gamma band activity detected in the tEEG was often well below 70 Hz, in one case as low as 63 Hz, and in these cases the gamma band activity was still undetected in the conventional EEG. When a low-pass digital filter was applied to the tEEG at 70 Hz the HFOs were still present in

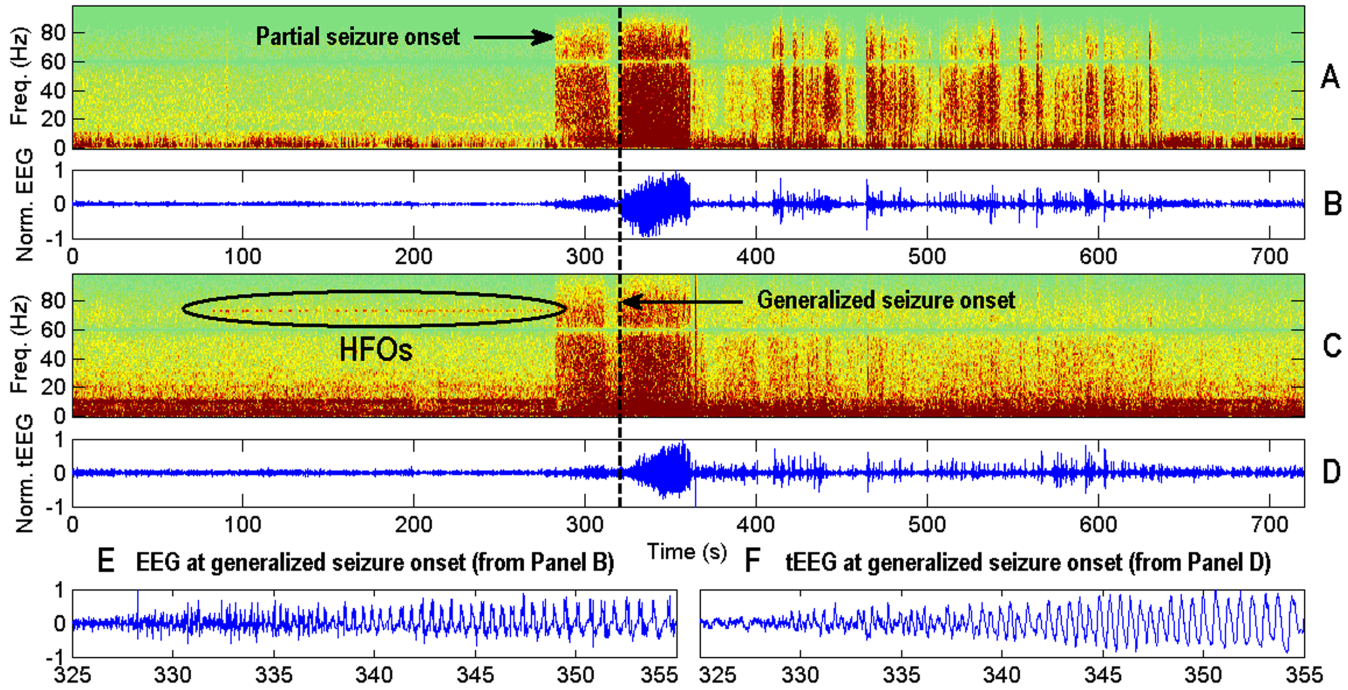

FIGURE 6. Panel B shows 12 minutes of bipolar EEG from Fp2-F4 (1-70 Hz, 200 S/s). Panel A is the corresponding spectrogram. Panel E shows 30 seconds of EEG from Panel B at the onset of the generalized seizure (dashed line). Panels C, D, and F are the corresponding tEEG signals from Fp2. (1-100 Hz, 200 S/s). Note the high gamma-band burst HFOs just prior to the partial seizure (highlighted by ellipse in panel C).

