**Differential ripple propagation along the hippocampal longitudinal axis**

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# Abstract

Hippocampal ripples are highly synchronous neural events critical for memory consolidation and retrieval. A minority of strong ripples has been shown to be of particular importance in situations of increased memory demands. The propagation dynamics of strong ripples inside the hippocampal formation are however still opaque. Using an open access database of large-scale electrophysiological recordings in 49 mice we extensively analyzed ripple propagation in the septal half of the hippocampal formation. Strong ripples propagate differentially in the septal and temporal direction along the hippocampal longitudinal axis, the hippocampus is therefore anisotropic in relation to ripple propagation. Hippocampal anisotropy is explained by the ability of the septal hippocampal pole to generate longer strong ripples that engage more neurons and elicit spiking activity for an extended time along the entire septal half of the hippocampal formation.

# Introduction

Hippocampal ripples are brief oscillatory events detected in the local field potential (LFP) of the hippocampal formation, they play a crucial role in memory processes such as consolidation and retrieval {Buzsáki, 2015 #1110;Diba, 2007 #1111;Foster, 2006 #1112;Xu, 2019 #1113;Takahashi, 2015 #1114;Jadhav, 2012 #1115;Davidson, 2009 #1116;Pfeiffer, 2015 #1117;Dragoi, 2011 #1118;Girardeau, 2009 #1120}. We studied ripple propagation along the hippocampal longitudinal axis in an open-access dataset provided by the Allen Institute {Siegle, 2021 #1127}.

# Results

**Distance explains the majority of the ripple strength correlation variability.**

We analyzed the LFP signals across the visual cortex, hippocampal formation and brain stem (Supplementary Figure 1) simultaneous to ripples detected in the CA1 of 49 animals (average session duration = 9877.4 ± 43.1 seconds, average ripple incidence = 2.49 ± 0.12 per 10s). Ripples were detected on the CA1 channel with the strongest ripple activity (n ripples = 120462). Ripple strength (∫Ripple) was calculated as the integral of the filtered LFP envelope (Supplementary Figure 2B). Clear ripples were observed uniquely in the hippocampal formation (CA1, CA2, CA3, DG, SUB, ProS). Likewise, ripple-induced voltage deflections (RIVD) were also noticeably stronger in hippocampal areas (Supplementary Figure 2C-F). ∫Ripple was noticeably irregular in single sessions both across time and space, even between different CA1 locations (Supplementary Figure 2C). We focused on the variability in ∫Ripple across pairs of CA1 recording locations with clear ripple activity (n CA1 pairs = 303, n sessions = 46). Correlation of ∫Ripple across different CA1 regions was highly variable (Figure 1A-B-C) with a lower and upper quartiles of 0.66 and 0.87 (mean = 0.76, SEM = 0.01). Distance between recording location could explain the majority (57.6%) of this variability (Figure 1B) with the top and bottom quartiles of ∫Ripple correlation showing significantly different average distances (Figure 1C-D). Given the correlation variability we asked how reliably a ripple can travel along the hippocampal longitudinal axis. To answer this question we looked at ripples lag in sessions that included both long-distance (> 2126.66 µm) and short-distance (< 857.29 µm) CA1 recording pairs (n sessions = 32, n CA1 pairs = 64, Figure 1E). Reference for the lag analysis was always the most medial recording location in each pair. Almost half of the ripples in long-distance pairs (49.3 ± 2.2%) were detected in both locations (inside a 120 ms window centered on ripple start at the reference location). Unsurprisingly short-distance pairs showed a more reliable propagation (69.59 ± 3.51%). Moreover, lag between long-distance pairs had a much broader distribution (Figure 1F) and a significantly bigger absolute lag (Figure 1G). Neither high nor short-distance pairs showed clear directionality (lag long-distance = -1.14 ± 0.64 ms, lag short-distance = -0.5 ± 0.41 ms). Looking at the relationship between lag and ∫Ripple in long-distance pairs, however, an asymmetric distribution was apparent (Figure 1F top), suggestive of a possible interaction between these two variables: stronger ripples appear to be predominantly associated with positive lags (i.e. ripples moving medial→lateral). To further investigate this relationship we divided ripples into two groups: strong (top 10% ∫Ripple per session at the reference location) and common (remaining ripples). The septal half of the hippocampus was divided in three sections with equal number of recordings: medial, central and lateral (Supplementary Figure 3). Strong ripples identified in the medial section, in opposition to common ripples, showed a markedly positive lag (17.83 ± 1.02 ms) indicative of a preferred medial→lateral travelling direction (Figure 1H top). Surprisingly, the same was not true for strong ripples identified in the lateral section (lag = 3.62 ± 1.05 ms, Figure 1I). Strong and common ripples lag was significantly different between medial and lateral locations both in common and strong ripples. A biased direction of propagation can be explained by an unequal chance of ripple generation across space. We could assume that selecting strong ripples we are biasing our focus towards ripples whose generation point (seed) is situated nearby our reference location, this would contribute to explain the unbalanced lag. This notion would, however, fail to explain the different directionality we observed between strong ripples in medial and lateral locations, this hints at a more complex situation.

