Commentary

High-frequency oscillations (HFOs) of the electrical brain activity have attracted considerable attention. By the term HFOs, as we know them today, we mean frequencies of brain activity over > 80 Hz. HFOs represent not only the electrical manifestation of neuronal events but, above all, the very effective mechanisms of brain function. HFOs play a pivotal role in synchronizing local and distributed neuronal networks, as is critical for normal brain function. These oscillations can be detected by both non-invasive and invasive electroencephalography (EEG). However, most published papers have presented HFOs results from invasive EEG due to a significantly better signal-to-noise ratio using this approach.

HFOs represent a heterogeneous group of (patho)physiological phenomena, including different oscillations classified by many criteria, most often frequency. Furthermore, oscillations can be classified according to the mechanisms of origin, pathogenicity or physiological function, location, morphology, duration, amplitude, entropy, and other characteristics.

In clinical medicine, HFOs have been predominantly studied in epileptology due to the need to detect HFOs by invasive EEG monitoring, used to evaluate intractable focal epilepsies. At first, HFOs were considered to be mainly pathological events occurring primarily in the area responsible for seizure generation. Thus, the first substantial application of HFOs took place in the context of epilepsy surgery in order to find out and remove this pathological area. This is now followed by other applications such as assessment of epilepsy severity and antiepileptic therapy monitoring. Over the past years, HFOs were also found in vast areas of the human brain distant from the epileptic network, having a physiological role. HFOs and the mechanisms of their formation are currently attracting considerable attention to research in identifying the epileptogenic region of the brain on the one hand, and on the other hand, in studying their physiological function within cognitive functions, memory, movement control, and others.

The submitted habilitation thesis represents a summary of current knowledge regarding HFOs and a collection of the author's previously published research (as the principal author or co-author) relevant to the topic. This work aims to show my contribution to the study of high-frequency oscillations.

For the HFO detection and analysis, our research group uses the automated detection. The iEEG data were processed by automated algorithms that were already used in other published studies. The Python codes of these algorithms are part of the ElectroPhYsiology Computation Module (EPYCOM) and can be found online at https://gitlab.com/icrc-bme/epycom. We proved standard automated detection of HFOs, in comparison with visual analysis of HFOs, achieves comparable results,

and enables the evaluation of HFO characteristics (several frequency bands, changes in time, changes concerning seizures) in whole data. This detection allows general purpose and objective evaluation without any bias from the neurophysiologist's experiences and practice. Based on our data, and also data of other published papers, very simplified, pathologic HFOs tend to be of higher frequency than physiologic HFOs and are thought to be a feature of the seizure onset zone/epileptogenic zone in patients with epilepsy. Furthermore, as we showed in our study based on HFO rates, it is possible to distinguish between unilateral and bilateral mesial temporal lobe epilepsy. However, there are no unambiguous characteristics of HFOs (clear cut off values) that would distinguish pathological and physiological HFOs. Nevertheless, based on our studies, it seems pathological HFOs have higher rate frequencies, amplitude and lower spectral entropy in epileptogenic zone. The occurrence of HFOs over time is not constant and depends on many factors. Interestingly, in our recent studies, we revealed the differences in HFOs activity between epileptic and non-epileptic hippocampus during cognitive processing. These studies bring new insight in delineation between pathological and physiological processes, particularly the suppression of pathological HFOs in the epileptic hippocampus during a cognitive task. For patients with drug-resistant focal epilepsy, there is an increasing body of evidence pointing toward the use of HFOs for delineating the epileptogenic zone with a potential to improve surgical success. As we showed in our published study, multiple invasive EEG and connectivity features in presurgical evaluation using machine learning tools could improve epileptogenic tissue localization, which is superior to using a single feature. Finally, an essential contribution in this field was the discovery of very high-frequency oscillations (over 1000 Hz) in intracerebral EEG recordings. The phenomena of very high-frequency oscillations are more spatially restricted and seem to be more specific biomarkers for epileptogenic zone when compared to traditional interictal HFOs

I have chosen 7 research articles related to high-frequency oscillations as a part of my thesis. My contribution to these articles is summarised in the following tables with special attention to the conceptualization of the study, project administration, data curation, and manuscript preparation.

PAIL, Martin, Jan CIMBALNIK, Robert ROMAN, Pavel DANIEL, Daniel J. SHAW, Jan CHRASTINA a Milan BRAZDIL. High frequency oscillations in epileptic and non-epileptic human hippocampus during a cognitive task. *Scientific Reports* [online]. 2020, 10(1),18147 (IF = 3,998)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
70	40	40	70

CIMBALNIK, Jan, **Martin PAIL**, Petr KLIMES, Vojtech TRAVNICEK, Robert ROMAN, Adam VAJCNER a Milan BRAZDIL. Cognitive processing impacts high frequency intracranial EEG activity of human

hippocampus in patients with pharmacoresistant focal epilepsy. *Frontiers in neurology* [online]. 2020, 11, 578571 (IF = 2,889)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	20	30	30

CIMBALNIK, Jan, Petr KLIMES, Vladimir SLADKY, Petr NEJEDLY, Pavel JURAK, **Martin PAIL**, Robert ROMAN, Pavel DANIEL, Hari GURAGAIN, Benjamin BRINKMANN, Milan BRAZDIL a Greg WORRELL. Multi-feature localization of epileptic foci from interictal, intracranial EEG. *Clinical Neurophysiology* [online]. 2019, 130(10), 1945–1953 (IF = 3,214)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
-	20	20	10

REHULKA, Pavel, Jan CIMBALNIK, **Martin PAIL**, Jan CHRASTINA, Marketa HERMANOVA a Milan BRAZDIL. Hippocampal high frequency oscillations in unilateral and bilateral mesial temporal lobe epilepsy. *Clinical Neurophysiology* [online]. 2019, 130(7), 1151–1159. ISSN 1388-2457 (IF = 3,214)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	20	30	10

BRAZDIL, Milan, **Martin PAIL**, Josef HALAMEK, Filip PLESINGER, Jan CIMBALNIK, Robert ROMAN, Petr KLIMES, Pavel DANIEL, Jan CHRASTINA, Eva BRICHTOVA, Ivan REKTOR, Gregory A. WORRELL a Pavel JURAK. Very High-Frequency Oscillations: Novel Biomarkers of the Epileptogenic Zone. *Annals of Neurology* [online]. 2017, 82(2), 299–310 (IF = 10,250)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
20	20	20	10

PAIL, Martin, Pavel REHULKA, Jan CIMBALNIK, Irena DOLEZALOVA, Jan CHRASTINA a Milan BRAZDIL. Frequency-independent characteristics of high-frequency oscillations in epileptic and non-epileptic regions. *Clinical Neurophysiology* [online]. 2017, 128(1), 106–114 (IF = 3,614)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
50	70	30	60

PAIL, Martin, Josef HALAMEK, Pavel DANIEL, Robert KUBA, Ivana TYRLIKOVA, Jan CHRASTINA, Pavel JURAK, Ivan REKTOR a Milan BRAZDIL. Intracerebrally recorded high frequency oscillations: Simple visual assessment versus automated detection. *Clinical Neurophysiology* [online]. 2013, 124(10), 1935–1942 (IF = 2,979)

Conceptualization of the study (%)	Project administration (%)	Data curation (%)	Manuscript preparation (%)
50	30	30	80