**Hippocampal neural fluctuation between memory encoding and retrieval states during a working memory task in humans**

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# **Summary**

Working memory (WM) is essential for various cognitive functions, yet its underlying neural mechanisms remain enigmatic. While the hippocampus is established in roles relating to memory consolidation and retrieval, its specific involvement in WM tasks is still under investigation. This study posits that multiunit activity patterns in the hippocampus vary based on the memory load, task phase, and type of a WM task. The research specifically targets time intervals linked with sharp-wave ripple complexes (SWRs), potentially viewed as a fundamental representation of hippocampal processing and thus significant for WM functions. To empirically test this hypothesis, intracranial electroencephalogram (iEEG) data were collected from the medial temporal lobe (MTL) regions of nine patients with epilepsy. Subjects performed an eight-second Sternberg test, comprising an encoding phase to memorize letter sets, a maintenance phase, and a retrieval phase to identify if a probe letter was in the memorized set. Gaussian-process factor analysis was deployed to map the low-dimensional neural trajectories in the MTL during the task. SWRs were detected from putative hippocampal CA1 regions. Results indicate that the hippocampus exhibited the most significant variations in neural trajectory during the WM task compared to other MTL areas. The trajectory distance between encoding and retrieval phases was dependent on the memory load. During the retrieval phase, the hippocampus displayed fluctuation between encoding and retrieval states, with a notable shift towards retrieval state during SWR events. These findings indicate the role of the hippocampus in WM tasks, contributing new insights to the two-stage model of memory formation.

3 tables; 7 figures; 3,541 words

**Keywords:** working memory, memory load, hippocampus, sharp-wave ripples, SWR

# **Introduction**

Working memory (WM) is crucial in everyday life; however, its neural mechanism has yet to be fully elucidated, and the role of the hippocampus in WM tasks remains unclear. A famous patient, H.M., had his hippocampus removed. Despite this, he did not show WM impairments (Scoville & Milner, 1957). For example, he was able to retain numbers for over 15 minutes through continuous rehearsal (Squire, 2009). Moreover, recent studies have highlighted the involvement of the hippocampus in working memory (WM) tasks, particularly during the maintenance period. This is evident from the presence of persistent spiking (Boran et al., 2019; Jan Kamiński et al., 2017; Kornblith et al., 2017; Faraut et al., 2018) and increased gamma oscillation power (van Vugt et al., 2010). Additionally, the effective performance of WM relies on the coordination between local field potential (LFP) power and delta oscillations in the hippocampus (Leszczyński et al., 2015).

Among the hippocampal phenomena, a transient and synchronous oscillation called sharp-wave ripple (SWR; Buzsáki, 2015) is associated with various cognitive functions, including memory replay (Wilson and McNaughton, 1994; Nádasdy et al., 1999; Lee and Wilson, 2002; Diba, K., & Buzsáki, G, 2007; Davidson et al., 2009), memory consolidation (Girardeau et al., 2009; Ego-Stengel et al., 2010; Fernández-Ruiz et al., 2019; Kim et al., 2022), memory recall (Wu et al., 2017; Norman et al., 2019; Norman et al., 2021), and neural plasticity (Behrens et al., 2005; Norimoto et al., 2018). Thus, SWR might be a fundamental observation reflecting the information processing of the hippocampus, although its role in WM remains unclear (Jadhav et al., 2012; Fernández-Ruiz et al., 2019).

Hippocampal neurons may exhibit low-dimensional representations during WM tasks. For instance, the firing patterns of place cells (O’Keefe and Dostrovsky, 1971; O’Keefe, 1976; Ekstrom et al., 2003; Kjelstrup et al., 2008; Harvey et al., 2009) in the hippocampus were found to be embedded within a dynamic, nonlinear 3D hyperbolic geometry while navigating (Zhang et al., 2022). Furthermore, grid cells in the entorhinal cortex (EC) — the primary gateway to the hippocampus (Naber et al., 2001; van Strien et al., 2009; Strange et al., 2014) — exhibited toroidal topology during exploration (Gardner et al., 2022). In addition to navigation tasks, it is anticipated that the hippocampus would demonstrate low-dimensional latent spaces during WM tasks.

However, studying hippocampal functions in WM poses significant challenges due to experimental design limitations. In nonhuman animals, WM tasks are often trained through multiple trials using maze or classical conditioning methods, which do not distinguish between the acquisition and recall of information. In humans, noninvasive recording methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have limited spatial and temporal resolution. Invasive recordings of deep brain regions, such as intracranial EEG (iEEG), provide higher noise-to-ratio signals but limit the number of experiments and pose challenges in the histological verification of recording sites.

