**Memory-load-dependent, directional hippocampal representation during sharp-wave ripple in a working memory task in humans**

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# **Abstract**

# **Background: Working memory (WM) is essential for everyday life, yet its neural basis remains unclear. Although the hippocampus plays a critical role in memory consolidation and retrieval, its involvement in WM tasks is controversial. We hypothesized that the hippocampus exhibits distinct representations during a WM task.**

# **Methods: We administered an eight-second Sternberg test, which required nine patients with epilepsy to memorize sets of four, six, or eight letters. Simultaneously, we recorded intracranial electroencephalogram data in the medial temporal lobe (MTL), including the hippocampus, entorhinal cortex, and amygdala, during the task. We used Gaussian-process factor analysis to determine the trajectories of MTL regions based on their multi-unit activity. Hippocampal channels were validated by identifying sharp-wave ripple complexes (SWRs) with distinct unit spike patterns.**

# **Findings: The trajectory during the Sternberg task was the largest in the hippocampus among the MTL regions. The distance between the encoding and retrieval phases increased with the memory load in the trajectory. The trajectory speed of the hippocampus increased at − 250 to 250 ms of SWR in the encoding, maintenance, and retrieval phases, but not in the fixation phase. The trajectory length during SWR in the encoding and maintenance phases depended on the memory load.**

**Interpretation: Our results suggest that the hippocampus participates in WM tasks, particularly during SWRs in the encoding and maintenance phases, depending on memory load. The SWR during the encoding phase may be associated with memory acquisition.**

# 5 tables; 5 figures; 3,217 words

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

# **1 Introduction**

Working memory (WM) is crucial in everyday life; however, its neural basis is not fully understood, and the role of the hippocampus in WM tasks has been controversial. This may be due to the fact that the famous patient H.M., who had his hippocampus removed, did not show WM impairments (Scoville & Milner, 1957) and could retain numbers for over 15 minutes by continuous rehearsal (Squire, 2009). However, recent studies have shown that during the maintenance period of WM tasks, 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) are observed in the hippocampus. Moreover, WM performance depends on local field potential (LFP) power fluctuations phase-locked to delta oscillations in the hippocampus (Leszczyński et al., 2015). These findings suggest that the hippocampus may be involved in other phases of WM tasks besides the maintenance phase.

Among the hippocampal phenomena, a transient and synchronous oscillation, called sharp-wave ripple (SWR; Buzsáki, 2015), is associated with various cognitive functions. For example, following the two-stage model of memory formation (Marr, 1971; Buzsáki, 1989), SWR in the hippocampus and slow-wave oscillations in the primary motor cortex were coupled in post-training sleep for the first week in mice (Kim et al., 2022). Moreover, SWR contains memory replay (Wilson and McNaughton, 1994; Nádasdy et al., 1999; Lee and Wilson, 2002; Diba, K., & Buzsáki, G, 2007; Davidson et al., 2009), is involved in memory consolidation (Girardeau et al., 20009; Ego-Stengel et al., 2010; Fernández-Ruiz et al., 2019), and correlated with memory recall (Wu et al., 2017; Norman et al., 2019; Norman et al., 2021). Thus, SWR might be a fundamental observation reflecting the information processing of the hippocampus, although their role in memory acquisition is not fully understood (Jadhav et al., 2012; Fernández-Ruiz et al., 2019).

The hippocampal neurons may exhibit low dimensional representations during WM tasks. For example, 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) were embedded into a dynamic, non-linear 3D hyperbolic geometry during rats navigating environments (Zhang et al., 2022). Also, grid cells in the entorhinal cortex (EC), the main gate of the hippocampus (Naber et al., 2001; van Strien et al., 2009; Strange et al., 2014), showed toroidal topology during rats exploring a square space (Gardner et al., 2022). Thus, as well as navigation tasks, the hippocampus may show low-dimensional latent spaces for WM tasks.