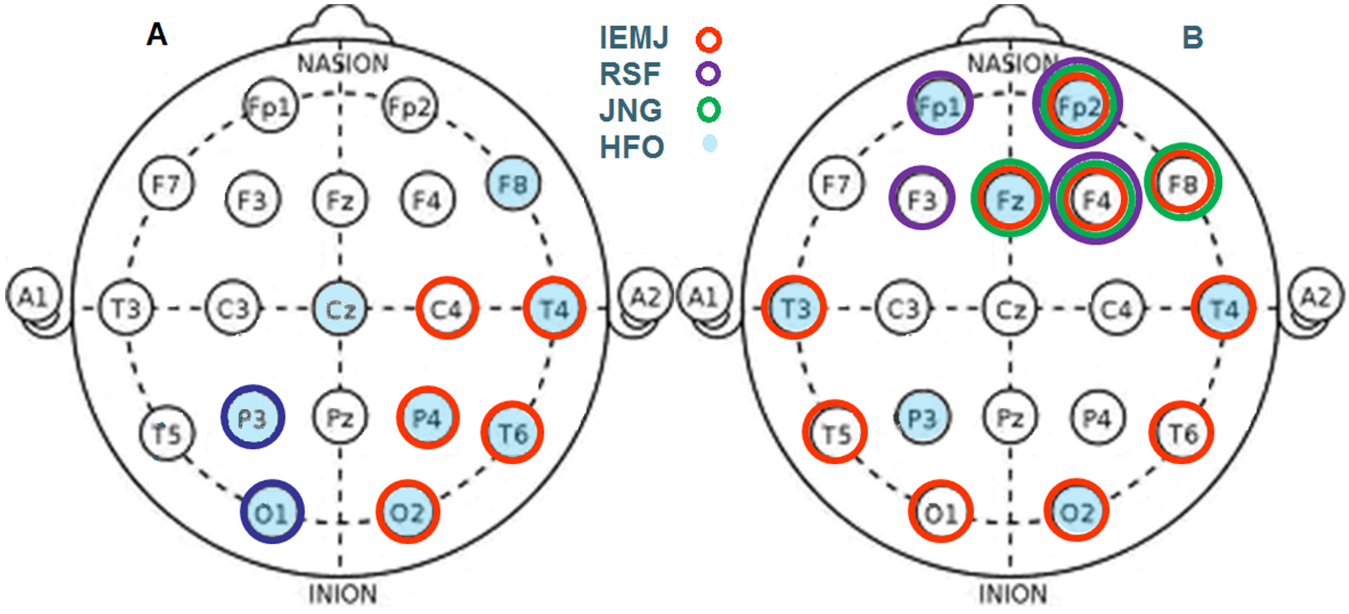

FIGURE 7. Panel A shows the relationship between the clinical seizure onset zone (SOZ) and HFO-containing channels for the patient from Fig. 5. Panel B shows the relationship between the clinical irritative zone (IZ) and HFO-containing channels for the patient from Fig. 6. SOZ or IZ was determined for each patient independently by three epileptologists (IEMJ, JNG, and RSF) based on EEG data and videos only.

the tEEG for patients whose HFOs were below 70 Hz. We do not know what the upper limit is for detecting HFOs on the scalp. In rats we have found an increase in power up to 300 Hz during PTZ-induced seizure electrographic activity recorded with tEEG [53]. In two patients having seizures for whom the data were filtered 1-250 Hz and 1-500 Hz respectively and digitized at 1600 S/s we have detected HFO preceding seizures in gamma, ripple, and fast ripple bands at frequencies up to 425 Hz.

A potential disadvantage of recording with TCRE is deemphasis of non-artifactual signals with wide spatial distribution, for example, spike-waves [54]. Therefore, recording

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with TCREs may be complementary to conventional recordings for some purposes. We intend to develop the circuitry to record both tEEG and an EEG approximation from the same sensor in the near future.

