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Opponent's report of the dissertation "Effect of sepsis on dynamics of hippocampal oscillations and CA1 cells" by Annu Kala, MSc.

The present dissertation introduces the topic of the influence of sepsis on brain activity with a focus on sleep dynamics as a critical process for maintaining physical and mental health. The topic studied is very actual, and, as the author suggests, addressing sleep-wake dynamics in the hippocampal network could offer a promising avenue for therapeutic intervention to enhance outcomes in individuals affected by sepsis.

The study used an injection of lipopolysaccharide (LPS) to mimic sepsis in rats under urethane anesthesia and in awake animals. In anesthetized rats, a high LPS dose led to extensive state fragmentation in REM-like and NREM-like sleep states without altering the overall time spent in each state. LPS also increased the similarity between these states. Analysis of the periodic and aperiodic components of REM and NREM spectra revealed that spectral alterations during sepsis were primarily influenced by changes in the oscillatory component. Even a lower LPS dose induced comparable vigilance state fragmentation in awake animals, and resulted in REM suppression. In the CA1 hippocampal area, both pyramidal and interneuron activities were inhibited during this sepsis model, with interneuron activity decreasing before pyramidal cells; and the number of sharp wave ripples (SWRs) during NREM sleep increased after LPS injection. The main results of the work are very valuable and significantly develop the knowledge in the studied area.

The thesis is 127 pages long (97 pages without citations) and has a standard structure and layout. The introduction provides a comprehensive and clear insight into the topic studied, and the objectives and hypotheses are clearly defined and formulated. The methodology is sufficiently described; I would suggest only separating it more clearly concerning the

individual experiments. The methodology also describes the analysis of firing rate maps (3.13 Linearized Firing Rate Maps), while this type of analysis is not used for the results described. The results are clearly reported, although I would suggest a more distinct separation related to individual objectives and experiments. The discussion starts with a summary of the main results, followed by their interpretation in the context of relevant literature. The author also successfully communicates the significance and originality of the results obtained, which are very valuable. Nevertheless, I would still welcome a Conclusions section with a brief statement of the main conclusions. The thesis contains an impressive number of 360 citations. Many recent original publications are also included, indicating the author's excellent orientation in the studied topic. Formally, I would only criticize a few typos, occasionally inconsistent font for headings, or inconsistent format for some references in the image descriptions. The final list of references is then listed in the order in which they appear in the text, but since the references appear in the actual text in the format "Author's name, year of publication", this ordering is impractical. I would recommend alphabetizing the citations in their final list. Despite these minor formal shortcomings, the work is of a very high standard overall.

Annu Kala, MSc. is the author of three impacted publications (1x first author, 2x co-author), with a cumulative impact of 11.09. The dissertation is primarily based on a first-authored article. The author played a crucial role in preparing this publication, having been involved in all aspects of its generation, from designing the experiments, conducting advanced electrophysiological experiments and data analysis, to writing the manuscript. All publications are of high quality, and the author has demonstrated a broader understanding of neuroscience fields and techniques also through her participation in thematically and methodologically distinct co-authored papers.

The submitted thesis fulfilled the pursued objectives, and the author demonstrated her ability to work independently as a scientist by preparing and submitting impacted publications. The author can conceive scientific questions and formulate hypotheses, design and conduct scientific experiments, process, analyze, and interpret the data obtained, and write a scientific publication. Therefore, I recommend the thesis for defense.

Questions:

1. LPS administration has been used in various modifications as an animal model for a broader range of neurological diseases (e.g., Alzheimer's or Parkinson's disease).

What about sleep disturbances in patients at different stages of Alzheimer's and Parkinson's disease? Is sleep fragmentation also considered a key factor for developing these diseases?

2. The author presents somewhat surprising results regarding the higher incidence of SWRs during NREM sleep after the LPS administration in awake animals. However, the observed incidence of SWRs appears to be lower, even after the LPS administration (20-50 SWRs/10 min, i.e., 0.033-0.083 Hz), than the values typically reported during slow-wave (NREM) sleep. I would like to ask the author to comment on this.

Yours sincerely,
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