One of the difficulties in studying hippocampal function in WM is the lack of appropriate experiments. In non-human animals, on the one hand, WM tasks are trained through multiple trials, often using mazes or classical conditioning methods; but these designs do not dissect when animals acquire and recall information. In humans, on the other hand, noninvasive recording methods such as fMRI (functional magnetic resonance imaging), EEG (electroencephalogram), and MEG (magnetoencephalogram), suffer limited resolutions in time and space, while invasive recordings for deep brain regions, such as intracranial EEG (iEEG) recording, ceils the number of experiments and pose challenges in histological verification of recording sites.

In this study, we hypothesized that the hippocampal neurons express distinct representations during a WM task, and SWRs are time-locked to representational changes in certain directions. To prove these hypotheses, we utilized a dataset in which patients conducted a WM task with high temporal resolutions (1 s for fixation, 2 s for encoding, 3 s for maintenance, and 2 s for retrieval) while their iEEG data were recorded with tetrodes in the medial temporal lobe (MTL). Based on the multi-unit activity, we observed the low-dimensional trajectory in the MTL calculated by Gaussian-process factor analysis (GPFA; Yu et al., 2009), especially during SWRs with distinct unit spike patterns.

# **2 Methods**

## ***2.1 Dataset***

A public dataset was employed, in which nine subjects performed a modified Sternberg task that consisted of the 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 letters in the encoding phase and were expected to recall whether a probe letter in the retrieval phase was also displayed (Match IN) or was not (Mismatch OUT) in the previous encoding phase. iEEG signals were recorded at 32 kHz (0.5–5,000 Hz passband) during the modified Sternberg task with depth electrodes in the medial temporal (MTL) regions (*i.e.*, left and right hippocampal head [AHL and AHR], hippocampal body [PHL and PHR], EC [ECL and ECR], and amygdala [AL and AR]; Figure 1A & Table 1). iEEG signals were resampled at 2 kHz. Among experimental variables, correlations were found (Fig. S1). The timings of unit 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 1B).

## ***2.2 Defining hippocampal SWRs from SWR-detectable regions***

The hippocampal SWRs were detected based on a consensus made by researchers in this field (Liu et al., 2022) as follows. LFP signals of iEEG recording at a region of interest (ROI; *e.g.*, AHL) were re-referenced by subtracting a control signal, which was calculated by averaging out-of-ROI signals (*e.g.*, AHR, PHL, PHR, ECL, ECR, AL, and AR; Figure 1A). SWR candidates were defined from the ripple-band passed, re-referenced LFP signals using a published tool (<https://github.com/Eden-Kramer-Lab/ripple_detection>; Kay et al., 2016; Figure 1B) with modifications such as ripple band range from 150–250 to 80–140 Hz. SWR candidates of hippocampal ROIs (*i.e.*, AHL, AHR, PHL, PHR). For every SWR+ candidate of all trials across subjects, a SWR− candidate was defined in a randomly chosen trial at the same timestamp (Figure 1). SWR+ candidates and SWR− candidates were also visually inspected (Figure 4A–C).

## ***2.3 Neural trajectory calculation by Gaussian-process factor analysis***

For each session, the GPFA (Yu et al., 2009) determined neural trajectories of the hippocampus, EC, and amygdala of each trial (~ 50 trials per session) based on multi-unit activities using the Python elephant package (<https://elephant.readthedocs.io/en/latest/reference/gpfa.html>). The hyperparameter, bin size, was set as 50 ms.

The optimal dimension for GPFA was determined as follows. First, the log-likelihood of a GPFA model with a dimension (from one to six) was evaluated by the three-fold cross-validation (CV) method. The log-likelihood values were pooled by a MTL region (*e.g.*, the hippocampus) and were line-plotted (Figure 2A). The elbow method determined the optimal dimension as three.

Each of factor #1, factor #2, and factor #3 was z-normalized by session. From every trial trajectory at a region (*e.g.*, AHL; Figure 2B), (i) “trial geometric medians” for phases (*i.e.*, gtF for fixation; gtE for encoding; gtM for maintenance; and gtR for retrieval phase) were calculated by taking medians of coordinates at the central 500-ms window of the phase (*e.g.*, gtF was the median coordinate of 250–750 ms of a trial; Figure 2C). Similarly, geometric phases for trial subsets were determined by taking medians of the corresponding coordinates: (ii) “session geometric medians” for phases (*e.g.*, gsF for fixation), (iii) “set size geometric medians” for phases (*e.g.*, gkF for fixation; where is set size). Distances (Euclidian distance) between geometric medians were calculated (Figure 2D & 3A).