**Ripples propagation along the hippocampal longitudinal axis is anisotropic.**

To analyze the propagation of ripples along the hippocampal longitudinal axis we focused on sessions from which ripples were clearly detected in at least two different hippocampal sections at the same time (n = 41). We followed the propagation of strong and common ripples detected in the reference location across the hippocampus (Figure 2A-B) and built an average spatio-temporal propagation map per session (Figure 2C). Strong and common ripples in the medial section showed a divergent propagation pattern: strong ripples travelling medio→laterally and common ripples travelling in the opposite direction (Figure 2C-D-E). Ripples detected in the lateral section did not show such strikingly divergent propagation (Figure 2F-G) whereas in the central section the propagation was divergent only laterally and not medially (Figure 2H-I). This peculiar propagation profile suggests a not previously described underlying anisotropy along the hippocampal longitudinal axis, the property of exhibiting direction-dependent qualities. To understand the mechanism underlying such variability in propagation we examined the location of the seed for each ripple in sessions in which ripples were clearly detected in every hippocampal section (n sessions = 25). In common ripples, regardless of the reference location, the majority of ripples started from the lateral section (Figure 3A). On the other hand, strong ripples displayed a more heterogenous picture. We identified two principles relative to strong ripples generation: In all hippocampal sections the majority of strong ripples are locally generated, and a greater number of strong ripples is generated medially than laterally. Looking at the central section we can appreciate the difference between the number of strong ripples generated medially and laterally (Figure 3A right, mean medial=36.83 ± 2.66%, mean lateral = 20.55 ± 2.04%, p-value = 3e-05). Strong and common ripples had significantly different seed location profiles only in the medial and central section, not in the lateral section (Figure 3B). These seed location profiles explain the propagation anisotropy, major unbalances in seeds location cause propagation patterns with clear directionality on the contrary lag measurements hovering around zero are the result of averaging between two similarly numbered groups of ripples with opposite direction of propagation. Conversely, propagation speed did not change depending on the seed location (Supplementary Figure 4). The reason why strong ripples are only in a minority of cases generated in the lateral section remains nevertheless unclear. Using a 'strength conservation index' (SCI) we measured the ability of a ripple to retain its strength during propagation (a ripple with SCI = 1 is in the top 10% in all hippocampal sections). We observed that ripples generated laterally were effectively less able to retain their strength propagating towards the medial pole (Supplementary Figure 5). This result is not simply explained by differences in ∫Ripple along the medio-lateral (M-L) axis, as no such gradient was observed (R² = 0.0012, Supplementary Figure 6). Curiously, ripple amplitude showed a weak trend in the opposite direction (R² = 0.06), with higher amplitude ripples in the lateral section (Supplementary Figure 7).

