

Highlights

- Neural trajectories in the hippocampus exhibited greater variability during a working memory (WM) task compared to those in the entorhinal cortex and amygdala regions.
- The distance of neural trajectories between encoding and retrieval states in the hippocampus was memory-load dependent during a WM task.
- Hippocampal neural trajectories fluctuated between the encoding and retrieval states in a task-dependent manner during both baseline and sharp-wave ripple (SWR) periods.
- Hippocampal neural trajectories shifted from encoding to retrieval states during SWR period.

Hippocampal Neural Fluctuations Between Memory Encoding and Retrieval States During a Working Memory Task in Humans

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Abstract

Working memory (WM) is crucial for a multitude of cognitive functions, but its underlying neural mechanisms at play remain to be fully understood. Interestingly, the hippocampus and sharp-wave ripples (SWRs)—transient and synchronous oscillation observed in the hippocampus—garner recognition for their significance in memory consolidation and retrieval, albeit their correlation with WM tasks remains to be elucidated. Here we show that during a WM task, multi-unit activity patterns in the hippocampus display distinctive dynamics, especially during SWR periods. This study analyzed intracranial electroencephalography data from the medial temporal lobe (MTL) of nine patients with epilepsy, recorded during an eight-second Sternberg task. Utilizing Gaussian-process factor analysis, we extracted low-dimensional neural representations or trajectories (NT) within MTL regions during the Sternberg WM task. The results revealed significant variations in NT of the hippocampus compared to those of the entorhinal cortex and the amygdala. Additionally, the distance of the NT between the encoding and retrieval phases was dependent on memory load. Crucially, hippocampal NT oscillated during the retrieval phase between encoding and retrieval states in a task-dependent manner. Notably, these fluctuations shifted from encoding to retrieval states during SWR episodes. These findings reaffirm the role of the hippocampus in WM tasks and propose a hypothesis: the hippocampus transitions its functional state from encoding to retrieval during SWRs in WM tasks.

Keywords: working memory, memory load, hippocampus, sharp-wave ripples, humans

7 figures, 3 tables, 221 words for abstract, and 3114 words for main text

1. Introduction

Working memory (WM) is crucial in everyday life; however, its neural mechanism has yet to be fully elucidated. Specifically, the hippocampus's involvement in WM processing, a pivotal region for memory, is the subject of ongoing research [1] [2] [3] [4] [5] [6] [7] [8] [9]. Understanding the hippocampus' role in working memory is instrumental in deepening our comprehension of

cognitive processes and could potentially enhance cognitive abilities.

Current evidence suggests that a transient, synchronized oscillation, called sharp-wave ripples (SWRs) [10], is associated with several cognitive functions. These include memory replay [11] [12] [13] [14] [15], memory consolidation [16] [17] [18] [19], memory recall [20] [21] [22], and neural plasticity [23] [24]. These associations suggest that SWR may be a fundamental computational manifestation of hippocampal processing, contributing to working memory performance as well.

Recent studies have found that low-dimensional representations in hippocampal neurons can explain WM task performances. Specifically, the firing patterns of

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place cells [25] [26] [27] [28] [29], found in the hippocampus, have been identified within dynamic, non-linear three-dimensional hyperbolic spaces in rats [30]. Additionally, grid cells in the entorhinal cortex (EC), which is the main pathway to the hippocampus [31] [32] [33], exhibited a toroidal geometry during exploration in rats [34].

However, these studies primarily focus on spatial navigation in rodents, which poses limitations. To illustrate, the temporal resolution of navigation tasks is inadequate as the timing of memory acquisition and recall is not clearly delineated. Consequently, there is a relative paucity of research on the impact of SWRs on WM performance [35]. Further, the presence of noise in signals recorded during rodent movement complicates the detection of SWRs [36]. Therefore, to clarify the relationship between SWRs and WM tasks, research with human subjects is necessary.

