

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. We analyzed ripple propagation within the hippocampal formation in a large open access dataset comprising 267 Neuropixel recordings in 49 awake, head-fixed mice. Surprisingly, strong ripples (top 10% in ripple strength) propagate differentially depending on their generation point along the hippocampal longitudinal axis. The septal hippocampal pole is able to generate longer ripples that engage more neurons and elicit spiking activity for an extended time even at considerable distances. Accordingly, a substantial portion of the variance in strong ripple duration ($R^2 = 0.463$) is explained by the ripple generation location on the longitudinal axis. Our results are consistent with a possible distinctive role of the hippocampal septal pole in conditions of high memory demand.

32 Introduction

33 Hippocampal ripples are brief oscillatory events detected in the local field potential (LFP) of
34 the hippocampal formation, these events correspond to the synchronized depolarization of a
35 substantial number of neurons in various hippocampal subregions (Hulse et al., 2016, Ylinen
36 et al., 1995). An higher ripple incidence during memory encoding is associated with superior
37 recall performance (Norman et al., 2019), furthermore, ripple incidence is increased during
38 successful memory retrieval (Vaz et al., 2019, Carr et al., 2011). Ripples are also involved in
39 memory consolidation both in awake and sleep conditions (Jadhav et al., 2012, Roux et al.,
40 2017, Sirota et al., 2003, Girardeau et al., 2009), disrupting awake ripples during learning
41 causes a persisting performance degradation, the same effect can be achieved by silencing
42 ripples during post-learning sleep. Accordingly, ripples are considered to play a crucial role in
43 memory processes and reorganization of memory engrams (Girardeau and Zugaro, 2011,
44 Buzsáki, 2015, Diba and Buzsáki, 2007, Foster and Wilson, 2006, Xu et al., 2019, Takahashi,
45 2015, Davidson et al., 2009, Pfeiffer and Foster, 2015, Dragoi and Tonegawa, 2011, Girardeau
46 et al., 2009). Ripples duration exhibits a skewed distribution with only a minority of long-
47 duration ripples (> 100 ms). The fraction of long-duration ripples, ripple amplitude and within-
48 ripple firing rate of both excitatory and inhibitory neurons are increased in both novel contexts
49 and memory-demanding tasks (Fernández-Ruiz et al., 2019). Reducing ripple duration
50 artificially causes a degraded working memory performance (Jadhav et al., 2012, Fernández-
51 Ruiz et al., 2019) and, on the contrary, prolongation induced by optogenetic-activation has a
52 beneficial effect (Fernández-Ruiz et al., 2019). Importantly, the artificial recruitment of
53 additional neurons seems to be constrained by pre-existing resting potential dynamics
54 (Noguchi et al., 2022). Hippocampal-neocortical interactions, suggested to be important for
55 memory consolidation (Klinzing et al., 2019, Gais et al., 2007, Tukker et al., 2020), are
56 increased specifically during long-duration compared to short-duration ripples (Ngo et al.,
57 2020).

58 Ripple amplitude and duration are significantly correlated (Tong et al., 2021, Patel et al., 2013),
59 moreover, they are both related to the amount of underlying spiking activity (Tong et al., 2021,
60 Khodagholy et al., 2017). It is possible to combine ripple strength and amplitude by
61 considering the area of the high-pass filtered envelope ('ripple strength').

62 These results point at a specific role of strong ripples (ripples with high strength) in situations
63 of high mnemonic demand and are consistent with a possible power law distribution where a
64 minority of ripples is responsible for a substantial part of memory requirements. For this
65 reason, it is of interest to identify the possible electrophysiological peculiarities of this