## ***2.4 Defining hippocampal SWRs from SWR-detectable regions***

SWR-detectable regions were defined as follows. Based on the superimposed spike counts per unit, SWR+ candidates and SWR− candidates were embedded into a two-dimensional space 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 more than 0.6 silhouette score on average across sessions (75 percentile) (Figure 4B) were defined as SWR-detectable regions: AHL of subject #1, AHR of subject #3, PHL of subject #4, AHL of subject #6, and AHR of subject #9 (Table 3). SWR+ candidates and SWR− candidates in SWR-detectable regions were defined as SWR+ and SWR−, respectively. The duration [ms] and ripple band peak amplitude [SD of baseline] of detected SWRs were calculated (Figure 4F). SWR+ and SWR− were also visually inspected.

## ***2.5 Peri-SWR speed and length***

From peri-SWR (SWR− or SWR+) absolute trajectory (Figure 5A), peri-SWR (SWR− or SWR+) absolute trajectory speeds were calculated from two consecutive 50-ms bins during – 500–500 ms of SWR central time (Figure 5B). Peri-SWR (SWR− or SWR+) trajectory lengths were determined by cumulating Peri-SWR absolute speeds during – 250–250 ms of SWR central time (Figure 5D, E).

## ***2.6 Statistical evaluation***

The Brunner–Munzel test and the Kruskal–Wallis test were conducted by the Python package scipy (Virtanen et al., 2020). Memory-load dependency was identified when the parameters and the task dificulty yielded significant correlation coefficient (α = 0.05) compaired to task-difficulty-shuffled surrogate created by an in-house Python script. Bootstrap test was also conducted by an in-house Python script.

## ***2.7 Code availability***

The source code is available at <https://github.com/yanagisawa-lab/iEEG_trajectory_with_SWR>.

# **3 Results**

## ***3.1 iEEG recording in the MTL regions during a WM task***

LFP signals in the MTL regions (*i.e.*, left and right hippocampal head [AHL and AHR], hippocampal body [PHL and PHR], EC [ECL and ECR], and amygdala [AL and AR]; Table 1) were recorded during a modified Sternburg task (Figure 1A). In the hippocampal regions, from the ripple-band passed LFP signals (Figure 1B), SWR+ candidates were determined (Figure 1). SWR− candidates were defined at the same timestamps of SWR+ but in different trials (Figure 1). Multiunit spikes were identified using a spike sorting algorithm (Niediek et al., 2016) during the modified Sternburg task (Figure 1C). Based on 50-ms bins of the multiunit activity without overlaps, GPFA (Yu et al., 2009) computed the neural trajectory (factors) of the MTL regions by session and region (Figure 1D). Each factor was z-normalized by session and region (*e.g.*, session #2 in AHL).

## ***3.2 Neural trajectory calculated by GPFA of the MTL regions during a working memory task***

Regarding the neural trajectory of the MTL regions (Figure 2A), the optimal dimension for GPFA models to embed was estimated as three with the elbow method (Figure 2B). The distances between all combinations of session geometric medians (Table 2; *e.g.*, d(gsF, gsE); Figure 2C) were pooled and longer in the hippocampus (*n* = 7,338; 1.10 [1.21]; median [IQR]) than in the EC (*n* = 5,016; 0.55 [0.99]; *p* < 0.01; Brunner–Munzel test) or amygdala (*n* = 6,198; 0.50 [0.94]; *p* < 0.01; Brunner–Munzel test) (Figure 2D).