Despite a limited sample size of patients having seizures in this study (5 patients) we were able to investigate a possible correlation between the clinically determined SOZ (IZ) and the location of HFOs detected by TCREs. HFOs preceding seizures were present in tEEG data from all five patients whose seizures were recorded in an average of 35.5% of the patient's tEEG channels. Out of those channels containing HFOs an average of 78.2% were within SOZ (IZ) determined independently by three epileptologists based on EEG data and videos. In all five patients who had recorded seizures, at least one channel in the SOZ exhibited HFOs (in one out of five patients HFOs were present in a single tEEG channel). In two patients no specific SOZ was determined but rather an IZ. For those two patients HFOs were present in 7 and 4 tEEG channels respectively out of 20 (35%) and 19 (21%) channels total respectively which is on par with the population average of 35.5%. Examples of the relationship between the SOZ (IZ) and HFO-containing channels are presented in Fig. 7. Panel A portrays a SOZ for the patient from Fig. 5. For this patient SOZ definitions from two epileptologists (IEMJ and RSF) did not overlap. The third epileptologist (JNG) mentioned 4 Hz activity over central leads but no clear electrographic onset. Panel B portrays an IZ for the patient from Fig. 6. For this patient SOZ definitions from all three epileptologists (IEMJ, JNG, and RSF) overlapped for two channels (Fp2 and F4) over the right frontal lobe. These preliminary results support that tEEG is capable of detecting HFOs from the scalp, which are not usually seen in conventional EEG records. Further studies with more patients are needed to more accurately correlate locations of (presumably abnormal) HFO activity with clinically determined SOZ as well as the resected tissue in surgical cases.

Due to the improved signal quality of tEEG we hope that in the future we will be able to use tEEG to detect seizures and trigger stimulation to attenuate seizures. We have shown that transcranial focal electrical stimulation (TFS) via TCREs in rat models was effective in reducing penicillin-induced myoclonic jerks [55], [56], pilocarpine-induced status epilepticus (an extreme form of continuing seizures) [57] and in a third model, we applied TFS in rats treated by pentylenetetrazole (PTZ). TFS significantly reduced PTZ-induced hypersynchrony at the beta and gamma frequencies [58], Most recently we developed an automatic non-invasive seizure control system based on TFS and tested it successfully on rats [59].

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REFERENCES

[1] W. A. Hauser and J. F. Annegers, "Risk factors for epilepsy," *Epilepsy Res. Suppl.*, vol. 4, pp. 45–52, 1991.

[2] E. H. Reynolds, "ILAE/IBE/WHO Global Campaign 'out of the shadows': Global and regional developments," *Epilepsia*, vol. 42, no. 8, pp. 1094–1100, 2001.

[3] G. K. Dash, A. Radhakrishnan, C. Kesavadas, M. Abraham, P. S. Sarma, and K. Radhakrishnan, "An audit of the presurgical evaluation and patient selection for extratemporal resective epilepsy surgery in a resource-poor country," *Seizure, Eur. J. Epilepsy*, vol. 21, no. 5, pp. 361–366, 2012.

[4] S. Sinha, D. K. Prashantha, K. Thennarasu, R. G. S. Umamaheshwara, and P. Satishchandra, "Refractory status epilepticus: A developing country perspective," *J. Neurol. Sci.*, vol. 290, nos. 1–2, pp. 60–65, 2010.

[5] G. A. Worrell, L. Parish, S. D. Cranstoun, R. Jonas, G. Baltuch, and B. Litt, "High-frequency oscillations and seizure generation in neocortical epilepsy," *Brain*, vol. 127, no. 7, pp. 1496–1506, 2004.

[6] J. Jacobs, P. LeVan, R. Chander, J. Hall, F. Dubeau, and J. Gotman, "Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain," *Epilepsia*, vol. 49, no. 11, pp. 1893–1907, 2008.

[7] J. Jacobs *et al.*, "High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery," *Ann. Neurol.*, vol. 67, no. 2, pp. 209–220, 2010.

[8] M. Zijlmans, P. Jiruska, R. Zelmann, F. S. Leijten, J. G. Jefferys, and J. Gotman, "High-frequency oscillations as a new biomarker in epilepsy," *Ann. Neurol.*, vol. 71, no. 2, pp. 169–178, 2012.

[9] I. Matoth, I. Taustein, B. S. Kay, and Y. A. Shapira, "Overuse of EEG in the evaluation of common neurologic conditions," *Pediatric Neurol.*, vol. 27, no. 5, pp. 378–383, 2002.