In this study, we investigated the hypothesis that hippocampal neurons exhibit distinct representations as trajectories in low-dimensional spaces during a WM task, with a specific focus on SWR periods. To test this hypothesis, we used a dataset of patients performing a WM task with high temporal resolution (1 s for fixation, 2 s for encoding, 3 s for maintenance, and 2 s for retrieval) (Boran et al., 2020). Simultaneously, their iEEG signals in the medial temporal lobe (MTL) regions were recorded with tetrodes. We used Gaussian-process factor analysis (GPFA; Yu et al., 2009) on the multiunit activity to calculate low-dimensional neural trajectories in the MTL.

# **2 Methods**

## ***2.1 Dataset***

A publicly available dataset was employed, in which nine subjects performed a modified Sternberg task that consisted of fixation (1 s), encoding (2 s), maintenance (3 s), and retrieval (2 s) phases (Boran et al., 2020). Subjects were presented with four, six, or eight alphabetical letters in the encoding phase. They were expected to recall whether a probe letter in the retrieval phase was also displayed (Match IN) or was not (Mismatch OUT). iEEG signals were recorded at a sampling rate of 32 kHz, within the frequency range of 0.5–5,000 Hz, using depth electrodes implanted in the medial temporal regions. Specifically, electrodes were placed in the left and right hippocampal head (AHL and AHR), hippocampal body (PHL and PHR), entorhinal cortex (ECL and ECR), and amygdala (AL and AR) (as depicted in Figure 1A and Table 1). Subsequently, the iEEG signals were resampled at a rate of 2 kHz. Correlations were found among the experimental variables (Fig. S1). The timings of multiunit spikes were estimated by a spike sorting algorithm (Niediek et al., 2016) by the Combinato package (<https://github.com/jniediek/combinato>) from the 32-kHz LFP signals (Figure 1C).

## ***2.2 Calculation of neural trajectories using Gaussian-process factor analysis***

## To ascertain the neural trajectories (referred to as factors; Figure 1D) of trials in the hippocampus, EC, and amygdala (Figure 1D), GPFA (Yu et al., 2009), was employed on the multiunit activity data for each session. GPFA was executed using the Python elephant package (<https://elephant>.readthedocs.io/en/latest/reference/gpfa.html). The bin size was set at 50 ms, with no overlapping. Each factor was z-normalized based on the session. The Euclidean distance was then calculated from the origin (O (0,0,0)) using the trajectories (Figure 1E).

For every trajectory within a region (*e.g.*, AHL), the “geometric medians” were determined during the four phases (*i.e.*, gF, gE, gM, and gR represent the fixation, encoding, maintenance, and retrieval phases, respectively) by computing the medians of the trajectory coordinates during each respective phase (Figure 1D). The optimal dimensionality for GPFA was established as three, which was determined through the elbow method utilizing the log-likelihood values and evaluated using the threefold cross-validation approach (Figure 2B).

## ***2.3 Defining hippocampal sharp wave-ripple (SWR) candidates within hippocampal regions***

To identify potential SWR events within the hippocampus, a consensus approach was employed, as described by Liu et al. (2022). Specifically, local field potential (LFP) signals from a region of interest (ROI), such as AHL, were rereferenced by subtracting a control signal obtained by averaging signals from regions outside the ROI (*e.g.*, AHR, PHL, PHR, ECL, ECR, AL, and AR) (see Figure 1A). The LFP signals were then subjected to a ripple band filter (80–140 Hz) to isolate SWR candidates (referred to as SWR+ candidates) (see Figure 1B). SWR detection utilized a previously published tool (https://github.com/Eden-Kramer-Lab/ripple\_detection; Kay et al., 2016), with specific modifications including an updated ripple band range of 80–140 Hz for humans (previously 150–250 Hz for rodents).

To establish control events for SWR+ candidates, SWR− candidates were defined by randomly shuffling the timestamps of SWR+ candidates across all trials from all subjects. The resulting SWR+/SWR− candidates were visually inspected (see Figure 1).

## ***2.4 Defining hippocampal SWRs from putative CA1 regions***

Putative CA1 regions were defined as follows. SWR+/SWR− candidates were embedded into a two-dimensional space based on their superimposed spike counts per unit using UMAP (uniform manifold approximation and projection; Mclnnes et al., 2018) in a supervised fashion (Figure 4A). The silhouette score (Rousseeuw et al., 1987), a validation barometer for clustering, was calculated from clustered samples (Table 2). The hippocampal regions with silhouette scores greater than 0.6 on average across sessions (75th percentile) (Figure 4B) were defined as putative CA1 regions (Table 3; *i.e.*, AHL of subject #1, AHR of subject #3, PHL of subject #4, AHL of subject #6, and AHR of subject #9). SWR+/SWR− candidates in putative CA1 regions were defined as SWR+/SWR− (no longer candidates). The duration and ripple band peak amplitude of detected SWRs were calculated (Figure 4C & E). SWR+/SWR− were visually inspected as shown in Figure 1.