## ***3.3 Neural trajectory distances among phases in the hippocampus during a working memory task***

The geometric medians for a set size and a task type (Match IN or Mismatch OUT) were determined as show in Table 2 (*e.g.*, gkEm, where k is set size 4, 6, or 8 and m is Match “IN” or Mismatch “OUT”). Regarding task difficulty (Table 3), the Kruskal–Wallis test identified differences among d(gkEm, gkRm) (Figure 3A; *p* < 0.05 but not among d(gkFm, gkEm), *p* = 0.17; d(gkFm, gkMm), *p* = 0.87; d(gkFm, gkRm), *p* = 0.52; d(gkEm, gkMm), *p* = 0.30; nor d(gkMm, gkRm), *p* = 0.89. However, the post–hoc test using Brunner–Munzel test and Bonferroni correction did not find significant differences among d(gkEm, gkRm) (*e.g.*, corrected *p* = 0.07; effect size 0.057; g4FIN [0.970 [1.04]] vs. g8FOUT [1.23 [1.38]]; [median [IQR]]).

The correlation coefficient between task difficulty (Table 3) d(gkEm, gkRm) (0.09) was significantly greater than that between d(gkEm, gkRm) and task-difficulty-shuffled surrogate (*n* = 1000, 0.00 [0.04]; median [IQR]; *p* < 0.001; Figure 3B). Correct rate and response time (Figure 3C) were negatively and positively correlated with task difficulty (Figure 3D; *p*s < 0.001; vs. task-difficulty-shuffled surrogate).

## ***3.4 Detection of hippocampal SWR from SWR-detectable regions***

Because hippocampal SWR is observed mainly in the CA1 region of the hippocampus (Buzsáki, 2015; Schomburg et al., 2012; Sullivan et al., 2011), we verified electrode positions where SWR events with distinct unit spike patterns were recorded.

From each session, SWR− candidates and SWR+ candidates were embeded to a two-dimensional space (Figure 4A) using UMAP (uniform manifold approximation and projection; Mclnnes et al., 2018). The silhouette score, a clustering barometer, was determined by every session (Figure 4B). Setting a threshold of the silhouette score as 0.6 (75 percentile), the following five regions were identified as SWR-detectable regions: AHL of subject #1, AHR of subject #3, PHL of subject #4, AHL of subject #6, and AHR of subject #9 (Table 4). One of the SWR-detectable regions (PHL of subject #4) was a seizure onset zone but the other four were not (Table 1). SWR+ candidate and SWR− candidate in SWR-detectable regions were defined as SWR+ (*n* = 1,170) and SWR− (*n* = 1,170), respectively (Figure 4 & Table 5).

SWR+ incidence increased during 0–350 ms from the probe time (vs. booststrap samples; *p* < 0.05; Figure 4C). Log10(duration [ms]) of both SWR+ and SWR− were 1.98 ± 0.22 (mean ± SD; Figure 4D). Log10(peak ripple band amplitude [SD of baseline]) of SWR+ was 0.50 ± 0.12 (mean ± SD; *n* = 1,170) and that of SWR− was 0.38 ± 0.05 (mean ± SD; *n* = 1,170) (*p* < 0.001; Brunner–Munzel test; Figure 4E).

## ***3.5 Transient neural trajectory change during SWR***

SWR− (SWR+) in the fixation, encoding, maintenance, and retrieval phases were labeled as fSWR− (fSWR+), eSWR− (eSWR+), mSWR− (mSWR+), and rSWR− (rSWR+), respectively.

From peri-SWR trajectory (Figure 5A), peri-SWR trajectory speed (Figure 5B) was calculated and showed a transient increase in the encoding (*p* < 0.001; Brunner–Munzel test; *n*s = 234; eSWR−, 0.91 ± 1.15; eSWR+, 1.26 ± 1.71; mean ± SD), maintenance (*p* < 0.001; Brunner–Munzel test; *n*s = 410; mSWR−, 0.99 ± 1.37; mSWR+, 1.26 ± 1.66; mean ± SD), and retrieval phases (*p* < 0.001; Brunner–Munzel test; *n*s = 166; rSWR−, 0.97 ± 1.25; rSWR+, 1.20 ± 1.48; mean ± SD) but in the fixation phase (*p* = 0.35; Brunner–Munzel test; *n*s = 118; fSWR−, 1.05 ± 1.50; fSWR+, 1.07 ± 1.47; mean ± SD) (Figure 5C).