66 subgroup of ripples. Do strong ripples propagate differently compared to common ripples?
67 Are strong ripples generated homogeneously along the hippocampal longitudinal axis? Do
68 ripples have a preferred longitudinal directionality? In this study we focused our attention on
69 ripples generation and propagation within the hippocampal formation. Hippocampal
70 connectivity with cortical and sub-cortical areas varies considerably along the longitudinal
71 axis (Moser and Moser, 1998, Fanselow and Dong, 2010) and gene expression, as well,
72 exhibits both gradual and discrete transitions along the same axis (Vogel et al., 2020, Strange
73 et al., 2014). Consequently, the hippocampus is considered to be functionally segmented
74 along its long axis. The different connectivity contributes to explain the functional organization
75 gradient between a predominantly spatio-visual (septal pole) and emotional (temporal pole)
76 processing. Ripples generated in the septal and temporal hippocampal pole have already
77 been shown to be temporally independent and able to engage different neuron
78 subpopulations, even in the same downstream brain area (Sosa et al., 2020). Consequentially,
79 a heterogeneous ripple generation chance along the longitudinal axis most probably has an
80 impact on the frequency with which different brain areas and neurons subgroups are activated
81 by ripples. Our work is based on a dataset provided by the Allen Institute (Siegle et al., 2021),
82 this dataset enabled us to study comprehensively ripples features across the septal half of
83 the hippocampus. Previous studies have looked at ripple propagation along the longitudinal
84 axes of the hippocampus (Patel et al., 2013, Kumar and Deshmukh, 2020), however, the size
85 of this dataset made it possible to unveil propagation details previously overlooked.

86 **Results**

87 **Distance explains most of the ripple strength correlation variability.**

88 We studied ripple propagation along the hippocampal longitudinal axis in an open-access
89 dataset provided by the Allen Institute. We analyzed the LFP signals across the visual cortex,
90 hippocampal formation and brain stem (Supplementary Figure 1) simultaneous to ripples
91 detected in the CA1 of 49 animals (average session duration = 9877.4 ± 43.1 seconds, average
92 ripple incidence during non-running epochs = 2.49 ± 0.12 per 10s). Ripples (n ripples =
93 120462) were detected on the CA1 channel with the strongest ripple activity. Ripple strength
94 (J_{Ripple}) was calculated as the integral of the filtered LFP envelope between the start and end
95 points for every detected ripple. Ripple strength and duration are highly correlated in each
96 session (mean $r = 0.87 \pm 0.005$, Supplementary Figure 2). Notably ripple strength correlates
97 significantly better with the hippocampal population spiking rate on a ripple-to-ripple basis

98 compared to ripple duration alone ($p = 4.31e-11$, Supplementary Figure 3). Clear ripples were
99 observed uniquely in the hippocampal formation (CA1, CA2, CA3, DG, SUB, ProS). Likewise,
100 ripple-induced voltage deflections (RIVD, integral of the unfiltered LFP envelope) were also
101 noticeably stronger in hippocampal areas (Supplementary Figure 4B-F). Ripple strength was
102 noticeably irregular in single sessions both across time and space, even within the CA1 region
103 (Supplementary Figure 4C). We focused on the variability in ripple strength across pairs of
104 CA1 recording locations with clear ripple activity (n CA1 pairs = 303, n sessions = 46).
105 Correlation of ripple strength across different CA1 regions was highly variable (Figure 1A-B-
106 C) with a lower and upper quartiles of 0.66 and 0.87 (mean = 0.76, SEM = 0.01). Distance
107 between recording location could explain the majority (57.6%) of this variability (Figure 1B)
108 with the top and bottom quartiles of ripple strength correlation showing significantly different
109 average distances (Figure 1C-D). Given the correlation variability we asked how reliably a
110 ripple can travel along the hippocampal longitudinal axis. To answer this question, we looked
111 at ripples lag in sessions that included both long-distance ($> 2126.66 \mu\text{m}$) and short-distance
112 ($< 857.29 \mu\text{m}$) CA1 recording pairs (n sessions = 32, n CA1 pairs = 64, Figure 1E). Reference
113 for the lag analysis was always the most medial recording location in each pair. Almost half of
114 the ripples in long-distance pairs ($49.3 \pm 2.2\%$) were detected in both locations (inside a 120
115 ms window centered on ripple start at the reference location). Unsurprisingly short-distance
116 pairs showed a more reliable propagation ($69.59 \pm 3.51\%$). Moreover, lag between long-
117 distance pairs had a much broader distribution (Figure 1F) and a significantly bigger absolute
118 lag (Figure 1G). Neither high nor short-distance pairs showed clear directionality (lag long-
119 distance = -1.14 ± 0.64 ms, lag short-distance = -0.5 ± 0.41 ms). Looking at the relationship
120 between lag and ripple strength in long-distance pairs, however, an asymmetric distribution
121 was apparent (Figure 1F top), suggestive of a possible interaction between these two
122 variables: stronger ripples appear to be predominantly associated with positive lags (i.e.
123 ripples moving medial→lateral). To further investigate this relationship we divided ripples into
124 two groups: strong (top 10% ripple strength per session at the reference location) and
125 common (remaining ripples). The septal half of the hippocampus was divided in three sections
126 with equal number of recordings: medial, central and lateral (Supplementary Figure 5). Strong
127 ripples identified in the medial section, in opposition to common ripples, showed a markedly
128 positive lag (lag = 17.83 ± 1.02 ms) indicative of a preferred medial→lateral travelling direction
129 (Figure 1H top). Surprisingly, the same was not true for strong ripples identified in the lateral
130 section (lag = 3.62 ± 1.05 ms, Figure 1I). Strong and common ripples lags were significantly
131 different between medial and lateral locations both in common and strong ripples. A biased