## ***2.5 Statistical evaluation***

The Brunner–Munzel test and the Kruskal-Wallis test were executed using the scipy package in Python (Virtanen et al., 2020). A correlational analysis was undertaken through the determination of the rank of the observed correlation coefficient in the associated set-size-shuffled surrogate, using a custom Python script. Additionally, the bootstrap test was carried out by utilizing an internally developed Python script.

# **3 Results**

## ***3.1 iEEG recording and neural trajectory in MTL regions during a WM task***

We employed an open dataset (Boran et al., 2020) for this analysis. During a modified Sternberg task, LFP signals (Figure 1A) within the MTL regions (Table 1; for instance, left hippocampal head [AHL]) were recorded. SWR+ candidates were identified from LFP signals passed through the ripple band (Figure 1B) within the hippocampal regions (refer to methods), while SWR− candidates were designated at identical timestamps of the SWR+ candidates but across different trials (Figure 1). The multiunit spikes (Figure 1C) were established using a spike sorting algorithm (Niediek et al., 2016), and were provided as a component of the dataset. Using the 50-ms binned multiunit activity without overlaps, GPFA (Yu et al., 2009) determined the neural trajectory (or factors) of the MTL regions by session and region (Figure 1D). Each factor was z-normalized by session and region (for example, session #2 in AHL of subject #1). Subsequently, the Euclidean distance from the origin (O) was calculated (Figure 1E).

## ***3.2 Hippocampal neural trajectory correlated with a WM task***

In Figure 2A, the median neural trajectories of 50 trials are depicted as points within the three major factor space. The optimal embedding dimension for the GPFA model was determined to be three using the elbow method (Figure 2B). The trajectory distance from the origin (O) for the hippocampus was found to be significantly different compared to the EC and amygdala. Specifically, the hippocampus exhibited a larger distance than the EC and amygdala.[[1]](#footnote-1) Furthermore, the distance between geometric medians (e.g., d(gF, gE)) in trials showed that the hippocampus had a larger distance compared to both the EC and amygdala.[[2]](#footnote-2)

## ***3.3 Memory load-dependent neural trajectory distance between the encoding and retrieval states in the hippocampus***

In the hippocampus, there was a significant correlation between the set size (i.e., the number of alphabetical letters to encode) and the correct rate, response time, and trajectory distance between gE and gR (= d(gE, gR)) during the WM task.

Specifically, the correct rate of trials decreased as the set size increased from four to eight[[3]](#footnote-3) (Figure 3A). Similarly, the response time increased with the set size[[4]](#footnote-4) (Figure 3B). Set size and the log10 of the distance between geometric medians of the encoding and retrieval phases were found to be positively correlated[[5]](#footnote-5) (Figure 3C). However, no significant correlation was observed for the distances of other combinations of geometric medians (Figures 3D & S2).

## ***3.4 Detection of hippocampal SWR from putative CA1 regions***

We identified electrodes situated in putative CA1 regions of the hippocampus, based on the observation of distinct multiunit spike patterns during SWR events when compared to baseline periods. For each session and hippocampal region, SWR+/SWR− candidates were depicted in a two-dimensional space via UMAP[[6]](#footnote-6) (Figure 4A). We calculated the silhouette score as a measure of clustering quality for each session and MTL region (Figure 4B & Table 2). Sites with an average silhouette score across sessions exceeding 0.6 were designated as putative CA1 regions[[7]](#footnote-7) (Tables 2 & 3). Notably, the PHL of subject #4 was identified as a seizure onset zone, but the other four regions were not associated with this designation (Table 1).

Subsequently, SWR+/SWR− candidates within these putative CA1 regions were labeled as SWR+ and SWR−, respectively[[8]](#footnote-8) (Table 3). Both SWR+ and SWR− exhibited an identical duration[[9]](#footnote-9) (Figure 4C). A marked increase in SWR+ incidence was detected during the initial 400 ms from the probe time[[10]](#footnote-10) (Figure 4D). Additionally, the peak ripple band amplitude for SWR+ surpassed that of SWR− [[11]](#footnote-11) (Figure 4E).

## ***3.5 Transient neural trajectory change in the hippocampus during SWR***

The peri-SWR distance from the origin (O) was calculated in the encoding and retrieval phases (*i.e.*, eSWR+, eSWR−, rSWR+, and rSWR−) (Figure 5A). Based on the steep peak in the distance from O during SWR, we split SWR into the following three periods of events: pre SWR (= event at − 800 to – 300 ms from SWR center), mid SWR (= event at – 250 to + 250 ms from SWR center), and post SWR (= event at + 300 to + 800 ms from SWR center).