**The hippocampal medial/septal pole can generate longer strong ripples able to better engage neural networks.**

To understand the reason behind the differential propagation we focused uniquely on the central section, here it was possible to distinguish between ripples generated laterally or medially ('lateral ripples' and 'medial ripples'). We included in the analysis sessions in which ripples were clearly detected in each hippocampal section and with at least 100 ripples of each kind (n sessions = 24). We looked at spiking activity associated with these two classes of ripples in the hippocampal formation across the M-L axis (n clusters per session = 650.42 ± 33.16, Figure 4A-B-C). To compare sessions we created interpolated maps of the difference between spiking induced by medial and lateral ripples (Figure 4D). Immediately following ripple start (0-50 ms, "early phase") spiking was predictably influenced by ripple seed proximity: in the lateral section, lateral ripples induced more spiking (indicated by the blue color), whereas in the medial section it was the medial ripples that dominated (indicated by the red color). Surprisingly, in the 50-120 ms window post ripple start ("late phase"), medial ripples could elicit significantly higher spiking activity than lateral ripples along the entire M-L axis (Figure 4E). Dividing clusters in putative excitatory and inhibitory using the waveform duration we observed the same effect in both types of neuron (Supplementary Figure 8). In accordance with this result we found that the medial hippocampal section is able to generate longer ripples (Figure 4F). An important portion of the variance in ripple duration is indeed explained by location on the M-L axis both in common (R² = 0.133) and especially in strong ripples (R² = 0.463). The observed extended spiking could be due to a increased number of neurons participating in the ripple, to a higher spiking rate per neuron or a combination of these two elements. Fraction of active neurons and spiking rate were both significantly higher in medial ripples (Supplementary Figure 9). Focusing only on the late phase the difference in fraction of active neurons per ripples between medial and lateral ripples was even more striking (Cohen's d = 1.7, Figure 4G). Inversely, in the early phase lateral ripples could engage more neurons, although, the effect size was much smaller (Cohen's d = 0.39). The same results was found in relation to the spiking rate, medial ripples caused a significant and considerable increase in spiking rate in the late phase (Cohen's d = 1.75, Figure 4H). Dividing again the clusters into putative excitatory and inhibitory, significant differences between medial and lateral ripples were present only in the late phase. Spiking frequency and number of engaged neurons were significant higher in medial ripples both in putative excitatory and inhibitory clusters (Supplementary Figure 10). In summary, the prolonged spiking observed in medial ripples was caused both by an increased number of engaged neurons and a higher spiking rate per cell, both in putative excitatory and inhibitory neurons.

# Discussion

Our work shows for the first time that strong ripples propagation is anisotropic along the hippocampal longitudinal axis. This anisotropy can be explained by a specific ability of the hippocampal septal (medial) pole to produce longer strong ripples that better entrain the hippocampal network and spread across the M-L axis. Long duration ripples has been shown to be of particular importance in situations of high-memory demand {Fernández-Ruiz, 2019 #1121}, these results suggest a possible distinctive role of the hippocampal septal pole in these situations. This is consistent with previous studies that highlighted the role of the septal hippocampus in memory tasks and information processing {Hock, 1998 #1122;Moser, 1993 #1123;Moser, 1995 #1124;Steffenach, 2005 #1128;Kheirbek, 2013 #1126;McGlinchey, 2018 #1125;Fanselow, 2010 #1129;Maras, 2014 #1130;Bradfield, 2020 #1131;Qin, 2020 #1132}.

# Materials and Methods

**Dataset**

Our analysis was based on the Visual Coding - Neuropixels dataset provided by the Allen Institute and available at https://allensdk.readthedocs.io/en/latest/visual\_coding\_neuropixels.html. We excluded one session (session id = 743475441) because of an artifact in the LFP time series (time was not monotonically increasing). Two other sessions (session ids = 746083955, 756029989) were excluded because of duplicated LFP traces. Other 6 sessions were excluded because of absence of recording electrodes in CA1 (session ids=732592105, 737581020, 739448407, 742951821, 760693773, 762120172). Our analysis was therefore focused on 49 sessions, average animal age = 119.22 ± 1.81. Sex: males n = 38, females n = 11. Genotypes: wt/wt n = 26, Sst-IRES-Cre/wt;Ai32(RCL-ChR2(H134R)\_EYFP)/wt n = 10, Vip-IRES-Cre/wt;Ai32(RCL-ChR2(H134R)\_EYFP)/wt n = 7, Pvalb-IRES-Cre/wt;Ai32(RCL-ChR2(H134R)\_EYFP)/wt n = 6. Average probe count per session = 5.73 ± 0.08. Average number of recording channels per session = 2129.45 ± 29.46. Probes in each session were numbered according to the position on the M-L axis, with probe number 0 being the most medial. Channels with ambiguous area annotations were discarded (e.g. HPF instead of CA1). We found a number of of small artifacts in a variety of sessions, all this timepoints were excluded from the analysis (for more informations: https://github.com/RobertoDF/Allen\_visual\_dataset\_artifacts). Further details about data acquisition can be found at https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer\_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels\_visual\_coding\_-\_white\_paper\_v10.pdf. Visualization of recording locations was performed with brainrender {Claudi, 2021 #1134}.

