Point-by-Point Replies for Editor and Reviewers
Hippocampal Neural Fluctuation between Memory Encoding and Retrieval States During a Working Memory Task in Humans
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Introduction

We appreciate the Editor and Reviewers' insightful comments and suggestions, which have been invaluable in enhancing our manuscript. We have conducted revisions to address all the raised concerns. *The original comments from the Editor and Reviewers are presented in inclined gray text for reference.* Our responses are provided in blue , and the corresponding revisions are presented with highlights for added text (underlined with a wave) and ~~deleted text~~ (struck through).

Reviewer #2's Comments #1

1. The authors provide sufficient details for most of the analysis. However, some methods are presented with insufficient details.
2. All the results that support the conclusion are directly shown.
3. I find that the conclusion drawn by the authors are an exaggerated extension of the results obtained. I think a major flaw is present in the definition of 'states', which are the core of the study. Clear definition of the term 'state' is needed, together with additional analysis to show their existence. At this stage, the results are too weak to support the conclusion.
4. The study complies with the ethical guidelines.

Response

We value your constructive feedback, particularly concerning the necessity for a solid definition of "states". We will address each of your points in a line-by-line manner in the subsequent paragraphs.

Reviewer #2's Comments #2

Major comments: - Defining 'encoding' and 'retrieval' states requires a careful, complete, and clear analysis. From Fig.2, it seems that NT points are scattered and do not have stable 'states'. This could be a major flaw of the study, since the 'transition between states' could be no longer valid. To define states, authors would need to explicitly show that points that belong to 'encoding' and 'retrieval' phases are clustered in different regions of the state space and have small overlap.

Response

Thank you for your comments regarding the definitions of states. We would like to respond in the following three dimensions.

First, the definition of "states" should have been clarified. In the current study, "states" are equivalent to the median coordinate of NTs for a session (= 50 trials) in the corresponding phase (g_F for fixation, g_E for encoding, g_M for maintenance, and g_R for retrieval phase). The choice of the median, rather than the mean, for example, is due to concerns about the significant effects of outliers and the need to find a stable metric, which aligns with your point.

Second, Figure **??**A was constructed using data from Subject #6, Session #2, encompassing all 50 trials. The point here is that trials here include the following six different conditions: memory load (4, 6, and 8) and task type (Match IN versus Mismatch OUT). Thus, the instability of the scatter plots in Figure **??**A might not be invalid. To check the effects of these merged conditions, we scatter-plotted NTs for each condition separately. [FIXME ->][<- FIXME]

Lastly, to quantify this, we checked whether the four phases are linearly distinguishable in these spaces using a support vector machine classifier (SVC) in a self-supervised manner with cross-validation methods. The balanced accuracy of the classification was XXX, which was above the chance level. Thus, while we are uncertain about how concentrated and segregated each state should be, we believe the median values have the representative metrics for each phase.

Considering all factors, irrespective of the "stability of states", we assert that our findings continue to be valid. In light of these considerations, we have accordingly updated our manuscript:

Revision

0.1 Calculation of NT using GPFA and Definitions of States

NTs, also referred to as 'factors', in the hippocampus, EC, and amygdala were determined using GPFA [?] applied to the multi-unit activity data for each session, performed with the elephant package (`https://elephant.readthedocs.io/en/latest/reference/gpfa.html`). The bin size was set to 50 ms, without overlaps. Each factor was z-normalized across all sessions, and the Euclidean distance from the origin (O) was then computed.

An optimal GPFA dimensionality was found to be three using the elbow method obtained by examining the log-likelihood values through a three-fold cross-validation approach (Figure ??B).

For each NT within a region such as AHL, ~~geometric medians~~ the geometric median of each phase was calculated (g_{F} for fixation, g_{E} for encoding, g_{M} for maintenance, and g_{R} for retrieval phase)~~were calculated by determining the median coordinates of the NT during the four phases. An optimal GPFA dimensionality was found to be three using the elbow method obtained by examining the log-likelihood values through a three-fold cross-validation approach (Figure ??B)~~. In this paper, these geometric medians will also be referred to as "states".