The trajectory distance from O was larger for mid eSWR+ (Match IN: 1.25 [1.30], median [IQR], *n* = 1,281; Mismatch OUT: 1.12 [1.35], median [IQR], *n* = 1,163) compared to pre eSWR+ (Match IN: 1.08 [1.07], median [IQR], *n* = 1,149; Mismatch OUT: 0.90 [1.12], median [IQR], *n* = 1,088) (Figure 5B). Similarly, the trajectory distance from O of mid rSWR+ (1.32 [1.24], median [IQR], *n* = 935, Match IN; 1.15 [1.26], median [IQR], *n* = 891, Mismatch OUT) was larger than that of pre rSWR+ (1.19 [0.96], median [IQR], *n* = 673, Match IN; 0.94 [0.88], median [IQR], *n* = 664, Mismatch OUT).

## ***3.6 Visualization of hippocampal neural trajectory during SWR in two-dimensional spaces*** Based on our earlier findings of neural trajectory changes during SWR (Figure 5), we now aim to visualize the trajectories around SWR events concerning the encoding and retrieval states, which were shown to depend on memory load (Figure 3).

In Figure 6, we present pre-, mid-, and post-SWR trajectories in two-dimensional spaces. To achieve this, we linearly aligned the peri-SWR trajectories, positioning gE at the origin (0, 0) and placing gR at (d(gE, gR), 0). We then rotated the trajectories around the x-axis (gEgR axis) for better visualization. Importantly, key distances and angles from the original three-dimensional spaces were preserved.

The scatter plot in these two-dimensional spaces reveals distinct distributions of peri-SWR trajectories based on phases and task types. For instance, we observe a longer distance between gE and mid eSWR+ compared to gE and pre eSWR−, consistent with our earlier findings (Figure 5B).

## ***3.7 Fluctuation of hippocampal neural trajectories between encoding and retrieval states***

Subsequently, we determined the trajectory "direction" in relation to the encoding and retrieval states. The "SWR direction" was defined by the trajectory positions at − 250 ms and + 250 ms around SWR events.

The cosine similarity between the eSWR+ and rSWR+ directions showed a bias towards + 1 during the Match IN task (Figure 7A), and a bias towards − 1 during the Mismatch OUT task (Figure 7B). These tendencies were also observed between the eSWR− and rSWR− directions (Figure 7C–F).

During the Match IN task, the cosine similarity between the rSWR+ direction and the gEgR direction showed a biphasic distribution (Figure 7A). However, during the Mismatch OUT task, it showed a monophasic distribution with a positive peak (Figure 7B). The cosine similarity between the rSWR− direction and the gEgR direction displayed a biphasic distribution in both tasks, but with a positive peak in the Match IN task (Figure 7C) and a negative peak in the Mismatch OUT task (Figure 7D). Compared to the rSWR− directions, the rSWR+ directions were more inclined towards the retrieval states (Figure 7E & F).

# **4 Discussion**

In this study, we hypothesized that hippocampal neurons express distinct representations as trajectories in low-dimensional spaces during a WM task, with a specific focus on the SWR periods. First, we embedded neural representations of the MTL regions in three-dimensional spaces (Figure 2A). The distances among trajectory geometric medians during phases were greater in the hippocampus than in the EC (entorhinal cortex) and amygdala (Figure 2E). Second, the distance between the encoding and retrieval phases (d(gE, gR)) was positively correlated with memory load (Figure 3C&D). The trajectory distance from O increased during SWR (Figure 5). Consistently, the peri-SWR trajectory exhibited a characteristic distribution in three-dimensional space (Figure 6). Finally, the hippocampal neural representation proceeded in different directions based on the encoding and retrieval phases, especially during SWR periods. In sum, these results suggest the involvement of hippocampal neurons and SWR in a WM task.

First, we found that the distance of the trajectory geometric medians during the four phases of the WM task was longer in the hippocampus than in the EC and amygdala, even after considering the distance from O in those regions (Figure 2C–E), indicating hippocampal participation in the WM task. These results are partly supported by previous findings of persistent firing rate increases in the maintenance phase in the hippocampus (Boran et al., 2019; Kamiński et al., 2017; Kornblith et al., 2017; Faraut et al., 2018). However, when we applied GPFA to our data, we found that the distance between the encoding and retrieval phase, d(gE, gR), was correlated with memory load (Figure 3). Overall, these results provide evidence that the hippocampus is linked to WM.