[10] K. Aydin, C. Okuyaz, A. Serdaroglu, and K. Gücüyener, "Utility of electroencephalography in the evaluation of common neurologic conditions in children," *J. Child Neurol.*, vol. 18, no. 6, pp. 394–396, 2003.

[11] R. S. Fisher, W. R. Webber, R. P. Lesser, S. Arroyo, and S. Uematsu, "High-frequency EEG activity at the start of seizures," *J. Clin. Neurophysiol.*, vol. 9, no. 3, p. 441, 1992.

[12] P. J. Allen, D. R. Fish, and S. J. M. Smith, "Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy," *Electroencephalogr. Clin. Neurophysiol.*, vol. 82, no. 2, pp. 155–159, 1992.

[13] R. D. Traub, J. G. Jefferys, and M. A. Whittington, *Fast Oscillations in Cortical Circuits*. Cambridge, MA, USA: MIT Press, 1999.

[14] C. S. Herrmann and T. Demiralp, "Human EEG gamma oscillations in neuropsychiatric disorders," *Clin. Neurophysiol.*, vol. 116, no. 12, pp. 2719–2733, 2005.

[15] S. Rampp and H. Stefan, "Fast activity as a surrogate marker of epileptic network function?" *Clin. Neurophysiol.*, vol. 117, no. 10, pp. 2111–2117, 2006.

[16] J. R. Hughes, "Gamma, fast, and ultrafast waves of the brain: Their relationships with epilepsy and behavior," *Epilepsy Behavior*, vol. 13, no. 1, pp. 25–31, 2008.

[17] S.-A. Lee, D. D. Spencer, and S. S. Spencer, "Intracranial EEG seizure-onset patterns in neocortical epilepsy," *Epilepsia*, vol. 41, no. 3, pp. 297–307, 2000.

[18] A. V. Medvedev, "Temporal binding at gamma frequencies in the brain: Paving the way to epilepsy?" *Austral. Phys. Eng. Sci. Med.*, vol. 24, no. 1, pp. 37–48, 2001.

[19] A. Bragin, C. L. Wilson, R. J. Staba, M. Reddick, I. Fried, and J. Engel, Jr., "Interictal high-frequency oscillations (80–500Hz) in the human epileptic brain: Entorhinal cortex," *Ann. Neurol.*, vol. 52, no. 4, pp. 407–415, Oct. 2002.

[20] A. V. Medvedev, "Epileptiform spikes desynchronize and diminish fast (gamma) activity of the brain: An 'anti-binding' mechanism?" *Brain Res. Bull.*, vol. 58, no. 1, pp. 115–128, 2002.

[21] R. J. Staba, C. L. Wilson, A. Bragin, I. Fried, and J. Engel, "Quantitative analysis of high-frequency oscillations (80–500 Hz) recorded in human epileptic hippocampus and entorhinal cortex," *J. Neurophysiol.*, vol. 88, no. 4, pp. 1743–1752, 2002.

[22] G. A. Worrell *et al.*, "Focal ictal β discharge on scalp EEG predicts excellent outcome of frontal lobe epilepsy surgery," *Epilepsia*, vol. 43, no. 3, pp. 277–282, Mar. 2002.

[23] F. Grenier, I. Timofeev, and M. Steriade, "Neocortical very fast oscillations (ripples, 80–200 Hz) during seizures: Intracellular correlates," *J. Neurophysiol.*, vol. 89, no. 2, pp. 841–852, 2003.

[24] J. O. Willoughby *et al.*, "Persistent abnormality detected in the non-ictal electroencephalogram in primary generalised epilepsy," *J. Neurol. Neurosurgery Psychiatry*, vol. 74, no. 1, pp. 51–55, 2003.

[25] A. B. Gardner, G. A. Worrell, E. Marsh, D. Dlugos, and B. Litt, "Human and automated detection of high-frequency oscillations in clinical intracranial EEG recordings," *Clin. Neurophysiol.*, vol. 118, no. 5, pp. 1134–1143, 2007.