The correlation coefficients between set size and peri-SWR (− 250–250 ms of SWR) trajectory length in the corresponding direction of geometric phases for set size four and eight were as follows: 0.05, fSWR−; − 0.01, fSWR+; 0.05, eSWR−; 0.08, eSWR+, \*\**p* < 0.01 vs. set-size-shuffled surrogate; − 0.02, mSWR−; 0.07, mSWR+, \*\**p* < 0.01 vs. set-size-shuffled surrogate; 0.04, rSWR−; 0.02, rSWR+ (Figure 5D & E).

# **4 Discussion**

In this study, we observed neural trajectory in the MTL regions, especially the hippocampus, during a working memory task in humans. First, the distances among geometric medians for phases were longer in the hippocampus than the EC and amygdala. Second, the distance between the encoding and retrieval phases depended on memory-load (set size and task type). Third, transient increase in trajectory speed was identified during SWR in the encoding, maintenance, and retrieval phases but not in the fixation phase. Last, the trajectory length during SWR in the encoding and maintenance phases was memory-load dependent and biased by directions.

To begin with, the distances of the geometric medians for the four phases (*i.e.*, fixation, encoding, maintenance, and retrieval phases) were longer in the hippocampus than in the EC and amygdala. The distance among phases was a barometer of how much the neurons (units) correlated with phases in the WM task, because the mean and variance of any trajectory were zero and one through z-normalization by a session and ROI (*e.g.*, session #2 in AHL). Thus, the hippocampal representations were most related in the MTL regions for phases in the WM task. This result is partly consistent with the firing rate increase in the maintenance phase (Boran et al., 2019; Kamiński et al., 2017; Kornblith et al., 2017; Faraut et al., 2018). However, being applied GPFA, our data showed compatitive distances among the four phases (Figure 3A), demonstrating characteristic states of the hippocampus not only in the maintenance phase but also in the other phases.

Next, the distance between encoding and retrieval was memory-load dependent, implying it as a cognitive biomarker in the hippocampus. We first doubted this result as an artifact originating from the persistent firing in the maintenance phase because GPFA links representations smoothly in the time dimension (Yu et al., 2009). However, distance between encoding and retrieval was not only dependent on the set size (the number of letters to encode) but also on task type (Match-IN or Mismatch-OUT; Figure 3A & B). Because Match-IN and Mismatch-OUT trials did not disect the first three phases (*i.e.*, fixation, encoding, and maintenance phases), our result is not fully explained by the persistent firing in the maintenance phase and the feature of GPFA model. Interestingly, the representations in the encoding and the retrieval phases were closer in Match-IN tasks than in Mismatch-OUT tasks. This is reasonable because the same letter was presented twice in Match-IN trials, probably due to the activations of engram cells (Liu et al., 2012).

To test the involvement of SWR, we first determined SWR-detectable regions, in other words, hippocampal regions where SWRs with their underlying, distinct firing patterns were observed. This strategy would enhance the true positive rate of detecting physiological SWRs (Liu et al., 2022). Consequently, the SWR incidence increased at 0–350 ms from the probe, which is consistent with previous studies showing that hippocampal SWR increased by 1–2 s before spontaneous verbal recall (Norman et al., 2019; Norman et al., 2021), although our data were acquired in a stimulus-triggered condition. Also, the duration and ripple band peak amplitude profile of detected SWR neally followed log-normal distribution (Figure 4D & E), verifying the defined SWRs as physiological SWRs.

Transient trajectory change was observed during SWRs in the encoding, maintenance, and retrieval phases but not in the fixation phase (Figure 5A–C ). Previous studies have reported that SWRs are time-locked to synchronous spikes of interneurons and pyramidal neurons (Quyen et al., 2008; Royer et al., 2012; Hajos et al., 2013) probably around ~50 μm of the recording electrode (Schomburg et al., 2012). Thus, transient trajectory changes during SWRs were not surprising. However, during the fixation phase, such a transient change was not identified, possibly due to the low intensity of the memory load. This finding was first revealed by using this high-temporal resolution dataset. SWR would be a cognitive biomarker (Buzsáki, 2015) for the WM task as well.