We limited our analysis to only putative CA1 regions where distinct spike unit patterns underlying SWRs were observed (Figure 4). This decision was based on the fact that SWR is time-locked to the synchronous spike bursts of interneurons and pyramidal neurons (Buzsáki, 1989; Quyen et al., 2008; Royer et al., 2012; Hajos et al., 2013), possibly ~50 μm from the recording electrode (Schomburg et al., 2012). In fact, in our analysis, the SWR incidence increased at 0–400 ms from the probe starting time (Figure 4D), which is consistent with previous reports that hippocampal SWR occurrence increases before spontaneous verbal recall (Norman et al., 2019; Norman et al., 2021). The log-normal distribution of SWR duration and ripple band peak amplitude (Figure 4C & E) further supports the validity of the detection of physiological SWRs in this study (Liu et al., 2022). Therefore, we would have precisely captured a subclass of SWRs. One limitation is that because of the selection of channels, the increase in trajectory distance from O during SWR (Figure 5) would be biased to be greater, although it is not a critical problem in this study. In short, we were able to verify the selection of putative CA1 channels and determined SWRs, as well as the calculation of trajectory by GPFA.

Interestingly, the trajectory direction during SWR was distributed differently according to the phases (= encoding and retrieval phases) and task types (= Match IN or Mismatch OUT task) of the WM task (Figure 6). For example, the directions of eSWR+ and rSWR+ were not similar in the Mismatch OUT task but in the Match IN task. This result is reasonable because all letters should be recalled in the Mismatch OUT task, while only a part of the letters was enough to be recalled in the Match IN task. Furthermore, in the Mismatch OUT task, the probe letter was not included in the letters in the encoding phase. Thus, it might be suggested that the role of SWR in the WM task was expressed as their directions in the low-dimensional spaces.

Last, the directions of the trajectory in the retrieval phase oscillated between the encoding and retrieval states (Figure 7C & D), and the balance of such fluctuation was shifted to the retrieval state during SWR (Figure 7 E & F). These results are reasonable from the engram cell theory (Liu et al., 2012) because both the Match IN and Mismatch OUT tasks required subjects to recall the letters in the encoded phase, but the probe letter first appeared during the retrieval phase in the Mismatch OUT task. In addition, again, these results are partially consistent with previous reports that suggest the role of SWR in memory recall (Norman et al., 2019; Norman et al., 2021). Therefore, our results provide a new aspect of the hippocampal representations during retrieval periods, the neural fluctuation between the encoding and retrieval phases, and suggest the role of SWR in the retrieval phase in WM tasks.

In conclusion, this study suggests the involvement of the hippocampus in a WM task. We showed that hippocampal neural representations fluctuated between the encoding and retrieval states in low-dimensional spaces during a WM task. Thus, our results provide an update to the two-stage model of memory formation (Marr, 1971; Buzsáki, 1989).

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**Contributors**

Y.W. and T.Y. conceptualized the study; Y.W. performed the data analysis; Y.W. and T.Y. wrote the original draft; and all authors reviewed the final manuscript.

**Acknowledgments**

This research was funded by a grant from the Exploratory Research for Advanced Technology (JPMJER1801).

**Declaration of interests**

The authors declare that they have no competing interests.

**Data and code availability**

The data is available on G-Node (<https://doi.gin.g-node.org/10.12751/g-node.d76994/>). The source code is available on GitHub (<https://github.com/yanagisawa-lab/hippocampal-neural-trajectory-fluctuations-during-a-WM-task>).

**Inclusion and diversity statement**

We support inclusive, diverse, and equitable conduct of research.

**Declaration of generative AI in scientific writing**  
The authors utilized ChatGPT by OpenAI to enhance the English language quality of this work, as the authors are not native English speakers. Following the use of ChatGPT, the authors meticulously reviewed and made necessary edits to the content. The authors assume full responsibility for the entirety of the publication's content.

# **Tables**

## **Table 1. Electrode positions of the dataset**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Hipp. head | | Hipp. Body | | EC | | Amy. | |  |  |
| Subject ID | # of  sessions | AHL | AHR | PHL | PHR | ECL | ECR | AL | AR |  | SOZ |
| #1 | 4 | o | x | o | o | o | x | o | x |  | AHR, LR |
| #2 | 7 | o | o | o | o | o | o | o | o |  | AHR, PHR |
| #3 | 3 | o | o | o | o | o | o | o | x |  | AHL, PHL |
| #4 | 2 | o | o | o | o | o | o | o | o |  | AHL, AHR, PHL, PHR |
| #5 | 3 | o | x | x | o | x | x | o | x |  | DRR |
| #6 | 6 | o | o | o | o | o | o | o | o |  | AHL, PHL, ECL, AL |
| #7 | 4 | o | o | o | o | o | o | o | o |  | AHR, PHR |
| #8 | 5 | o | o | o | o | o | o | o | o |  | ECR |
| #9 | 2 | o | o | o | o | o | o | o | o |  | ECR, AR |

The electrode positions and the seizure onset zones. Regions marked as “o” were available, but those marked as “x” (*Navy*) were not available in the dataset. Abbreviations: AHL, left hippocampal head; AHR, right hippocampal head; PHL, left hippocampal body; PHR, right hippocampal body; ECL, left entorhinal cortex; ECR, right entorhinal cortex; AL, left amygdala; AR, right amygdala, SOZ: seizure onset zone.