**Ripples detection**

The LFP traces sampled at 1250 Hz were filtered using a 6th order Butterworth bandpass filter between 120.0 and 250.0. Ripples were detected on CA1 LFP traces, the best channel (higher ripple strength) was selected by looking at the SD of the envelope of the filtered trace, if multiple SD peaks were present across space (possibly caused by sharp waves in stratum radiatum and ripple activity in stratum pyramidale) we subsequently looked at the channel with higher skewness, in this way we could reliably identify the best ripple channel. The envelope of the filtered trace was calculated using the Hilbert transform (scipy.signal.hilbert). Ripple threshold was set at 5 SDs. Start and stop times were calculated using a 2 SDs threshold on the smoothed envelope with window = 5 (pandas.DataFrame.rolling) to account for ripple phase distortions. Ripple duration was limited at >0.015 s and <0.25 s. Candidate ripples were excluded if preceded by another ripple in a window of 0.05 s. We estimated power density of each candidate using a periodogram with constant detrending (scipy.signal.periodogram) on the raw LFP trace, we checked the presence of a peak > 100 Hz, candidates not fulfilling this condition were discarded, this condition was meant to reduce the number of detected false positives. Ripple candidates detected during running epochs were discarded, an animal was considered to be running if his standardized speed was higher than the 10th percentile plus 0.06. Candidates were also discarded if no behavioral data was available. Code for the detection of ripples resides in 'Calculate\_ripples.py'.

**Correlation and lag analysis**

In each session we uniquely used ripples from the CA1 channel with the strongest ripple activity, we looked at the LFP activity in all brain areas recorded in a window of 100.0 ms pre ripple start and 200.0 ms post ripple start, this broad windows account for possible travelling delays due to distance. For each brain area we picked the channel with higher SD of the envelope of the filtered trace. For each ripple considered we calculated integral of the envelope of the filtered trace (∫Ripple) and the integral of the raw LFP (ripple-induced voltage deflection, RIVD). After discarding channels with weak ripple activity (envelope variance < 5), we computed the pairwise pearson correlation of the envelope traces of CA1 channels (pandas.DataFrame.corr). For the lag analysis we first identified pairs of CA1 that satisfied a distance requirements. Distance threshold were set at 25% (857.29 µm) and 75% (2126.66 µm) of the totality of distances. For each ripple detected in the reference channel we identifired the nearest neighbour in the other channel. The analysis was repeated after dividing ripples in strong (top 10% ∫Ripple) and common ripples (all remaining ripples) per session. Code for the correlation and lag analysis resides in 'Calculations\_Figure\_1.py'.

**Ripple spatio-temporal propagation maps and ripple seed analysis**

The hippocampus was divided in three section with equal number of recordings. Channels with weak ripple activity (envelope variance < 5) were discarded. Sessions with recording locations only in one hippocampal sections or with less than 1000 ripples in the channel with strongest ripple activity were discarded as well. For each ripple detected on the reference CA1 channel we identified ripples in other CA1 channels happening in a window of ± 60.0 ms, this events were grouped together in a 'cluster'. If more than one event was detected on the same probe we kept only the first event. 'Clusters' were subsequently divided according to ∫Ripple on the reference electrode in strong and common ripples. Lag maps were result of averaging lags for each probe. Code for the calculations of propagation maps resides in 'Calculate\_trajectories.py'.