[26] R. J. Staba *et al.*, "Increased fast ripple to ripple ratios correlate with reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients," *Epilepsia*, vol. 48, no. 11, pp. 2130–2138, 2007.

[27] G. A. Worrell *et al.*, "High-frequency oscillations in human temporal lobe: Simultaneous microwire and clinical macroelectrode recordings," *Brain*, vol. 131, no. 4, pp. 928–937, 2008.

[28] J. A. Blanco *et al.*, "Unsupervised classification of high-frequency oscillations in human neocortical epilepsy and control patients," *J. Neurophysiol.*, vol. 104, no. 5, pp. 2900–2912, 2010.

[29] A. V. Medvedev, A. M. Murro, and K. J. Meador, "Abnormal interictal gamma activity may manifest a seizure onset zone in temporal lobe epilepsy," *Int. J. Neural Syst.*, vol. 21, no. 2, p. 103, 2011.

[30] L. P. Andrade-Valenca, F. Dubeau, F. Mari, R. Zelmann, and J. Gotman, "Interictal scalp fast oscillations as a marker of the seizure onset zone," *Neurology*, vol. 77, no. 6, pp. 524–531, 2011.

[31] H. Berger, "Über das elektrenkephalogramm des menschen," *Eur. Archives Psychiatry Clin. Neurosci.*, vol. 87, no. 1, pp. 527–570, 1929.

[32] P. L. Nunez and R. Srinivasan, *Electric Fields of the Brain: The Neurophysics of EEG*. London, U.K.: Oxford Univ. Press, 2006.

[33] G. Buzsaki, *Rhythms of the Brain*. New York, NY, USA: Oxford Univ. Press, 2009.

[34] A. von Stein and J. Sarntin, "Different frequencies for different scales of cortical integration: From local gamma to long range alpha/theta synchronization," *Int. J. Psychophysiol.*, vol. 38, no. 3, pp. 301–313, 2000.

[35] G. Buzsaki and A. Draguhn, "Neuronal oscillations in cortical networks," *Science*, vol. 304, no. 5679, pp. 1926–1929, 2004.

[36] F. Babiloni, C. Babiloni, L. Fattorini, F. Carducci, P. Onorati, and A. Urbano, "Performances of surface Laplacian estimators: A study of simulated and real scalp potential distributions," *Brain Topogr.*, vol. 8, no. 1, pp. 35–45, 1995.

[37] T. Gasser, L. Sroka, and J. Möcks, "The transfer of EOG activity into the EEG for eyes open and closed," *Electroencephalogr. Clin. Neurophysiol.*, vol. 61, no. 2, pp. 181–193, 1985.

[38] T. Gasser, L. Sroka, and J. Möcks, "The correction of EOG artifacts by frequency dependent and frequency independent methods," *Psychophysiology*, vol. 23, no. 6, pp. 704–712, 1986.

[39] S. K. Law, P. L. Nunez, and R. S. Wijesinghe, "High-resolution EEG using spline generated surface Laplacians on spherical and ellipsoidal surfaces," *IEEE Trans. Biomed. Eng.*, vol. 40, no. 2, pp. 145–153, Feb. 1993.

[40] P. L. Nunez, R. B. Silberstein, P. J. Cadusch, R. S. Wijesinghe, A. F. Westdorp, and R. Srinivasan, "A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging," *Electroencephalogr. Clin. Neurophysiol.*, vol. 90, no. 1, pp. 40–57, 1994.

[41] J. E. Desmedt, V. Chalklin, and C. Tomberg, "Emulation of somatosensory evoked potential (SEP) components with the 3-shell head model and the problem of Śghost potential fieldsŠ when using an average reference in brain mapping," *Electroencephalogr. Clin. Neurophysiol. Potentials Section*, vol. 77, no. 4, pp. 243–258, 1990.

[42] G. Besio, K. Koka, R. Aakula, and W. Dai, "Tri-polar concentric ring electrode development for Laplacian electroencephalography," *IEEE Trans. Biomed. Eng.*, vol. 53, no. 5, pp. 926–933, May 2006.