132 direction of propagation can be explained by an unequal chance of ripple generation across
133 space. We can assume that selecting strong ripples we are biasing our focus towards ripples
134 whose generation point (seed) is situated nearby our reference location, this would contribute
135 to explain the unbalanced lag. This notion would, however, fail to explain the different
136 directionality we observed between strong ripples in medial and lateral locations. This hints
137 at a more complex situation.

138 **Ripples propagates differentially along the hippocampal longitudinal axis.**

139 To analyze the propagation of ripples along the hippocampal longitudinal axis we focused on
140 sessions from which ripples were clearly detected in at least two different hippocampal
141 sections at the same time ($n = 41$). We followed the propagation of strong and common ripples
142 detected in the reference location across the hippocampus (Figure 2A-B) and built an average
143 spatio-temporal propagation map per session (Figure 2C). Strong and common ripples in the
144 medial section showed a divergent propagation pattern: strong ripples travelling
145 medio→laterally and common ripples travelling in the opposite direction (Figure 2D-E). Ripples
146 detected in the lateral section did not show such strikingly divergent propagation (Figure 2F-
147 G) whereas, in the central section, the propagation was divergent only laterally and not
148 medially (Figure 2H-I). This peculiar propagation profile suggests a not previously described
149 underlying directionality along the hippocampal longitudinal axis and can be possibly
150 explained by a spatial bias in strong ripples generation. To understand the mechanism
151 underlying such difference in propagation we examined the location of the seed for each ripple
152 in sessions in which ripples were clearly detected in every hippocampal section (n sessions =
153 25). While we found no differences in the number of ripples detected in each hippocampal
154 section (p -value = 0.55, Kruskal-Wallis test), we observed differences regarding ripple
155 generation. In common ripples, regardless of the reference location, most ripples started from
156 the lateral section (Figure 3A left). On the other hand, strong ripples displayed a more
157 heterogenous picture (Figure 3A right). We identified two principles relative to strong ripples
158 generation: In all hippocampal sections the majority of strong ripples are locally generated,
159 and a greater number of strong ripples is generated medially than laterally. Looking at the
160 central section we can appreciate the difference between the number of strong ripples
161 generated medially and laterally (Figure 3A right, mean medial = $36.83 \pm 2.66\%$, mean lateral
162 = $20.55 \pm 2.04\%$, p -value = $3e-05$, Pairwise Tukey test). Strong and common ripples had
163 significantly different seed location profiles only in the medial and central section, not in the
164 lateral section (Figure 3B). These seed location profiles contribute to explain the propagation