## **Table 2. The silhouette score of UMAP clustering between** SWR+ candidates and SWR− **candidates**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Hipp. head | | Hipp. body | |
| Subject | AHL | AHR | PHL | PHR |
| #1 | 0.60 ± 0.14 | n.a. | n.a. | 0.1 ± 0 |
| #2 | 0.21 ± 0.16 | 0.17 ± 0.21 | 0.18 ± 0.22 | 0.20 ± 0.15 |
| #3 | 0.40 ± 0.42 | 0.83 ± 0.12 | n.a. | n.a. |
| #4 | 0.10 ± 0.00 | 0.10 ± 0.00 | 0.90 ± 0.00 | 0.10 ± 0.14 |
| #5 | n.a. | n.a. | n.a. | n.a. |
| #6 | 0.63 ± 0.06 | n.a. | n.a. | 0.27 ± 0.06 |
| #7 | 0.10 ± 0.00 | 0.35 ± 0.35 | 0.37 ± 0.47 | 0.10 ± 0.00 |
| #8 | 0.13 ± 0.10 | n.a. | 0.28 ± 0.49 | n.a. |
| #9 | n.a. | 0.85 ± 0.07 | 0.15 ± 0.07 | n.a. |

The silhouette scores (mean ± SD for sessions by subject) of UMAP clustering on SWR+ candidates and SWR− candidates (Figure 4A) were based on their underlying multiunit spike patterns (mean values were 0.205 [0.285], median [IQR]; Figure 4B).

## **Table 3. The number of defined SWR events**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Subject ID | # of sessions | # of trials | ROI | # of SWRs | SWR incidence [Hz] |
| #1 | 2 | 100 | AHL | 274 | 0.34 |
| #3 | 2 | 97 | AHR | 325 | 0.42 |
| #4 | 2 | 99 | PHL | 202 | 0.26 |
| #6 | 2 | 100 | AHL | 297 | 0.37 |
| #9 | 2 | 97 | AHR | 72 | 0.09 |
|  | Total = 10 | Total = 493 |  | Total = 1,170 | 0.30 ± 0.13 (mean ± SD) |
|  |  |

The table summarizes the statistics of putative CA1 regions and SWRs. Only the first two sessions (sessions #1 and #2) from each subject were utilized to reduce the sampling bias.

# **Figures**

****

## **Figure 1. Examination of hippocampal local field potential (LFP) and neural trajectories during a working memory task**

***A.*** Wideband LFP Trace: Displaying the intracranial encephalogram (iEEG) data for subject #6, session #2, trial #5, located in the left hippocampal head. This trace showcases the varying phases of the modified Sternberg working memory task, including fixation (*gray*, 1 s), encoding (*blue*, 2 s), maintenance (*green*, 3 s), and retrieval (*red*, 2 s). ***B.*** Ripple Band LFP: This presents the LFP trace in the ripple frequency band from the same trial and session. ***C.*** Multiunit Spike Raster: A plot illustrating multiunit spikes recorded during the mentioned trial. ***D.*** Neural Trajectory Factors: Depicting the first three factors of the hippocampal trajectory for the trial, determined by Gaussian-process factor analysis on spike counts with 50-ms bins. The *dot circles* signify the geometric median coordinates for each of the four task phases. ***E.*** Trajectory Distance Analysis: Shows the distance of the initial three trajectory factors from the origin (O). Highlighted rectangles overlaying the figure indicate the timings for SWR+ candidates (in purple) and SWR− candidates (in *yellow*).



## **Figure 2. State-dependent hippocampal neural trajectory**

***A.*** Neural Trajectory Visualization: This three-dimensional plot represents the neural trajectory of the left hippocampus derived from the Gaussian-process factor analysis (GPFA). Smaller points indicate coordinates of 50-ms neural trajectory bins within a session (median of 50 trials). Larger points with *black* edges represent geometric medians for each phase of the Sternberg working memory task, distinguished by colors for fixation (*gray*), encoding (*blue*), maintenance (*green*), and retrieval (*red*). ***B.*** GPFA Model Log-likelihoods: The graph showcases the log-likelihood predictions of GPFA models concerning the number of dimensions. Notably, the optimal dimension was identified as three using the elbow method. ***C.*** Distance Analysis from Origin: The plot represents the trajectory distance from the origin (O) for the hippocampus (Hipp.), entorhinal cortex (EC), and amygdala (Amy.), plotted against the time since probe onset. ***D.*** Trajectory Distance in Medial Temporal Regions: The box plots display the trajectory distances from O for each region, with the hippocampus showing the greatest distance, followed by the EC and the Amygdala. ***E.*** Inter-phase Trajectory Distances: This visualizes the distance variations between trial trajectory geometric medians of task phases. The distances in the hippocampus were observed to be more pronounced compared to the EC or Amygdala.

