

HABILITATION THESIS REVIEWER'S REPORT

Masaryk University

Applicant

MUDr. Martin Pail, Ph.D.

Habilitation thesis

Human intracranial high-frequency oscillations – both physiological and pathological phenomena

Reviewer

Michal Tomasz Kucewicz, PhD

Reviewer's home unit, institution

Brain and Mind Electrophysiology laboratory, BioTechMed Center, Gdansk University of Technology

Dr. Pail prepared an impressive thesis based on his comprehensive review of the existing body of literature on the subject, including his own original research contributions to the field. The thesis encompasses most of the seminal papers published in the field clearly presented in a well-defined structure of chapters. Starting from a historical and conceptual background as an introduction to the topic of high frequency oscillations (HFO), consecutive chapters lead the reader through the methodology of HFO detection, mechanisms of generation, different HFO types, clinical applications, and the current hot topics in the HFO research, which include the very fast and ultra-fast HFO discovery (co-authored by Dr. Pail). His own scientific contributions to the HFO research field were clearly and compellingly presented in the areas of expertise that have been developed by the Brno epilepsy team led by Prof. Milan Brazdil and Dr. Jan Cimbalnik over the last 10 years or so. The resultant thesis offers an invaluable scientific work that aptly summarizes and depicts the current state of the HFO research. It provides a very useful resource for anyone interested in this research. Having investigated HFO myself for over a decade both in the animal and in the human brain, I have read Dr. Pail's thesis with utmost attention and great appreciation for the quality of this work. I have no major concerns about the content or merit of this excellent piece of scientific writing, which I strongly advise to be published in a condensed version for a larger audience as a review article.

My only comments pertain the individual contribution of Dr. Pail to this body of research achievements published by the Brno group, and a few issues regarding the contribution of other research teams around the world to some of the topics discussed in the thesis.

First of all, out of the seven original research articles presented in thesis, Dr. Pail was the lead author of only 3 of them and a second author of one. The remaining articles show only partial co-authorship contribution to the presented work. Dr. Pail is not a senior author on any of the articles. Compared to the other publications listed for the thesis, the 3 lead-author articles of Dr. Pail are not the most impactful in terms of the article or journal citation scores. His most cited article has 31 citations according to the Google Scholar database in a journal with the Impact Factor <4. Admittedly, most of the listed publications are relatively new but the other relatively new articles listed with Dr. Pail's co-authorship are more impactful. Depending on the local requirements, this may or may not be an issue to fulfill the criteria for habilitation.

Secondly, there are two points discussed in the thesis that would benefit from a further clarification. Dr. Pail presents his work pertaining the role of cognitive tasks in the generation of epileptiform (pathological) HFO activities. In particular, an interesting suppressing effect on the HFO counts is discussed, in contrast to the previous work of other groups showing a detrimental effect of epileptiform spikes (Kleen et al. 2013, Neurology; Horak et al. 2016, Epilepsia) and HFOs (Waldman et al. 2018, Epilepsy Behav). The reverse view of a cognitive task suppressing the rate of epileptiform activities is certainly original but misses a key reference of the previous work by Matsumoto et al. (2013, Brain) that I have been involved with. That work showed the suppressing effect on the rate of epileptiform spikes during a visual recognition memory task. Even though the thesis is about HFO and not the other epileptiform activities, the fact that many HFO detections co-occur with the spikes requires a mention of this previous work with the same effect, and of the other reports that had shown shown an opposite effect of the interictal activities on the performance of cognitive tasks.

In a similar way, using cognitive tasks to help in differentiating the pathological from the physiological HFO is discussed without a reference to the previous work of our group that employed a memory task to isolate a population of physiological HFO (Kucewicz et al. 2014, Brain), which was co-authored by Dr. Pail's teammate – Dr. Jan Cimbalnik. This report was followed by a commentary article that suggested task-induced HFO to be used as a new gold standard to dissociating pathological and physiological activities (Stacey 2015, Epilepsy Currents, 'Abby...Normal? A New Gold Standard for Identifying Normal High Frequency Oscillations'). I find these articles very complementary and critical to the views discussed in the thesis, yet missing in the present version.

Finally, some of the references in the thesis are over-used to support claims that were directly addresses in the cited articles. This applies especially to the review articles by Worrell et al. (2012, Progress in Neurobiology) and Frauscher et al. (2017, Epilepsia). I also found a statement in the thesis that was allegedly supported in my previous article: '*and some neocortical pyramidal neurons have similar properties (Kucewicz et al. 2014)*', even though that study was directly not investigating single neuron activities. I presume that Dr. Pail was citing ideas discussed in the review or in the original research articles, but not directly supported by the results presented. This form of referencing should be avoided.

Furthermore, there are a few language and style enhancements that could still be implemented in the interest of the highest quality of this work. I also generally discourage using the verb: 'to prove' in any scientific writing, as it sounds too definite and conclusive for the strength of evidence presented especially in biological sciences. Otherwise, I would like to sincerely congratulate Dr. Pail on delivering an excellent piece of scientific writing.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

1. My first question pertains to the above-mentioned comments about the bidirectional relationship between cognitive processes and the generation of epileptiform activities (HFO and spikes). In the light of the mechanisms of HFO generation presented by Dr. Pail, can the effect of/on cognitive processing be explained by the underlying neural oscillations? In the work by Matsumoto et al. (2013, Brain) these were the induced gamma oscillations that were implicated with the suppressive effect on spikes. Could this also apply to the suppression of pathological HFO?
2. Likewise, is there a qualitative difference between a physiologically-induced HFO in a task and a pathological HFO generated by the same or similar networks of neurons? In theory, the same assemblies that generate HFO to support cognitive processes could as well be the source of pathological discharges. It would explain why these cannot be easily separated by the characteristic frequency. The two types could belong to the same spectrum of activities, having roles both in epileptogenic and cognitive processes. In analogy to the micro-seizures (Stead et al. 2010, Brain), HFO would be generated both by the healthy and epileptic tissue but at different scales or properties.
3. What information or function, if any, do pathological HFO carry? It is rare to see biological activities that are completely redundant, hence even HFO occurring in the seizure onset zone could still be playing a role in a normal brain function. In animals, HFO in the ripple frequency range were shown to contain information about previous and future trajectories in space as sequences of place cells. A recent report in epilepsy patients showed analogous sequences of neuronal firing during ripples (Vaz et al. 2020, Science), which corresponded to the words remembered during a cognitive task. Is it possible that HFO generated at higher rates in the seizure onset zone also carry meaningful information?

Conclusion

The habilitation thesis entitled MUDr. Martin Pail, Ph.D., „Human intracranial high-frequency oscillations – both physiological and pathological phenomena” **fulfils** requirements expected of a habilitation thesis in the field of Neurology.

Date: 18.08.2021

Signature:

A handwritten signature in black ink, consisting of a series of connected loops and a final horizontal stroke, positioned below the 'Signature:' label.