165 idiosyncrasies: major unbalances in seeds location cause propagation patterns with clear
166 directionality, on the contrary, lag measurements hovering around zero are the result of
167 averaging between two similarly numbered groups of ripples with opposite direction of
168 propagation. Notably, propagation speed did not change depending on the seed location
169 (Supplementary Figure 6). The reason why strong ripples are only in a minority of cases
170 generated in the lateral section remains nevertheless unclear. Using a 'strength conservation
171 index' (SCI) we measured the ability of a ripple to retain its strength during propagation (a
172 ripple with SCI = 1 is in the top 10% in all hippocampal sections). We observed that ripples
173 generated laterally were effectively less able to retain their strength propagating towards the
174 medial pole (Supplementary Figure 7). This result is not simply explained by differences in
175 ripple strength along the medio-lateral (M-L) axis, as no such gradient was observed ($R^2 =$
176 0.0012 , Supplementary Figure 8). Curiously, ripple amplitude showed a weak trend in the
177 opposite direction ($r = 0.25$, $p\text{-value} = 7.21e-04$), with higher amplitude ripples in the lateral
178 section (Supplementary Figure 9).

179 **The hippocampal medial pole can generate longer ripples able to better engage neural** 180 **networks.**

181 To understand the reason behind the differential propagation we focused uniquely on the
182 central section, here it was possible to distinguish between ripples generated laterally or
183 medially ('lateral ripples' and 'medial ripples'). We included in the analysis sessions in which
184 ripples were clearly detected in each hippocampal section and with at least 100 ripples of
185 each kind (n sessions = 24). We looked at spiking activity associated with these two classes
186 of ripples in the hippocampal formation across the M-L axis (n clusters per session = 650.42
187 ± 33.16 , Figure 4A-B-C). To compare sessions, we created interpolated maps of the difference
188 between spiking induced by medial and lateral ripples (Figure 4D). Immediately following
189 ripple start (0-50 ms, "early phase") spiking was predictably influenced by ripple seed
190 proximity: in the lateral section lateral ripples induced more spiking (indicated by the blue
191 color), whereas in the medial section medial ripples dominated (indicated by the red color).
192 Surprisingly, in the 50-120 ms window post ripple start ("late phase"), medial ripples could
193 elicit significantly higher spiking activity than lateral ripples along the entire M-L axis (Figure
194 4E). Dividing clusters in putative excitatory and inhibitory using the waveform duration we
195 observed the same effect in both types of neurons (Supplementary Figure 10). In accordance
196 with this result, we found that the medial hippocampal section is able to generate longer
197 ripples (Figure 4F). An important portion of the variance in ripple duration is indeed explained

198 by location on the M-L axis both in common ($R^2 = 0.133$) and especially in strong ripples (R^2
199 = 0.463). The observed extended spiking could be due to a increased number of neurons
200 participating in the ripple, to a higher spiking rate per neuron or a combination of these two
201 elements. Fraction of active neurons and spiking rate were both significantly higher in medial
202 ripples (Supplementary Figure 11). Focusing only on the late phase the difference in fraction
203 of active neurons per ripples between medial and lateral ripples was even more striking
204 (Cohen's $d = 1.7$, Figure 4G). Inversely, in the early phase, lateral ripples could engage more
205 neurons, although, the effect size was much smaller (Cohen's $d = 0.39$). The same result was
206 found in relation to the spiking rate, medial ripples caused a significant and considerable
207 increase in spiking rate in the late phase (Cohen's $d = 1.75$, Figure 4H). Dividing again the
208 clusters into putative excitatory and inhibitory, significant differences between medial and
209 lateral ripples were present only in the late phase. Spiking frequency and number of engaged
210 neurons were significantly higher in medial ripples both in putative excitatory and inhibitory
211 clusters (Supplementary Figure 12). In summary, the prolonged spiking observed in medial
212 ripples was caused both by an increased number of engaged neurons and a higher spiking
213 rate per cell, both in putative excitatory and inhibitory neurons. The disparity in network
214 engagement can possibly be in part explained by electrophysiological differences across
215 hippocampal sections (e.g. higher firing rate). We did not find differences in the number of
216 firing neurons (medial = 74.73, lateral = 79.8, p -value = $3.56e-01$, Mann-Whitney U test), we
217 did, however, found differences in firing rate, waveform duration, and waveform shape
218 (recovery slope and peak-through ratio, Supplementary Figure 13). Firing rate and waveform
219 duration exhibited respectively a left- and right-shifted distribution in the lateral section,
220 reflecting lower firing rate and slower action potentials.

