May 2nd , 2023

Dear Editor,

Please consider our manuscript titled "Hippocampal neural fluctuation between memory encoding and retrieval states during a working memory task in humans" for publication as a Research Article in *Current Biology*.

In this study, we calculated the low-dimensional neural trajectory of the medial temporal lobe (*e.g.*, the hippocampus) based on multiunit activity, and found a fluctuating behavior of the hippocampus during a working memory task in humans. First, we found that the neural trajectory of the hippocampus exhibited memory load dependency in the distance of its neural trajectory between the encoding and retrieval states. Second, the neural trajectory of the hippocampus exhibited a transient increase during hippocampal sharp-wave ripple (SWR), a biomarker for various cognitive processes. Last, the direction of the neural trajectory of the hippocampus during the retrieval phase fluctuated between the encoding and retrieval phases, the balance of which shifted to the retrieval state during SWR. Such a fluctuation was reasonable based on the requirements of trial types (whether a probe letter was included in encoding letters) and previous studies. Therefore, we clarified a new mechanism of hippocampal information processing during the retrieval phase of a working memory task.

In *Current Biology*, Saint Amour di Chanaz et al.1 reported similar results in which the hippocampal gamma is coupled to opposing theta phases during the encoding and retrieval of episodic memories in humans. They focused on the oscillation patterns of the intracranial encephalogram data, which is believed to reflect the input signals to the hippocampus. We, on the other hand, focused on the output signals of the hippocampus (*i.e.*, multiunit activity). Thus, we strongly believe that our work will offer a comprehensive description of the hippocampal system during working memory tasks and be of broad and profound interest to the readers of *Current Biology*.

Reference

1. Saint Amour di Chanaz, L., Pérez-Bellido, A., Wu, X., Lonzano-Soldevilla, D., Pacheco-Estefan, D., Lehongre, K., Conde-Blanco, E., Roldan, P., Adam, C., Lambrecq, V., et al. (2023). Gamma amplitude is coupled to opposed hippocampal theta-phase states during the encoding and retrieval of episodic memories in humans. *Current Biology*. [10.1016/j.cub.2023.03.073](https://doi.org/10.1016/j.cub.2023.03.073).

We hereby certify that this study constitutes original research that has not been previously published and is not under consideration for publication elsewhere, in whole or in part, in any language. The experiments were carefully conducted in accordance with the University of Tokyo guidelines for laboratory animal care and safety.

We suggest the following potential reviewers for this paper:

1. Prof. Ph.D. Lluís Fuentemilla Garriga

Cognition & Brain Plasticity Unit, [University of Barcelona](https://scholar.google.com/citations?view_op=view_org&hl=en&org=15918451262755526508), Spain

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Reason: He is the corresponding and last author of the cited study (Saint Amour di Chanaz et al., *Current Biology*, 2023). Moreover, as the first author, he published a related paper titled “Theta-Coupled Periodic Replay in Working Memory” in Current Biology in 2010.

2. Prof. Ph.D. Johannes Sarnthein

Klinik für Neurochirurgie, UniversitätsSpital und Universität Zürich, 8091, Zürich, Switzerland

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Reason: He is the last author of the dataset we used in the manuscript.

3. Prof. Ph.D. Colin Lever

Psychology Department, the University of Durham, United Kingdom

[colin.lever@durham.ac.uk](mailto:colin.lever@durham.ac.uk)

Reason: He has experience working with hippocampal neural processing during working memory tasks.

4. Prof. Ph.D. Bernhard P Staresina

Department of Experimental Psychology, University of Oxford, United Kingdom

bernhard.staresina@psy.ox.ac.uk

Reason: He found a correlation between hippocampal activities during the encoding and retrieval phases of a working memory task in humans.

5. Associate Prof. Ph.D. MD. Anli A. Liu

Department of Neurology at NYU Grossman School of Medicine, USA

[anli.liu@nyumc.org](mailto:anli.liu@nyumc.org)

Reason: She published a paper for a consensus statement on detection of hippocampal sharp wave ripples.

6. Postdoctoral fellow. Ph.D. Yitzhak Norman

Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel

[itzik.norman@gmail.com](mailto:itzik.norman@gmail.com)

Reason: He found a correlation between sharp-wave ripples and spontaneous recall in humans.

We appreciate your consideration of our manuscript and look forward to your response.

Sincerely yours,

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