Last, directed and memory-load dependent trajectory change was observed during SWR in the encoding and maintenance phases (Figure 5D & E).

SWR in the encoding correlated with the direction between the 4-set-size- and 8-set-size encoding states in a memory-load dependent manner (g4E and g8E; Figure 5D & E). This result implies the functional role of SWR in memory acquisition, updating the two-stage model of memory formation (Marr, 1971; Buzsáki, 1989). In fact, a peak increase in SWR incidence was observed during the encoding phase as well as the retrieval phase (Figure 4C). These findings are intrieging from the viewpoint of memory re-consolidation theory (Nader, 2003) because SWR is linked to the plasticity of the hippocampal network (Behrens et al., 2005; Norimoto et al., 2018). Finally, SWR in the maintenance phase also memory-load dependently correlated to the direction between the 4-set-size- and 8-set-size maintenance states (g4M and g8M; Figure 5D & E). This implies the function of SWR in maintenance in addition to persistent firing.

In conclusion, our findings imply the role of the human hippocampus in encoding, especially during SWR. Encoding-SWR-specific disruption experiments are expected to clarify the causality.

**Contributors**

Y.W. 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.

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**Declaration of interests**

The authors declare that they have no competing interests.

**Data sharing**

The source code is available at https://github.com/yanagisawa-lab/ripples\_in\_encoding.

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# **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 table shows the electrode positions and the seizure onset zones. Regions marked as “o” were available but those 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: seazure onset zone.

## **Table 2. Definition of geometric medians**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  |  |  | |  | |  |  |  | |  | |  |  |  |  |  |
| Label of  geometric median | | Trials | | | Set size | | Task type | | | | Phase | |
|  | gtF | each trial | | | 4, 6, or 8 | | Match IN or Mismatch OUT | | | | Fixation | |
|  | gsF | the corresponding trials | | | 4, 6, and 8 | | Match IN and Mismatch OUT | | | | Fixation | |
|  | g4F | the corresponding trials | | | 4 | | Match IN and Mismatch OUT | | | | Fixation | |
|  | g6F | the corresponding trials | | | 6 | | Match IN and Mismatch OUT | | | | Fixation | |
|  | g8F | the corresponding trials | | | 8 | | Match IN and Mismatch OUT | | | | Fixation | |
|  | g4FIN | the corresponding trials | | | 4 | | Match IN | | | | Fixation | |
|  | g6FIN | the corresponding trials | | | 6 | | Match IN | | | | Fixation | |
|  | g8FIN | the corresponding trials | | | 8 | | Match IN | | | | Fixation | |
|  | g4FOUT | the corresponding trials | | | 4 | | Mismatch OUT | | | | Fixation | |
|  | g6FOUT | the corresponding trials | | | 6 | | Mismatch OUT | | | | Fixation | |
|  | g8FOUT | the corresponding trials | | | 8 | | Mismatch OUT | | | | Fixation | |

The table summarizes the definitions of geometric phases for the fixation phase. Similarly, the following labels were defined: gtE, gsE, g4E, g6E, g8E, g4EIN, g4EOUT, g6EIN, g6EOUT, g8EIN, g8EOUT for the encoding phase; gtM, gsM, g4M, g6M, g8M, g4MIN, g4MOUT, g8MIN, g8MOUT for the maintenance phase; and gtR, gsR, g4R, g6R, g8R, g4RIN, g4ROUT, g8RIN, g8ROUT for the retrieval phase.

## **Table 3. Definition of task difficulty**

|  |  |  |
| --- | --- | --- |
| Task difficulty | Set size | Task type |
| 1 | 4 | Match IN |
| 2 | 4 | Mismatch OUT |
| 3 | 6 | Match IN |
| 4 | 6 | Mismatch OUT |
| 5 | 8 | Match IN |
| 6 | 8 | Mismatch OUT |

Task difficulty was defined as the table based on set size and task type.

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

## **Table 5. 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 profile of SWR-detectable ROIs. The first two sessions (session #1 and #2) were utilized to balance the dataset.

