



CHARLES UNIVERSITY
Third Faculty of Medicine



Opponent Review of Doctoral Dissertation

Author: Annu Kala, MSc

Title: Effect of Sepsis on Dynamics of Hippocampal Oscillations and CA1 Cells

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Topic: The presented doctoral thesis addresses an important topic. Sepsis is a medical emergency. Even when it is successfully treated, the patients may have long-term cognitive impairment that leads to decreased life quality, prolonged hospitalization, and increased demands on social care after the hospitalization. Any medical care or treatment that has the potential to improve cognitive outcomes in septic patients would therefore be highly beneficial for both the patients and society. The importance of sleep for cognition, especially memory consolidation, has been well documented in the literature. The thesis investigates changes in sleep during the acute phase of sepsis. It brings our attention to sleep as a new possible therapeutic target for postseptic cognitive impairment.

Aims and Methods: The author reviews relevant and up-to-date literature about sepsis and its animal models, about sleep and memory physiology, and about their neural substrate with a focus on the hippocampus. The aims of the thesis are clearly formulated, deeply rooted in literature, and ambitious. The chosen methods are appropriate for answering the postulated hypotheses. However, description of some of the procedures in the Methods section was difficult to follow and repeated reading was required. It is not clear whether locomotion over the linear track was based solely on exploratory behavior or whether the animals were motivated to run across the platform by rewards.

Findings: The thesis provides novel and interesting findings about rat hippocampal activity in the lipopolysaccharid model of sepsis. To list just a few: high fragmentation of REM and NREM phases, blurring the differences between the REM and NREM, an overall decrease in neuronal spiking, and an interestingly increased number of SWRs that are considered to be the neuronal correlate of memory consolidation. The plausibility of the findings is further strengthened by demonstrating similar results in anesthetized and awake rats and by showing a strong correlation between the changes and inflammatory biomarkers. Some parts of the results are difficult to follow due to the large amount of statistical tests. I leave it to author's opinion whether some of the tests could be skipped or replaced by tests more targeted at the hypothesis in mind.

Formal standards: The thesis has a high formal standard. It has a standard division into sections. The formal site of the thesis could be improved by ordering the list of abbreviations alphabetically. It would make the search through the list faster. For the author, it would be easier to check that all abbreviations used in the text are also included in the list. For example, the abbreviations CLP and RA used in the thesis are not included in the list. Similarly, the search through the impressively long list of references is demanding. If the references were ordered alphabetically, then the search through it would be easier. There are a few typos in the thesis, e.g., the description of the x-axis in Figure 15 E-H, the reference jhadav et. al on page 52.

Questions:

1) Brain activity under urethane anesthesia was classified into two states: REM and NREM. LPS administration increased the number of REM as well as NREM episodes, as confirmed by two statistical tests, one for REM and the other for NREM states. The increase in REM states is tightly coupled with the increase in NREM states. Thus, one of the tests seems to be redundant. Was there a reason for performing the two tests instead of a single test evaluating changes in the number of transitions?

2) The experiment on awake animals showed an increased number of SWRs in the LPS group compared to the control group. Were there any differences in the electrophysiological characteristics of SWRs between the LPS and control groups? What is your opinion about the firing of pyramidal cells during SWRs in the LPS group—does it reflect memory consolidation or is it just a chaotic activity? Is it possible to answer this question from your data?

Final evaluation: The presented thesis postulates medically interesting hypotheses and tests them using appropriately chosen experimental methods and data analysis. The main findings extend our knowledge and open up new promising fields of research. The high quality of the thesis is confirmed by the fact that the results were published in highly impact journals.

I recommend the thesis be defended.

Daniel Klement

In Prague, March 27, 2024