**Ripple-associated spiking activity**

We focused on sessions with clear ripple activity (envelope variance > 5) in all three hippocampal sections and at least 100 ripples generated both medially and laterally. The reference was always placed in the central section, here it was possible to identify ripples generated medially and laterally. We only considered ripples that were detected in at least half of the recording electrodes (in the code: "spatial engagment" > 0.5). For each ripple we computed a histogram of spiking activity of regions belonging to the hippocampal formation (HPF) in a window of 0.5 s centered on the ripple start in each probe. We averaged all the computed histograms to create a spatial profile of spiking activity. To compare spiking activity between sessions we interpolated (xarray.DataArray.interp) the difference between medial ripples-induced spiking and lateral ripples-induced spiking over space (this was necessary because probes in each sessions have different M-L coordinates) and time. We calculated the number of active cells (at least one spike) and spiking rate of each cluster per ripple in a window of 0.12 s starting from ripple start. We repeated the analysis separating the 0-50 ms and 50-120 ms post ripple start windows.

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# Contributions

Conceptualization, data curation, formal analysis, investigation, visualization: RDF. Writing - original draft: RDF. Writing - review & editing: RDF, DS. Funding acquisition: DS.

# Data and materials availability

All the code used to process the dataset is available at https://github.com/RobertoDF/De-Filippo-et-al-2022, pre-computed data structures can be downloaded at 10.6084/m9.figshare.20209913. All figures and text can be reproduced using code present in this repository, each number present in the text is directly linked to a python data structure. The original dataset is provided by the Allen Institute and available at https://allensdk.readthedocs.io/en/latest/visual\_coding\_neuropixels.html.

# Figures

**Figure 1. ∫Ripple correlation depends significantly on distance.**

(A) Correlation matrices showing the variabilty of ripple strength correlation between pairs of recording sites located in different CA1 locations in 4 example sessions. The number on the x and y axis labels indicates the probe number. Probes are numbered according to the position on the hippocampal longitudinal axis (0 is the most medial probe). (B) Scatter plot and linear regression showing the relationship between distance and correlation strength. Distance between recording sites explains 0.576% of the variability in correlation of ripple strength. (C) Ripple strength correlation distribution. Pink represents bottom 25% (< Q₁) and blue top 25% (> Q₄). (D) Violinplots showing that the top and bottom correlation quartile show significantly different distance distributions (Q₁: 2077.57 ± 68.68 µm, Q₄: 633.56 ± 44.02 µm, p-value = 4.00e-23, Mann-Whitney U test). (E) Top: Rendering of the long distance (top) and short distance (bottom) CA1 pairs, dark circles are the reference locations in each pair. (F) Top and middle: scatter plots showing the relationship between ∫Ripple (at the reference location) and lag for long distance (top, n ripples = 31855) and short distance (middle, n ripples = 52858) pairs. Bottom: kernel density estimate of the lags of long distance (pink) and short distance (turquoise) pairs. (G): Lag (top) and absolute lag (bottom) comparison between long and short distance pairs (top: long distance =-1.47 ± 0.63 ms, Short distance = -0.51 ± 0.4 ms, p-value = 2.03e-01, Student's t-test; bottom: long distance = 17.69 ± 0.38 ms, Short distance = 8.69 ± 0.56 ms, p-value = 6.58e-20, Student's t-test). (H) Lag comparison in long distance pairs between common and strong ripples with reference located inthe medial (top) or lateral hippocampal section (bottom) (top: strong ripples=17.83 ± 1.02 ms, common ripples = -3.27 ± 0.68 ms, p-values = 2.28e-25, Student's t-test, bottom: strong ripples=3.62 ± 1.05 ms, common ripples = 0.88 ± 0.66 ms, p-values = 3.00e-02, Student's t-test). (I) Lag comparison in long distance pairs between ripples with reference located in the medial and lateral section in common (top) or strong ripples (bottom) (top: medial reference = -3.27 ± 0.68 ms, lateral reference = 0.88 ± 0.66 ms, p-values = 4.30e-05, Student's t-test, bottom: strong ripples = 17.83 ± 1.02 ms, common ripples = 3.62 ± 1.05 ms, p-values = 4.30e-05, Student's t-test).