Considering these factors, this study investigates the hypothesis that hippocampal neurons exhibit unique neural trajectories (NTs) in low-dimensional space, particularly during SWR periods, in response to WM tasks in humans. To test this hypothesis, we employed a dataset of patients performing an eight-second Sternberg task (1 s for fixation, 2 s for encoding, 3 s for maintenance, and 2 s for retrieval) with high temporal resolution. Intracranial electroencephalography (iEEG) signals within the medial temporal lobe (MTL) were recorded for these patients [37]. To investigate low-dimensional NTs, we utilized Gaussian-process factor analysis (GPFA), an established method for analyzing neural population dynamics [38].

2. Methods

2.1. Dataset

The dataset used in this study, which is publicly available, comprises nine epilepsy patients performing a modified the Sternberg task [37]. This task includes four phases: fixation (1s), encoding (2s), maintenance (3s), and retrieval (2s). During the encoding phase, participants were presented with a set of four, six, or eight alphabet letters. They were then tasked with determining whether a probe letter displayed during the retrieval phase had previously appeared (the correct response for Match IN task) or not (the correct response for Mismatch OUT task). Intracranial electroencephalography

(iEEG) signals were captured with a 32 kHz sampling rate within a 0.5–5,000 Hz frequency range, using depth electrodes in the MTL regions: the anterior head of the left and right hippocampus (AHL and AHR), the posterior body of the hippocampus (PHL and PHR), the entorhinal cortex (ECL and ECR), and the amygdala (AL and AR), as depicted in Figure ??A and Table 1. The iEEG signals were subsequently downsampled to 2 kHz. Correlations between variables such as set size and correct rate were examined (Figure ??S1). Multiunit spike timing was determined via a spike sorting algorithm [39] using the Combinato package (<https://github.com/jniediek/combinato>)(Figure ??C).

2.2. Calculation of NT using GPFA

NTs, also referred to as 'factors', in the hippocampus, EC, and amygdala were determined using GPFA [38] 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.

For each NT within a region such as AHL, geometric medians (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).

2.3. Identifying SWR candidates from hippocampal regions

Potential SWR events within the hippocampus were detected using a widely used method [40]. LFP signals from a region of interest (ROI) like AHL, were re-referenced by deducting the averaged signal from locations outside the ROI (for instance, AHR, PHL, PHR, ECL, ECR, AL, and AR). The re-referenced LFP signals were then filtered with a ripple-band filter (80–140 Hz) to determine SWR candidates, marked as SWR⁺ candidates. SWR detection was carried out using a published tool (https://github.com/Eden-Kramer-Lab/ripple_detection) [41], with the bandpass range adjusted to 80–140 Hz for humans

[21] [22], unlike the initial 150–250 Hz range typically applied to rodents.

Control events for SWR^+ candidates, labeled as SWR^- candidates, were detected by randomly shuffling the timestamps of SWR^+ candidates across all trials and subjects. The resulting $\text{SWR}^+/\text{SWR}^-$ candidates were then visually inspected.

2.4. Defining SWRs from putative hippocampal CA1 regions

Potential SWRs were differentiated from SWR candidates in putative CA1 (cornu Ammonis 1) regions. These regions were initially defined as follows: $\text{SWR}^+/\text{SWR}^-$ candidates in the hippocampus were projected into a two-dimensional space based on overlapping spike counts per unit using a supervised method, UMAP (Uniform Manifold Approximation and Projection) [42]. Clustering validation was performed by calculating the silhouette score [43] from clustered samples. Regions in the hippocampus, which scored above 0.6 on average across sessions (75th percentile), were identified as putative CA1 regions, resulting in the identification of five electrode positions from five patients.

$\text{SWR}^+/\text{SWR}^-$ candidates in these predetermined CA1 regions were categorized as $\text{SWR}^+/\text{SWR}^-$, and thus they no longer retained their candidate status. The duration and ripple band peak amplitude of SWRs were found to follow log-normal distributions. Each time period of SWR was partitioned relative to the time from the SWR center into pre- (at -800 ms to -300 ms from the SWR center), mid- (at -250 to $+250$ ms), and post-SWR (at $+300$ to $+800$ ms) times.

2.5. Statistical Evaluation

Both the Brunner–Munzel test and the Kruskal–Wallis test were executed using the SciPy package in Python [44]. Correlational analysis was conducted by determining the rank of the observed correlation coefficient within its associated set-size-shuffled surrogate using a customized Python script. The bootstrap test was implemented with an in-house Python script.

