Opponent review of doctoral dissertation thesis

English title: Hippocampal neuronal representation of a moving object in a novel spatial avoidance task

Czech title: Hipokampální neuronální reprezentace pohybujícího se objektu v nové úloze vyhýbání se prostoru

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Study programme: Charles University, Faculty of Science, Animal Physiology

General characteristics

The submitted thesis concerns spatial behavior of rats in relation to dynamic objects in the environment. The manuscript is written in English (except for the obligatory Czech abstract) and comprises of 124 pages including the list of approximately 200 references. The thesis is based on two original research papers published in scientific journals with impact factor. This includes a study *Frontiers in Behavioral Neuroscience* (IF=2.512) and *Neurobiology of learning and memory* (IF=2.768), where the applicant is the first and fourth author, respectively. In addition, the applicant published a study in *Progress in Neuropsychopharmacology and Biological Psychiatry* as a shared first author (IF=4.361). The topic of this paper is not directly related to the topic of the dissertation, but it's in a related field of hippocampal neuropharmacology and electrophysiology.

Thesis evaluation

The introduction section is written in clear and concise language and to high formal standards. In my opinion, this section could however benefit from somewhat better organization, such as division into subchapters and perhaps a separate subchapters concerning primate navigational system. In the present text, findings from rodent and primate models are somewhat confusingly combined. Despite the fact that the electrophysiological part of the experimental work focuses primarily on hippocampal place cells, I would appreciate a more thorough review on the remaining components of the hippocampal navigation circuitry, such as grid cells, head direction cells and other spatially-tuned neurons. However, the literary review clearly demonstrates applicant's strong expertise in animal spatial behavior and spatial navigation circuitry of the brain.

The thesis defines 4 specific aims which are clearly and logically outlined and consecutive to one another. The first aim was to establish a behavioral paradigm for navigation with respect to a moving object. While a similar test named 'Enemy avoidance task' was previously established in the laboratory

of Neurophysiology of Memory, this modified task developed by the applicant addresses the need to increase the stimulus salience, which was hypothetically a limiting factor for the subsequent electrophysiological study. This was achieved by training the animals to avoid more specifically defined shock zones, which effectively 'forced' the animal to pay attention to both orientation and position of the moving object. The next aim was to dissect behavioral variables such as animal trajectory, shock zone entry latencies and in-zone times. This was used to demonstrate that the animals can evaluate their position relative to a position and orientation of a moving object. Third aim was to determine the single unit activity of hippocampal place cells in freely moving rats in the modified Enemy avoidance test. The applicant found that a subset of place cells had place fields localized in positions relative to the moving object, confirming a hypothesis that place cells participate in representing object-centered space. The fourth and final aim was to determine how the spatial organization of place cell representations in well-trained and naïve animals. Surprisingly, the increased object salience in the trained group did not result in significant difference between representations.

The approaches used by the applicant are well chosen and appropriate. My only objection to methodology is a missing histological confirmation of electrode position, which are a standard verification of the neuroanatomical substrate in electrophysiological studies.

Questions for defense

1. Can you summarize the respective importance of rate and temporal coding for the processing of spatial information by hippocampal place cells? Would you hypothesize that temporal coding mechanisms such as theta phase precession play a significant role in your behavioral paradigm?
2. In your view, how did the study of the hippocampal model system contribute to our understanding of the general principles of neural coding in the nervous system?
3. Human data, especially from patients with hemispatial neglect resulting from parietal injury, suggest that left posterior parietal cortex is responsible for object-based orienting. This is confirmed by electrophysiological studies in non-human primates. However, object-oriented behavior in rats is disrupted after hippocampal impairment and object-associated neuronal activity was accordingly found by in the hippocampus and entorhinal cortex. Can you discuss this interspecies difference in spatial navigation circuitry and its possible proximate (neural) and ultimate (evolutionary) causes?
4. Comparison of spatial organization of place cell firing into object and room-based reference frames did not yield significant differences between trained and naïve animals. Do you therefore think that the modifications of 'Enemy avoidance task' you desinged in Aim 1 to increase stimulus salience brought any advantage compared to the older test? Do you plan on simplifying the task for future applications to save training time?
5. What are the future applications of the test you developed?

Overall assessment

Despite these minor complaints, the presented thesis represents a quality work, which brings original new results that advance our understanding of the neural mechanisms underlying spatial cognition in rodents. The thesis fulfills all necessary criteria for a PhD thesis at the Faculty of Science, Charles University. I therefore recommend this thesis for defense.

Prague, May 7th, 2021

Mgr. Petr Telenský, Ph.D.