[43] B. He, "Brain electric source imaging: Scalp Laplacian mapping and cortical imaging," *Critical Rev. Biomed. Eng.*, vol. 27, nos. 3–5, pp. 149–188, 1999.

[44] K. Koka and W. G. Besio, "Improvement of spatial selectivity and decrease of mutual information of tri-polar concentric ring electrodes," *J. Neurosci. Methods*, vol. 165, no. 2, pp. 216–222, 2007.

[45] S. Shinnar, "The new ILAE classification," *Epilepsia*, vol. 51, no. 4, pp. 715–717, 2010.

[46] ILAE, "Proposal for revised clinical and electroencephalographic classification of epileptic seizures," *Epilepsia*, vol. 22, no. 4, pp. 489–501, Aug. 1981.

[47] ILAE, "Proposal for revised classification of epilepsies and epileptic syndromes," *Epilepsia*, vol. 30, no. 4, pp. 389–399, 1989.

[48] F. Rosenow and H. Lüders, "Presurgical evaluation of epilepsy," *Brain*, vol. 124, no. 9, pp. 1683–1700, 2001.

[49] E. Niedermeyer and F. L. Da Silva, *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Baltimore, MD, USA: Williams & Wilkins, 2005.

[50] P. LeVan, E. Urrestarazu, and J. Gotman, "A system for automatic artifact removal in ictal scalp EEG based on independent component analysis and Bayesian classification," *Clin. Neurophysiol.*, vol. 117, no. 4, pp. 912–927, 2006.

[51] A. Vergult *et al.*, "Improving the interpretation of ictal scalp EEG: BSS-CCA algorithm for muscle artifact removal," *Epilepsia*, vol. 48, no. 5, pp. 950–958, 2007.

[52] H. Hallez *et al.*, "Removing muscle and eye artifacts using blind source separation techniques in ictal EEG source imaging," *Clin. Neurophysiol.*, vol. 120, no. 7, pp. 1262–1272, 2009.

[53] O. Makeyev *et al.*, "Feasibility of recording high frequency oscillations with tripolar concentric ring electrodes during pentylenetetrazole-induced seizures in rats," in *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, 2012, pp. 4599–4602.

[54] H. Yoshinaga, K. Kobayashi, M. Sato, E. Oka, and S. Ohtahara, "Investigation of bilateral synchronous spike-wave discharge by EEG topography," *Brain Topogr.*, vol. 8, no. 3, pp. 255–260, 1996.

[55] W. G. Besio, K. Koka, K. S. Gale, and A. V. Medvedev, "Preliminary data on anticonvulsant efficacy of transcutaneous electrical stimulation via novel concentric ring electrodes," in *Proc. Adv. Appl. Technol. Epilepsy Cimitnio Epilepsy Innov. Summit*, Boston, MA, USA, 2008, pp. 3–46.

[56] W. G. Besio, K. N. Gale, and A. V. Medvedev, "Possible therapeutic effects of transcutaneous electrical stimulation via concentric ring electrodes," *Epilepsia*, vol. 51, no. S3, pp. 85–87, 2010.

[57] W. G. Besio, K. Koka, and A. Cole, "Effects of noninvasive transcutaneous electrical stimulation via concentric ring electrodes on pilocarpine-induced status epilepticus in rats," *Epilepsia*, vol. 48, no. 12, pp. 2273–2279, 2007.

[58] W. G. Besio, X. Liu, L. Wang, A. V. Medvedev, and K. Koka, "Transcutaneous focal electrical stimulation via concentric ring electrodes reduces synchrony induced by pentylenetetrazole in beta and gamma bands in rats.," *Int. J. Neural Syst.*, vol. 21, no. 2, p. 139, 2011.

[59] O. Makeyev *et al.*, "Toward a noninvasive automatic seizure control system in rats with transcranial focal stimulations via tripolar concentric ring electrodes," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 20, no. 4, pp. 422–431, Jul. 2012.

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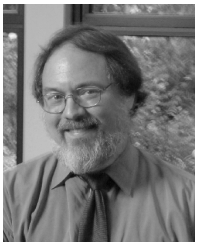

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