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Targeting high frequency oscillations in epilepsy

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Human brain oscillations organize across multiple temporal scales that can be measured directly with EEG. Once considered inessential epiphenomena, recent work has highlighted cortical oscillations as primary phenomena that cause and direct essential brain processes. Pioneering work has shown that brain rhythms can be augmented by external manipulation with direct cognitive impact. For example, auditory enhancement of slow wave oscillations during NREM sleep improves declarative memory (Ngo et al., 2013). Invasive studies have shown that direct stimulation of entorhinal (Suthana et al., 2012) and lateral temporal cortex (Kucewicz et al., 2018) in the gamma to ripple ranges improves spatial and verbal memory, respectively.

Among the brain oscillations that have emerged as important in epilepsy, brief, spontaneous, high frequency oscillations (HFOs, 100–500 Hz), have been repeatedly observed in brain tissue responsible for generating seizures (for a recent review, see Frauscher et al., 2017). Growing observations suggest that HFOs are highly specific for demarcating epileptogenic cortex. They are higher inside the seizure onset zone (SOZ) than control regions (Worrell et al., 2008), identify the SOZ with better specificity than spikes (Jacobs et al., 2010), correlate with disease severity (Kerber et al., 2013), and confer a better outcome if resected during epilepsy surgery than if left behind (for example, Jacobs et al., 2010).

In this issue of *Clinical Neurophysiology*, Cuello-Oderiz et al. evaluate the relationship between traditional epileptiform patterns and HFOs to the epileptogenic zone in focal cortical dysplasias, lesions caused by focal abnormalities in neuronal migration that have unique neurophysiological signatures (Cuello-Oderiz et al., 2018). Consistent with prior studies, these authors found that fast ripples (>250 Hz) tend to have a lower false positive rate for identifying epileptogenic tissue, compared with traditional markers. While this study was limited by small sample size and a subjective threshold to select pathological versus physiological HFOs using automated identification, this case series contributes to the growing evidence of the apparent specificity of interictal HFOs to epileptogenic tissue in epileptic patients. In addition, this work highlights the increased interest among the epilepsy community to better understand the utility of HFOs as a modern marker in epilepsy.

Though the first observations of HFOs were observed in invasive microwire (Bragin et al., 1999) and macroelectrode recordings (Jirsch et al., 2006), recently a small number of groups have also reported several observations of fast oscillations in the ripple range (100–250 Hz)

Conflict of interest

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in non-invasive scalp EEG recordings (Kobayashi et al., 2010; Andrade-Valenca et al., 2011; Iwatana et al., 2012; Melani et al., 2013; Pizzo et al., 2016; van Klink et al., 2016; Chu et al., 2017). As expected, these fast oscillations are better observed in scalp EEG recordings with increased spatial and temporal sampling (Chu et al., 2017). Consistent with intracranial observations, scalp observed ripples have also been shown to correlate with seizure severity (van Klink et al., 2016) and track with disease course (Kobayashi et al., 2015) in the populations that have been evaluated thus far. Though it remains unclear if intracranial and scalp observed ripples are directly related, the potential to observe these signals non-invasively has high clinical relevance.

HFOs have been proposed to be generated by multiple mechanisms at the cellular and network levels (for a review, see Jiruska et al., 2017). While the mechanisms that generate HFOs remain incompletely understood, HFOs associated with brain pathology are thought to reflect the aggregate action potentials generated by principal cells. Two broad categories of mechanisms proposed to support this coordinated fast activity include non-synaptic mechanisms (e.g., axo-axonal gap junctions (Traub et al., 2010) and ephaptic interactions (Draguhn et al., 1998)) and synaptic mechanisms (e.g., interneuron firing, synaptic interactions, and depolarizing GABA (Alvarado-Rojas et al., 2015)). HFOs may also represent the net frequency of neuronal populations, and require inclusion of additional network mechanisms, such as clustered network connectivity between neurons due to the presence of hub neurons. HFOs are likely generated by multiple mechanism that span the cellular and network level (Jiruska et al., 2017).

As continued research and publications suggest, short bursts of discrete and focal high frequency oscillations have clearly emerged as an important signal arising from epileptogenic cortex. Continued study of these events will help to further clarify their physiological significance, and potentially fundamental pathological relationship to epilepsy. Over a decade of experience has proven that external manipulation of brain oscillations can directly improve clinical symptoms in a variety of neurological disorders, including primary generalized dystonia (Vidailhet et al., 2005), depression (Mayberg et al., 2005), and Parkinson's disease (Deuschl et al., 2006). Recent animal work suggests potential applications even in Alzheimer's disease (Iaccarino et al., 2016). The mounting evidence implicating aberrant high frequency oscillations in epilepsy may provide a target beyond biomarker discovery, toward direct insights in epilepsy pathophysiology, and novel opportunities for manipulation and treatment.

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