3. Results

3.1. iEEG Recording and NT in MTL Regions during the Sternberg Task

Our analysis employed a publicly accessible dataset [37], which comprises LFP signals (Figure ??A) from MTL regions (Table 1) recorded during the execution of the modified Sternberg task. We extracted SWR^+ candidates from LFP signals that were filtered in the 80–140 Hz ripple band (Figure ??B), originating in all hippocampal regions (refer to Methods section). Meanwhile, SWR^- candidates, control events for SWR^+ candidates, were defined at the same timestamps but distributed across different trials (Figure ??). The dataset encompassed multi-unit spikes (Figure ??C), recognized via a spike sorting algorithm [39]. Employing GPFA [38], we applied this to 50-ms windows of binned multi-unit activity without overlaps to determine the NTs, or factors, of MTL regions by session and region (Figure ??D). We normalized each factor per session and region, for instance, session #2 in AHL of subject #1. We then calculated the Euclidean distance from the origin (O) (Figure ??E).

3.2. Correlation of Hippocampal NT with the Sternberg Task

Figure ??A exhibits a distribution of median NTs, comprising 50 trials, within the three main factor spaces. Utilizing the elbow method, we established the optimal embedding dimension for the GPFA model as three (Figure ??B). The NT distance from the origin (O) — represented as $\|g_F\|$, $\|g_E\|$, $\|g_M\|$, and $\|g_R\|$ — in the hippocampus surpassed the corresponding distances in the EC and amygdala (Figure ??C & D).¹

Similarly, we computed the distances between the geometric medians of four phases, namely $\|g_{FGE}\|$, $\|g_{FGM}\|$, $\|g_{FGR}\|$, $\|g_{EGM}\|$, $\|g_{EGR}\|$, and $\|g_{MGR}\|$. The hippocampus showed larger distances between phases than those in the EC and amygdala.²

¹Hippocampus: 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.

²Hippocampus: 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).

3.3. Memory-Load-Dependent NT Distance between Encoding and Retrieval States in the Hippocampus

Regarding memory load in the Sternberg task, we observed a negative correlation between the correct rate of trials and the set size, which denotes the number of letters to be encoded (Figure ??A).³ Concomitantly, a positive correlation was noted between the response time and set size (Figure ??B).⁴

Next, we discovered a positive correlation between set size and the NT distance separating the encoding and retrieval phases ($\log_{10}(\|g_{\text{EGR}}\|)$) (Figure ??C).⁵ However, distances between other phase combinations did not highlight statistically significant correlations (Figures ??D and ??).

3.4. Detection of Hippocampal SWRs from Putative CA1 Regions

To enhance the precision of recording sites and SWR detection, we approximated the electrode placements in the CA1 regions of the hippocampus using distinguished multi-unit spike patterns during SWR events. SWR⁺/SWR⁻ candidates from each session and hippocampal region were embedded in two-dimensional space using UMAP (Figure ??A).⁶ With the silhouette score as a quality metric for clustering (Figure ??B and Table 2), recording sites demonstrating an average silhouette score exceeding 0.6 across all sessions were identified as putative CA1 regions.⁷ (Tables 2 and 3). We identified five putative CA1 regions, four of which were not indicated as seizure onset zones (Table 1).

³Correct rate: set size four (0.99 ± 0.11 , mean \pm 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). Generally, $p < 0.001$ for Kruskal–Wallis test; correlation coefficient = -0.20 , $p < 0.001$.

⁴Response 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 Kruskal–Wallis test; correlation coefficient = 0.22 , $p < 0.001$.

⁵Correlation between set size and $\log_{10}(\|g_{\text{EGR}}\|)$: correlation coefficient = 0.05 , $p < 0.001$. Specific values: $\|g_{\text{EGR}}\| = 0.54$ [0.70] for set size four, $n = 447$; $\|g_{\text{EGR}}\| = 0.58$ [0.66] for set size six, $n = 381$; $\|g_{\text{EGR}}\| = 0.61$ [0.63] for set size eight, $n = 395$.