# **Figures**

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## **Figure 1. Representative LFP trace of the hippocampus during a working memory task**

***A-B.*** Representative wideband (***A***) and ripple band (***B***) local field potential **(**LFP) traces of intracranial encephalogram data (iEEG) (subject #6, session #2, and trial #5) recorded with 8-channels tetrodes at the left hippocampal head (AHL) during the modified Sternburg working memory task. ***C.*** Raster plot of multiunit spikes for the same trial. ***D***. The first three factors of hippocampal trajectory in the same trial calculated by Gaussian-process factor analysis (GPFA). Note that superimposed rectangles show the timings of SWR+ candidates (*purple*) and SWR− candidates (*yellow*).



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

***A.*** Representative trial trajectories of the left hippocampal head (AHL, *left*), left entorhinal cortex (ECL, *center*) and left amygdala (AL, *right*; subject #6, session #2, trial #5; z-normalized by session and region such as for session #2 in AHL) calculated by Gaussian-process factor analysis (GPFA) during the modified Sternburg working memory task (*gray*, fixation; *blue,* encoding; *green*, maintenance; and *red*, retrieval phase). ***B.***Log-likelihoods of GPFA models as a function of the number of dimensions to embed (mean ± SD / 5). Note the optimal dimension was determined as three with the elbow method. ***C*.** Representative trial geometric medians of trial trajectories in ***A***. The length of dotted lines was determined as distance between geometric medians. ***D***. Distances between all combinatnions of session geometric medians (*i.e.*, d(gtF, gtE), d(gtF, gtM), d(gtF, gtR), d(gtE, gtM), d(gtE, gtR), d(gtM, gtR)) were pooled and longer in the hippocampus (*n* = 7,338; 1.10 [1.21]; median [IQR]) than in the entorhinal cortex (*n* = 5,016; 0.55 [0.99]; *p* < 0.01; Brunner–Munzel test with Bonferroni correction) or amygdala(*n* = 6,198; 0.50 [0.94]; *p* < 0.01; Brunner–Munzel test with Bonferroni correction).



## **Figure 3. Memory load-dependent distance between the encoding and retrieval phases in the hippocampus**

***A***. Set size and correct rate (*left*) or response time (*right*). ***B***. Correct rate and response time were dependent on the task difficulty (\*\*\**p* < 0.001; vs. task-difficulty-shuffled surrogate). ***C***. For each of set size (the number of letters to encode; 4, 6, 8) and task type (Match IN or Mismatch OUT), geometric medians were defined (*e.g.*, g4FIN; Table 4) during the modified Stenberg test. The Kruskal–Wallis test identified differences among d(gkEm, gkRm), where k ∈ {4, 6, 8} and m ∈ {IN, OUT} (*bottom* *center*; *p* < 0.05; Bonferronig correction; *n*s = 239, 210, 187, 196, 188, 209 from left to right) but not among other distances (d(gkFm, gkFm), *p* = 0.17; d(gkFm, gkEm) *p* = 0.87; d(gkFm, gkRm) *p* = 0.52; d(gkEm, gkMm), *p* = 0.30; d(gkMm, gkRm), *p* = 0.89. ***D***. Correlation coefficient between task difficulty and distances of d(gkEm, gkRm) was larger than that of task-difficulty-shuffled surrogate (*white violin plot*; *n* = 1000) (*p* < 0.001).



## **Figure 4. Memory load-dependent distance between the encoding and retrieval phases in the hippocampus**

***A***. Set size and correct rate (*left*) or response time (*right*). ***B***. Correct rate and response time were dependent on the task difficulty (\*\*\**p* < 0.001; vs. task-difficulty-shuffled surrogate). ***C***. For each of set size (the number of letters to encode; 4, 6, 8) and task type (Match IN or Mismatch OUT), geometric medians were defined (*e.g.*, g4FIN; Table 4) during the modified Stenberg test. The Kruskal–Wallis test identified differences among d(gkEm, gkRm), where k ∈ {4, 6, 8} and m ∈ {IN, OUT} (*bottom* *center*; *p* < 0.05; Bonferronig correction; *n*s = 239, 210, 187, 196, 188, 209 from left to right) but not among other distances (d(gkFm, gkFm), *p* = 0.17; d(gkFm, gkEm) *p* = 0.87; d(gkFm, gkRm) *p* = 0.52; d(gkEm, gkMm), *p* = 0.30; d(gkMm, gkRm), *p* = 0.89. ***D***. Correlation coefficient between task difficulty and distances of d(gkEm, gkRm) was larger than that of task-difficulty-shuffled surrogate (*white violin plot*; *n* = 1000) (*p* < 0.001).