221 **Discussion**

222 Our results show for the first time that strong ripples propagate differentially along the
223 hippocampal longitudinal axis. This propagation idiosyncrasy can be explained by a specific
224 ability of the hippocampal septal pole (medial section in our analysis) to produce longer ripples
225 that better entrain the hippocampal network and spread across the longitudinal axis. It was
226 previously observed that ripples located at the septal and temporal pole are generated
227 independently from each other, in addition, despite the presence of connections within the
228 hippocampal longitudinal axis (Witter, 2007, van Strien et al., 2009), in the vast majority of
229 cases ripples do not propagate to the opposite pole (Sosa et al., 2020). In accordance with

230 these results, we observed a strong effect of spatial distance on ripple strength correlation
231 confirming a previous study (Nitzan et al., 2022): the strength correlation, predictably, was
232 higher in CA1 pairs closer to each other. The effect of distance was also apparent on the ripple
233 chance of propagation, only half of the ripples generated in the septal pole were detected
234 additionally in the intermediate hippocampus (lateral section in our analysis). This chance is
235 much higher compared to the ~3.7% reported regarding propagation between opposite poles
236 (Sosa et al., 2020), it would be interesting to understand whether the temporal pole is also
237 able to entrain the intermediate hippocampus in similar fashion or it is a peculiarity of the
238 septal pole. A limitation of our work derives from the dataset being limited to the septal and
239 intermediate hippocampus.

240 Ripples can arise at any location along the hippocampal longitudinal axis (Patel et al., 2013).
241 Our analysis shows that ripples are, however, not homogeneously generated across space.
242 We observed important differences between strong ripples and common ripples generation.
243 Common ripples followed a gradient with higher generation probability in the intermediate
244 section and lowest in the septal pole. Strong ripples, on the other hand, were mostly
245 generated locally (i.e. a strong ripple detected in the medial section is most likely generated
246 in the medial section itself). Furthermore, only rarely a strong ripple generated in the
247 intermediate hippocampus is able to propagate towards the septal pole retaining its strong
248 status (top 10%). Conversely strong ripples generated in the septal pole have a significantly
249 higher chance of propagate longitudinally and still be in the top 10% in terms of ripple
250 strength. Notably, this is not consequence of a simple longitudinal gradient in ripple strength,
251 indeed, we did not observe any difference in ripple strength along the longitudinal axis.
252 Additionally, we show that ripples generated in the septal pole and in the intermediate
253 hippocampus have a significantly different ability to engage hippocampal networks in the 50-
254 120 ms window post ripple start. Ripples generated in the septal pole activate more neurons,
255 both excitatory and inhibitory, and, moreover, elicit an higher spiking rate per neuron. This
256 prolonged network activation is reflected by the fact that the position on the longitudinal axis
257 explains 13.3% and 46.3% of the variability in ripple duration in common and strong ripples
258 respectively. Consistent with a duration gradient along the longitudinal axis, the temporal
259 hippocampus has been shown to produce shorter ripples both in awake and sleep conditions
260 (Sosa et al., 2020).

261 What is the reason that enables the septal pole to generate longer ripples? There might be for
262 example underlying electrophysiological differences between the septal and intermediate
263 hippocampus. Looking at units electrophysiological features we found some differences in

264 the waveform shape and duration. We can hypothesize that slower action potentials and,
265 consequentially, longer refractory periods hinder the ability to sustain protracted high
266 frequency spiking. Accordingly, we found an increased firing rate and a smaller waveform
267 duration in the septal pole. This might contribute to explain the prolonged ripples observed in
268 the septal pole. We can also speculate that the neuromodulatory inputs gradient, monoamine
269 fibers have been shown to be stronger in the ventral part (Strange et al., 2014), might influence
270 neurons responses. Serotonin (ul Haq et al., 2016, Wang et al., 2015), noradrenaline (Ul Haq
271 et al., 2012, Novitskaya et al., 2016) and acetylcholine (Zhang et al., 2021) have all been shown
272 to suppress ripples. In accordance with this, some ripples are coupled with a reduced
273 activation of the locus coeruleus and the dorsal raphe nucleus in vivo (Ramirez-Villegas et al.,
274 2015).