## **Figure 3. Influence of memory load on encoding and retrieval states in the hippocampus**

***A.*** Relationship between set size (number of letters encoded) and correct rate in the WM task. Notably, a negative correlation was observed (coefficient = − 0.20, \*\*\**p* < 0.001), analyzed using set-size-shuffled surrogate. Significance was determined using the Kruskal–Wallis test, followed by the Brunner–Munzel test with Bonferroni correction. ***B.*** Association between set size and response time post-probe initiation. A positive correlation was detected (coefficient = 0.23, \*\*\**p* < 0.001), analyzed using set-size-shuffled surrogate. Statistical tests included the Kruskal–Wallis and post hoc Brunner–Munzel tests with Bonferroni correction. ***C.*** Analysis of set size against the distance between geometric medians during encoding and retrieval phases (represented as d(gE, gR)). A correlation of 0.05 was noted for set size and log10(d(gE, gR)), analyzed using set-size-shuffled surrogate. ***D.*** Experimentally observed correlations between set size and various parameters are illustrated by red dots. The gray violin plots contrast these findings with set-size-shuffled surrogate data (*n* = 1,000), emphasizing the significant observed correlation coefficients (\*\*\**p* < 0.001). Abbreviations: gF, gE, gM, gR represent the geometric median of trajectories during fixation, encoding, maintenance, and retrieval phases, respectively.

## **Figure 4. SWR detection in putative CA1 regions**

***A.*** Two-dimensional UMAP (uniform manifold approximation and projection; Mclnnes et al., 2018) representation of unit activities during SWR+ candidates (*purple*; potential SWR events) and SWR− candidates (*yellow*; controls for SWR+ candidates). ***B.*** Cumulative density plot illustrating silhouette scores for different hippocampal regions (refer to Table 2). Regions with silhouette scores exceeding 0.60 (75th percentile) are considered as putative CA1 regions. Within these regions, SWR+ and SWR− candidates are identified and categorized as SWR+ (*n* = 1,170) and SWR− (*n* = 1,170), respectively. ***C.*** Overlapping duration distributions [ms] for SWR+ (*purple*; 93.0 [65.4], median [IQR]) and SWR− (*yellow*; 93.0 [65.4], median [IQR]). The identical overlap results from their definition criteria. ***D.*** Depiction of ripple incidence [Hz] for both SWR+ (*purple*) and SWR− (*yellow*) relative to time from the probe, represented as mean ± 95% confidence interval. However, the 95% confidence interval might not be readily discernible due to its narrow range. Note the significant elevation in SWR incidence between 0–400 ms post-probe, surpassing the 95th percentile of bootstrap samples (0.421 [Hz], \**p* < 0.05). ***E.*** Histogram showcasing ripple band peak amplitude distributions [SD of baseline] for SWR− (*yellow*; 2.37 [0.33], median [IQR]) versus SWR+ (*purple*; 3.05 [0.85], median [IQR]). A notable difference is present between the two, confirmed with \*\*\**p* < 0.001 using the Brunner–Munzel test.

## **Figure 5. Transient neural trajectory change during SWR**

***A.*** Distance from the origin (O) of the peri-sharp-wave-ripple (peri-SWR) trajectory was calculated and presented as the mean ± 95% confidence interval. Note: The interval may not be easily visible due to the narrow range. SWR+ represents a putative SWR event, while SWR− serves as a control event for SWR+. Based on the panels shown in ***A***, SWR events were classified into three parts: pre SWR (from − 800 to − 250 ms relative to the center of the SWR event), mid (from − 250 to + 250 ms relative to the center), or post (+ 250 to + 800 ms relative to the center). ***B.*** The distance from the origin during the mid SWR+ period was found to be longer compared to the corresponding pre SWR+ period (\**p* < 0.05, \*\**p* < 0.01, \*\*\**p* < 0.001; Brunner–Munzel test). Abbreviations used in this study include eSWR for sharp-wave-ripple events during the encoding phase and rSWR for those during the retrieval phase.



## **Figure 6. Coordinates of neural trajectory during sharp-wave ripple (SWR) aligned by encoding and retrieval states.**

Panels ***A*** and ***B*** depict neural trajectories during distinct SWR event segments: pre-SWR (− 800 to − 250 ms, shown in gray), mid-SWR (− 250 to + 250 ms, highlighted in *yellow* or *purple*), and post-SWR (+ 250 to + 800 ms, represented in *black*). Trajectories are arranged from left to right, capturing events of eSWR and rSWR in the Match IN task, followed by eSWR and rSWR in the Mismatch OUT task. All data points underwent adjustments and rotations to fit a two-dimensional representation, positioning gE at (0, 0) and gR at (d(gE, gR), 0). The d(gE, gR) metric varies across sessions, and its median ± IQR (with medians near 0.2) is presented on the x-axes. Note: Some intervals might be challenging to discern because of their narrow range. In this two-dimensional depiction, both the distances and angles preserve their relationships as in the original three-dimensional space. Abbreviations include eSWR and rSWR for SWR events during the encoding and retrieval phases, respectively, while the set size indicates the number of letters used during encoding.



