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Editorial OMICS International

High Frequency Neuromagnetic Signals: A New Biomarker for Localizing Epileptic Areas Running Title: High-Frequency Neuromagnetic Signals in Epilepsy

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Editorial

Approximately 20-30% of epilepsy cases are intractable to medical therapy [1-4]. There are 400,000 to 600,000 patients with refractory epilepsy in the United States [5,6]. For these patients, surgical removal of the brain regions causing the seizures is a necessity. Unfortunately, epilepsy surgery is offered to only 2-3% of potential surgical candidates in the United States [7-9]. This is because many patients are not considered candidates for surgical management because a single region causing the seizures (ictogenic zone) cannot be identified [4,8,9]. Although epilepsy surgery is expensive and the overall costs of surgical or medical management are similar in the first 2 years, patients who achieve seizure freedom after surgery have significantly lower costs compared with those treated with medication over the long-term [1,10]. The impact of intractable epilepsy extends far beyond seizures themselves. It is accompanied by poorer quality of life and a variety of comorbidities, including sudden unexpected death [1-4]. Epilepsy surgery is one potential cure [4,11]. Accurate identification of the ictogenic zones is essential to ensure a favorable surgical outcome [12]. This identification often necessitates:

- Invasive surgical electrode placement upon the brain surface to capture epileptogenic spikes (14-70 Hz) and seizures with electrocorticography (ECoG) [1,12-15] and
- Consequent return to the operating room for surgical removal of the ictogenic zones after days (or weeks) of ECoG data collection [1,12-15]. Such invasive and costly procedures are associated with morbidity and potential mortality.

Magnetoencephalography (MEG) is a technique that can be used to localize ictogenic zones and guide ECoG electrode implantation [16,17,22]. Ideally, non-invasive MEG will replace invasive ECoG [18-21], but proof of its reliability is still lacking [22]. Recent success in localizing high-frequency brain signals (HFBS, 70-2,500 Hz) using MEG opens a new window for reliably localizing ictogenic zones [16,23-27]. HFBS in epilepsy are also called High Frequency Oscillations (HFOs), ripples, fast ripples. Since localization of ictogenic zones with MEG is noninvasive [16,26], the localization of HFBS with MEG, or high frequency neuromagnetic signals, will minimize the risk and decrease the cost of epilepsy surgery, and result in more seizure freedom for intractable epilepsy patients in the future.

Although HFOs or ripple, fast ripples can record with intracranial recordings in epilepsy [28-31], it has significant limitation. Specifically, intracranial recordings are typically done with micro- or macro-electrode EEG placed within the scalp. Those recordings are also called intracranial EEG (iEEG), or ECoG [28-31]. The placement of electrodes require risky surgery, it is very invasive. Another method for recording HFOs is Stereo Electroencephalographic (SEEG) [32]. Although SEEG may be less risky as compared with iEEG or ECoG, it is still a very invasive procedure. MEG, one of the relatively new technologies, is much safer as compared with intracranial recordings.

Recent reports have shown that HFBS can also record with scalp Electrophotography (EEG) [33-40]. Scalp EEG is a non-invasive procedure as compared with intracranial recordings. However, the scalp EEG is characterized with "low-pass effect" [41], which means that low frequency electrical signals can pass through the brain, skull and scalp and skin without significant decay of signals, while high frequency electrical signals have difficulty to pass through the brain, skull, scalp and skin without significant decay of signals power. In other words, there is frequency dependence of the transmission of the EEG from cortex to scalp. It has been found that during paralysis, frequencies over 20 Hz show powers of 10-200 times the power of those frequencies in the unparalyzed state. These high powers have actually been shown in some cases to originate in EMG as opposed to EEG data. Although in some situations the bulk of high frequencies are EMG-related, some studies have successfully recorded HFOs from scalp EEG [34,40], some showing continuous spike-waves during interictal slow-wave sleep [40], and some with simultaneous scalp EEG and intracranial recordings [34]. These scalp HFOs are associated with spatially limited focal subdural sources. Interestingly, the rates of HFOs are higher inside than outside the SOZ [42], and when used for determining SOZs are more precise than spikes [43,44]. Nevertheless, the reliability of scalp EEG detection of HFOs has remained an open question. Recent data showed that MEG is superior to EEG in the detection of HFBS [45].

In summary, one of the most research areas is to improve the outcomes of epilepsy surgery by using cost-efficient and noninvasive biomarkers of epileptogenicity that have the potential of replacing more expensive and invasive procedures. It is more than likely that multi-frequency analyses of neuromagnetic HFBS and spikes, instead of analysis of spikes alone, will lead to much better localization of ictogenic zones and result in significantly improved rates of seizure freedom. We consider the future of the study of neuromagnetic HFBS is bright for several reasons:

- The occurrence of conventional spikes does not correlate with seizure severity (e.g., number of daily seizure) [46] but HFBS do correlate [47,48].
- Removal of brain regions generating HFBS has shown increased postoperative seizure freedom [21,49] and
- New MEG methods, which utilize both spikes and HFBS, can localize ictogenic zones interictally [50,51].

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