## **Figure 5. SWR detection from SWR-detectable regions**

**A.** A representative embedding of unit activities during SWR+ candidates (*purple*) and SWR− candidates (*yellow*) (subject #06, session #02) using supervised and two-dimensional UMAP (uniform manifold approximation and projection; Mclnnes et al., 2018). ***B***. Cumulative density plot of the mean silhouette scores of hippocampal regions. Note hippocampal regions with more than 0.60 silhouette score (75 percentile) were defined as SWR-detectable regions. Also, from SWR-detectable regions, SWR+ candidate and SWR− candidate were defined as SWR+ (*n* = 1,170) and SWR− (*n* = 1,170), respectively. ***C****.* Ripple incidence [Hz] of SWR+ (*purple*) and SWR− (*yellow*) as a function of the time from probe (mean (*solid* *lines*) ± SD (*filled areas*) of ten sessions in Table 3). ***D.*** Duration distribution of SWR+ (*purple*; 93.0 [65.4]; median [IQR]) and SWR− (*yellow*; 93.0 [65.4]; median [IQR]). Note the two distributions were exactly overlapped based on the definition of SWR−. ***E.*** Distribution of ripple band peak amplitude of SWR+ (*purple*; 3.05 [0.85]; median [IQR]) and SWR− (*yellow*; 2.37 [0.33]; median [IQR]) (\*\*\**p* <0.001; Brunner–Munzel test).



## **Figure 6. Transient change of hippocampal neural trajectory during SWR**

***A***. Representative peri-SWR− (*left*) or peri-SWR+ (*right*) session trajectory (mean ± SD; *n* = 50 trials of subject #6 and session #2). ***B***. Peri-SWR− (*left*) or peri-SWR+ (*right*) trajectory speed (mean ± SD / 2; *n* = 493 trials of five subjects). ***C***. Mean peri-event trajectory speeds of – 250–250 ms from the central time of SWR− or SWR+. Compared to during SWR−, during SWR+ trajectory speed was longer in the encoding, maintenance, and retrieval phases (\*\*\**p*s < 0.001; Brunner–Munzel test) but not in the fixation phase (*p* = 0.35; Brunner–Munzel test). ***D***. A representative directions of geometric medians from set size 4 to 8 (subject #6, session #2). ***E.*** Correlation coefficient between set size and mean peri-SWR- or peri-SWR+ trajectory length for the corresponding direction were as follows: 0.05, fSWR−; − 0.01, fSWR+; 0.05, eSWR−; 0.08, eSWR+, \*\**p* < 0.01; − 0.02, mSWR−; 0.07, mSWR+, \*\**p* < 0.01; 0.04, rSWR−; 0.02, rSWR+. Abbreviations: g4F (g8F), geometric median of the fixation phase for trials with set size 4 (8); g4E (g8E), geometric median of the encoding phase for trials with set size 4 (8); g4F (g8F), geometric median of the maintenance phase for trials with set size 4 (8); g4F (g8F), geometric median of the retrieval phase for trials with set size 4 (8); fSWR− (fSWR+), SWR− (SWR+) in the fixation phase; eSWR− (eSWR+), SWR− (SWR+) in the encoding phase; mSWR− (mSWR+), SWR− (SWR+) in the maintenance phase; rSWR− (rSWR+), SWR− (SWR+) in the retrieval phase.



## **Figure 7. Transient change of hippocampal neural trajectory during SWR**

***A***. Representative peri-SWR− (*left*) or peri-SWR+ (*right*) session trajectory (mean ± SD; *n* = 50 trials of subject #6 and session #2). ***B***. Peri



## **Figure 8. Directional fluctuation in hippocampal neural trajectory during SWR**

***A***.