⁶Consider the AHL in session #1 of subject #1 as a case in point.

⁷The identified regions were the AHL of subject #1, AHR of subject #3, PHL of subject #4, AHL of subject #6, and AHR of subject #9.

Subsequently, SWR⁺/SWR⁻ candidates within these putative CA1 regions were labeled as SWR⁺ and SWR⁻, respectively⁸ (Table 3). Both SWR⁺ and SWR⁻ manifested identical durations⁹ due to their definitions and followed a log-normal distribution (Figure ??C). During the initial 400 ms of the retrieval phase, an increase in SWR⁺ incidence was found¹⁰ (Figure ??D). The peak ripple band amplitude of SWR⁺ surpassed that of SWR⁻ and followed a log-normal distribution (Figure ??E).¹¹

3.5. Transient Change in Hippocampal NT during SWR

We assessed the 'distance' of the NT from the origin (O) during SWR events in both encoding and retrieval phases (Figure ??A). Observing the increase in distance during SWR, as illustrated in Figure ??A, we categorized each SWR into three stages: pre-, mid-, and post-SWR. Hence, the distances from the origin O during those SWR intervals are identified as $\|pre\text{-eSWR}^+\|$, $\|mid\text{-eSWR}^+\|$ and others.

As a result, $\|mid\text{-eSWR}^+\|$ ¹² exceeded $\|pre\text{-eSWR}^+\|$ ¹³, and $\|mid\text{-rSWR}^+\|$ ¹⁴ was larger than $\|pre\text{-rSWR}^+\|$ in both the Match IN and Mismatch OUT tasks.¹⁵

3.6. Visualization of Hippocampal NT during SWR in Two-Dimensional Spaces

Having observed NT 'jumping' during SWR (Figure ??), we visualized the three-dimensional NTs of pre-, mid-, and post-SWR events during the encoding and retrieval phases (Figure ??). The distance between

⁸These definitions produced equal counts for both categories: SWR⁺ ($n = 1,170$) and SWR⁻ ($n = 1,170$).

⁹These definitions result in equal durations for both categories: SWR⁺ (93.0 [65.4] ms) and SWR⁻ (93.0 [65.4] ms).

¹⁰SWR⁺ increased against the bootstrap sample; 95th percentile = 0.42 [Hz]; $p < 0.05$.

¹¹SWR⁺ (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).

¹² 1.25 [1.30], median [IQR], $n = 1,281$ in Match IN task; 1.12 [1.35], median [IQR], $n = 1,163$ in Mismatch OUT task

¹³ 1.08 [1.07], median [IQR], $n = 1,149$ in Match IN task; 0.90 [1.12], median [IQR], $n = 1,088$ in Mismatch OUT task

¹⁴ 1.32 [1.24], median [IQR], $n = 935$ in Match IN task; 1.15 [1.26], median [IQR], $n = 891$ in Mismatch OUT task

¹⁵ 1.19 [0.96], median [IQR], $n = 673$ in Match IN task; 0.94 [0.88], median [IQR], $n = 664$ in Mismatch OUT task

these was found to be memory-load dependent (Figure ??).

To provide two-dimensional visualization, we linearly aligned peri-SWR NTs by setting \mathbf{g}_E at the origin (0, 0) and \mathbf{g}_R at ($\|\mathbf{g}_{EGR}\|$, 0). Subsequently, we rotated these aligned NTs around the \mathbf{g}_{EGR} axis (the x axis), ensuring that the distances from the origin O in the original three-dimensional spaces and angles from \mathbf{g}_{EGR} are retained in the two-dimensional equivalent.

Scatter plot visualization of NTs within these two-dimensional spaces revealed distinct distributions of peri-SWR NTs based on phases and task types. A notable example of this is the observation that the magnitude of $\|\text{mid-eSWR}^+\|$ exceeds that of $\|\text{pre-eSWR}^+\|$ (Figure ??B), which is consistent with our previous observations (Figure ??).