## **Figure 7. Analysis of Neural Trajectory Directions during SWR, Encoding, and Retrieval States. *A–D.*** Panels show Kernel Density Estimation (KDE) distributions of cosine similarities for trajectory directions: (i) eSWR & rSWR (*circles*), (ii) eSWR & gEgR (*triangles*), and (iii) rSWR & gEgR (*squares*). Panels ***A*** and ***B*** depict SWR+ conditions for Match IN and Mismatch OUT tasks, respectively, while C and D illustrate the SWR− conditions. ***E–F.*** These panels present the difference in KDE values derived from the above panels, with ***E*** representing ***A*** minus ***C*** and ***F*** indicating ***B*** minus ***D***. Note the pronounced cosine similarity between eSWR and rSWR in the Match IN task (*pink circles* in ***A***) and its inversion in the Mismatch OUT task (*pink circles* in ***B***). The biphasic cosine similarity distribution between the baseline (rSWR−) and gEgR (*red triangles* in ***C*** and ***D***) shifts during the retrieval state in SWR periods (*red triangles* in ***E*** and ***F***).

1. Hippocampus: Distance = 1.11 [1.01], median [IQR], *n* = 195,681 timepoints; EC: Distance = 0.94 [1.10], median [IQR], *n* = 133,761 timepoints; Amygdala: Distance = 0.78 [0.88], median [IQR], *n* = 165,281 timepoints (refer to Figure C & D).  
    [↑](#footnote-ref-1)
2. Hippocampus: Distance = 0.60 [0.70], median [IQR], *n* = 8,772 combinations; EC: Distance = 0.28 [0.52], median [IQR], *n* = 5,017 combinations (*p* < 0.01; Brunner–Munzel test); Amygdala: Distance = 0.24 [0.42], median [IQR], *n* = 7,466 combinations (*p* < 0.01; Brunner–Munzel test). [↑](#footnote-ref-2)
3. Correct rate: set size four (0.99 ± 0.11, mean ± SD; *n* = 333 trials) vs. set size six (0.93 ± 0.26; *n* = 278 trials; *p* < 0.001, Brunner–Munzel test with Bonferroni correction) and set size eight (0.87 ± 0.34; *n* = 275 trials; *p* < 0.05; Brunner–Munzel test with Bonferroni correction). Overall, *p* < 0.001 for the Kruskal–Wallis test; correlation coefficient = − 0.20, *p* < 0.001. [↑](#footnote-ref-3)
4. Response time: set size four (1.26 ± 0.45 s; *n* = 333 trials) vs. set size six (1.53 ± 0.91 s; *n* = 278 trials) and set size eight (1.66 ± 0.80 s; *n* = 275 trials). All comparisons *p* < 0.001, Brunner–Munzel test with Bonferroni correction; *p* < 0.001 for the Kruskal–Wallis test; correlation coefficient = 0.22, *p* < 0.001. [↑](#footnote-ref-4)
5. Correlation between set size and log10(d(gE, gR)): correlation coefficient = 0.05, *p* < 0.001. Specific values: d(gE, gR) = 0.54 [0.70] for set size four trials, *n* = 447; d(gE, gR) = 0.58 [0.66] for set size six trials, *n* = 381; d(gE, gR) = 0.61 [0.63] for set size eight trials, *n* = 395. [↑](#footnote-ref-5)
6. For illustrative purposes, consider the AHL in session #1 of subject #1. [↑](#footnote-ref-6)
7. The identified regions were: AHL of subject #1, AHR of subject #3, PHL of subject #4, AHL of subject #6, and AHR of subject #9. [↑](#footnote-ref-7)
8. Definitions lead to equal counts for both categories: SWR+ (*n* = 1,170) and SWR− (*n* = 1,170). [↑](#footnote-ref-8)
9. Definitions lead to equal duration for both categories: SWR+ (93.0 [65.4] ms) and SWR− (93.0 [65.4] ms). [↑](#footnote-ref-9)
10. Detailing the surge: SWR+ increased against the bootstrap sample; 95th percentile = 0.42 [Hz]; *p* < 0.05. [↑](#footnote-ref-10)
11. Amplitude differentiation: SWR+ (3.05 [0.85] SD of baseline, median [IQR]; *n* = 1,170) vs. SWR− (2.37 [0.33] SD of baseline, median [IQR]; *n* = 1,170; *p* < 0.001; Brunner–Munzel test). [↑](#footnote-ref-11)