**Figure 2. Direction-dependent differences in ripple propagation along the hippocampal longitudinal axis.**

(A) Recording locations for session 768515987. Circles colors represents medio-lateral location. Bigger circle represents the reference location. (B) Example propagation of a strong (left column) and common (right column) ripple across the different recording location from session 768515987, each filtered ripple is color-coded according to A. Grey traces represents raw LFP signal. Dashed vertical line represents the start of the ripple. In the top row the ripple envelope across all locations. Black scale bars: 50 ms, 0.5 mV. Red scale bars: 0.1 mV. (C) Average propagation map of strong and common ripples in session 768515987 across the medio-lateral axis. (D) Recording locations relative to E. Red circles represents the reference locations across all sessions (n sessions=41), black circles represents the remaining recording locations. (E) Left: Medio-lateral propagation of strong ripples, each line represents the average of one session. Middle: Medio-lateral propagation of common ripples, each line represents the average of one session. Right: Average propagation map across sessions of strong and common ripples. Reference locations are the most lateral per session. (F) Same as D. (G) Same as E. Reference locations are the most lateral per session. (H) Same as D. (I) Same as E. Reference locations are the most central per session.

**Figure 3. Ripples generation differences along the hippocampal longitudinal axis.**

(A) Ripple seed location comparison between the three reference locations in common ripples (left) and strong ripples (right). Majority of common ripples seeds are located in the lateral hippocampal section regardless of the reference location (medial reference = 42.43 ± 1.67 %, central reference = 43.77 ± 2.04 %, lateral reference = 42.83 ± 2.89 %). (B) Ripple seed location comparison between strong and common ripples using a medial (left), central (center) or lateral reference (right). 225 CA1 locations in 25 sessions. Asterisks mean P<0.05, Kruskal-Wallis test with pairwise Mann-Whitney post-hoc test.

**Figure 4. Ripples travelling in the medio→lateral direction show prolonged neural circuit engagement.**

(A) Recording location for session 771990200. Circles colors indicate medio-lateral location. Bigger circle represents the reference location. (B) Spiking activity across the hippocampal M-L axis associated with a ripple generated medially (left column) or lateraly (right column) across the different recording location from session 771990200. Spike raster plot and normalized density are plotted at each M-L location. In the top row filtered ripple, grey traces represents raw LFP signal. All plots are color coded according to A. Scale bar: 0.5 mV. (C) Kernel density estimates of the average spiking activity across different M-L locations and between seed type. Scale bar: 5 spikes per 10 ms. (D) Interpolated heatmap of the difference between medially and laterally generated ripple induced spiking activity in session 771990200. Vertical dashed lines represent borders between early and late post-ripple start phases. Horizontal dashed lines represent the spatial limits of the hippocampal sections. (E) Grand average of the differences between medially and laterally initiated ripple induced spiking activity across 24 sessions. Vertical dashed lines represent borders between early and late post-ripple start phases. Horizontal dashed lines represent the spatial limits of the hippocampal sections. (F) Regression plot between M-L location and ripple duration in common and strong ripples. Horizontal dashed lines represent the spatial limits of the hippocampal sections. (G) Average fraction of active neurons in medial (pink) and lateral (purple) ripples. Early/medial seed = 0.3 ± 0.69, early/lateral seed: 31.72 ± 0.84, p-value = 3.23e-05, Student's t-test; late/medial seed = 24.57 ± 0.64, late/lateral seed = 19.44 ± 0.58, p-value = 4.09e-07, Student's t-test. (H) Average spiking rate medial (pink) and lateral (purple) ripples. Early/medial seed = 0.12 ± 0.004, early/lateral seed = 0.13 ± 0.005, p-value = 1.35e-04, Student's t-test; late/medial seed =0.07 ± 0.002, late/lateral seed = 0.05 ± 0.002, p-valu = 1.24e-12, Student's t-test.