3.7. Fluctuations of Hippocampal NTs between Encoding and Retrieval States

Subsequently, we investigated the 'direction' of the NT in relation to \mathbf{g}_{EGR} , which was found to be dependent on memory load (Figure ??). The directions of the SWRs were determined by the NT at -250 ms and +250 ms from their center, denoted as, for example, \mathbf{eSWR}^+ . We calculated the cosine similarities between \mathbf{g}_{EGR} , \mathbf{eSWR} , and \mathbf{rSWR} in both SWR (SWR⁺) and baseline periods (SWR⁻) (Figure ??A – -D).

$\mathbf{rSWR}^- \cdot \mathbf{g}_{EGR}$ exhibited a biphasic distribution. By computing the difference between the distribution of $\mathbf{rSWR}^+ \cdot \mathbf{g}_{EGR}$ (Figure ??A & B) and that of $\mathbf{rSWR}^- \cdot \mathbf{g}_{EGR}$ (Figure ??C & D), we were able to determine the contributions of SWR (Figure ??E & F), which indicated a shift in the direction of \mathbf{g}_{EGR} (Figure ??E & F: *red rectangles*).

Furthermore, $\mathbf{eSWR}^+ \cdot \mathbf{rSWR}^+$ was less than $\mathbf{eSWR}^- \cdot \mathbf{rSWR}^-$ strictly in Mismatch OUT task (Figure ??F: *pink circles*). In other words, eSWR and rSWR pointed in the opposite direction exclusively in Mismatch OUT task but not Match IN task (Figure ??E: *pink circles*).

4. Discussion

This study hypothesizes that in low-dimensional spaces during a WM task in humans, hippocampal neurons form unique NTs, primarily during SWR periods.

Initially, multi-unit spikes in the MTL regions were projected onto three-dimensional spaces during a Sternberg task using GPFA (Figure ??D–E & Figure ??A). The NT distances across WM phases ($\|\mathbf{g}_{FGE}\|$, $\|\mathbf{g}_{FGM}\|$, $\|\mathbf{g}_{FGR}\|$, $\|\mathbf{g}_{EGM}\|$, $\|\mathbf{g}_{EGR}\|$, and $\|\mathbf{g}_{MGR}\|$) were significantly larger in the hippocampus compared to the EC and amygdala (Figure ??C–E), indicating dynamic and responsive neural activity in the hippocampus during the WM task. Also, in the hippocampus, the NT distance between the encoding and retrieval phases ($\|\mathbf{g}_{FGE}\|$) correlated positively with memory load (Figure ??C–D), reflecting WM processing. The hippocampal neural NT transiently expanded during SWRs (Figure ??). Lastly, the hippocampal neural NT alternated between encoding and retrieval states, transitioning from encoding to retrieval during SWR events (Figure ??). These findings explain aspects of hippocampal neural activity during a WM task in humans and offer new insights into SWRs as a state-switching element in hippocampal neural states.

The distance of the neural NT across the phases was significantly longer in the hippocampus compared to the EC and amygdala, even when considering the distance from O in these regions (Figure ??C–E). This establishes the involvement of the hippocampus in the WM task, corroborating previous studies indicating hippocampal persistent firing during the maintenance phase [3] [4] [5] [6]. However, in the present study, applying GPFA to multi-unit activity during a one-second level resolution of the WM task revealed that the neural NT in low-dimensional space presented a memory-load dependency between the encoding and retrieval phases, denoted as $\|\mathbf{g}_{EGR}\|$ (Figure ??). These findings support the association of the hippocampus with WM processing.

Our analysis focused on putative CA1 regions (Figure ??), is supported by several factors. This specific focus results from established observations that SWRs synchronize with interneuron and pyramidal neuron spike bursts [45] [46] [47] [48], potentially within a 50 μm radius of the recording site [49]. Furthermore, we identified an increased incidence of SWRs during the first 0–400 ms of the retrieval phase (Figure ??D). This finding aligns with previous reports of heightened SWR occurrence preceding spontaneous verbal recall [21] [22], supporting our results under a triggered retrieval condition. The observed log-normal distributions

of both SWR duration and ripple band peak amplitude in this study (Figure ??C & E) coincide with the current consensus in this field [40]. Consequently, our decision to limit recording sites to putative CA1 regions likely contributed to improving the precision, or true positive rate, of SWR detection. Although, the NT distance increase from *O* during SWRs (Figure ??) might be artificially inflated towards higher values due to channel selection, this potential bias does not substantially challenge our main findings.

Interestingly, during the retrieval phase, NT directions alternated between encoding and retrieval states during both baseline and SWR periods in a task-dependent manner (Figure ??C & D). Additionally, the balance of this fluctuation transitioned from encoding to retrieval state during SWR events (Figure ?? E & F). These results align with previous studies on the role of SWR in memory retrieval [21] [22]. Our findings suggest that (i) neuronal oscillation between encoding and retrieval states occurs during a WM task and (ii) SWR events serve as indicators of the transition in hippocampal neural states from encoding to retrieval during a WM task.

Moreover, our study noted differences specific to the WM-task type between encoding- and retrieval-SWRs (Figure ??E–F). Notably, opposing movements of encoding-SWR (eSWR) and retrieval-SWR (rSWR) were not observed in Match IN task but were apparent in Mismatch OUT task. Memory engram theory [50] might explain these observations: Match In task presented participants with previously shown letters, while Mismatch OUT task introduced a new letter absent in the encoding phase. This explanation underscores the significant role of SWR in human cognitive processes.

In conclusion, this study illustrates that during a WM task in humans, hippocampal activity fluctuate between encoding and retrieval states, uniquely transitioning from encoding to retrieval during SWR events. These findings offer novel insights into the neural correlates and functionality of working memory within the hippocampus.

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Declaration of Generative AI in Scientific Writing

The authors employed ChatGPT, provided by OpenAI, for enhancing the manuscript’s English language quality. After incorporating the suggested improvements, the authors meticulously revised the content. Ultimate responsibility for the final content of this publication rests entirely with the authors.

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.

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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.org/10.12751/g-node.d76994/>).

The source code is available on GitHub (<https://github.com/yanagisawa-lab/hippocampal-neural-fluctuation-during-a-WM-task-in-humans>).

Inclusion and Diversity Statement

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

Tables

Subject ID	# of sessions	AHL	AHR	PHL	PHR	ECL	ECR	AL	AR	SOZ
1	4	✓	n.a.	✓	✓	✓	n.a.	✓	n.a.	AHR & LR
2	7	✓	✓	✓	✓	✓	✓	✓	✓	AHR & PHR
3	3	✓	✓	✓	✓	✓	✓	✓	n.a.	AHL & PHL
4	2	✓	✓	✓	✓	✓	✓	✓	✓	AHL & AHR & PHL & PHR
5	3	✓	n.a.	n.a.	✓	n.a.	n.a.	✓	n.a.	DRR
6	6	✓	✓	✓	✓	✓	✓	✓	✓	AHL & PHL & ECL & AL
7	4	✓	✓	✓	✓	✓	✓	✓	✓	AHR & PHR
8	5	✓	✓	✓	✓	✓	✓	✓	✓	ECR
9	2	✓	✓	✓	✓	✓	✓	✓	✓	ECR & AR

Table 1 – Electrode Distribution within the Dataset

This figure denotes the placements of electrodes and seizure onset zones. Regions marked with ✓ were included in the dataset, while those imprinted with n.a. were absent. The abbreviations used are as follows: 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 represents the seizure onset zone.

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.

Table 2 – Silhouette Score of UMAP Clustering for SWR⁺ Candidates and SWR⁻ Candidates

The silhouette scores (mean ±SD across sessions per subject) for UMAP clustering of SWR⁺ candidates and SWR⁻ candidates are based on their respective multi-unit spike patterns (Figure ??A). The mean scores were 0.205 and the standard deviation was 0.285, calculated for the interquartile range (IQR; Figure ??B).

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 = 1170	0.30 ± 0.13 (mean ± SD)

Table 3 – Summary of Detected SWRs

The table provides statistics of presumptive CA1 regions and SWR events. Only the initial two sessions (sessions 1 and 2) from each subject were included in our analysis to reduce sampling bias.

Figures