275 Ripples can be subdivided in different types according to the relationship between the
276 hippocampal LFP and the ripple itself (Ramirez-Villegas et al., 2015). Intriguingly these
277 subtypes are associated with two different brain-wide networks, the first communicating
278 preferentially with the associative neocortex and a second one biased towards subcortical
279 structures. Moreover, these different types of ripples have been proposed to possibly fulfill
280 different functional roles. Given the different input/output connectivity between septal,
281 intermediate and temporal hippocampus (Fanselow and Dong, 2010) we hypothesize that
282 ripple generated at different points of the hippocampal longitudinal axis might as well have
283 functional differences, with the longer ripples generated septally possibly able to combine the
284 different kind of informations processed in the distinct hippocampal sections and additionally
285 relaying the integrated information back to the neocortex in accordance with the two-stage
286 memory hypothesis (Diekelmann and Born, 2010, Marr, 1971, Buzsáki, 1989, Rasch and Born,
287 2007, McClelland et al., 1995).

288 Long duration ripples have been shown to be of particular importance in situations of high-
289 memory demand (Fernández-Ruiz et al., 2019), at the same time, previous studies highlighted
290 the role of septal hippocampus in memory tasks and information processing (Hock and
291 Bunsey, 1998, Moser et al., 1993, Moser et al., 1995, Steffenach et al., 2005, Kheirbek et al.,
292 2013, McGlinchey and Aston-Jones, 2018, Fanselow and Dong, 2010, Maras et al., 2014,
293 Bradfield et al., 2020, Qin et al., 2020). Our results can contribute to explain the specific role
294 of septal hippocampus in memory-demanding tasks with its ability of generating particularly
295 long ripples that are able to strongly engage networks in the entire top half of the hippocampal
296 formation for an extended time.

297 **Materials and Methods**

298 **Dataset**

299 Our analysis was based on the Visual Coding - Neuropixels dataset provided by the Allen
300 Institute and available at
301 https://allensdk.readthedocs.io/en/latest/visual_coding_neuropixels.html. We excluded 6
302 sessions because of absence of recording electrodes in CA1 (session ids=732592105,
303 737581020, 739448407, 742951821, 760693773, 762120172). Furthermore, one session was
304 excluded (session id = 743475441) because of an artifact in the LFP time series (time was not
305 monotonically increasing) and two other sessions (session ids = 746083955,
306 756029989) because of duplicated LFP traces (see
307 [https://github.com/RobertoDF/Allen_visual_dataset_artifacts/blob/main/check_lfp_errors_fro](https://github.com/RobertoDF/Allen_visual_dataset_artifacts/blob/main/check_lfp_errors_from_files.ipynb)
308 [m_files.ipynb](https://github.com/RobertoDF/Allen_visual_dataset_artifacts/blob/main/check_lfp_errors_from_files.ipynb)). Our analysis was therefore focused on 49 sessions, average animal age =
309 119.22 ± 1.81 . Sex: males $n = 38$, females $n = 11$. Genotypes: wt/wt $n = 26$, Sst-IRES-
310 Cre/wt;Ai32(RCL-ChR2(H134R)_EYFP)/wt $n = 10$, Vip-IRES-Cre/wt;Ai32(RCL-
311 ChR2(H134R)_EYFP)/wt $n = 7$, Pvalb-IRES-Cre/wt;Ai32(RCL-ChR2(H134R)_EYFP)/wt $n = 6$.
312 Average probe count per session = 5.73 ± 0.08 . Average number of recording channels per
313 session = 2129.45 ± 29.46 . Probes in each session were numbered according to the position
314 on the M-L axis, with probe number 0 being the most medial. Channels with ambiguous area
315 annotations were discarded (e.g. HPF instead of CA1). We found a number of of small artifacts
316 in a variety of sessions, all this timepoints were excluded from the analysis (for more
317 informations: https://github.com/RobertoDF/Allen_visual_dataset_artifacts). Further details
318 about data acquisition can be found at [https://brainmapportal-live-4cc80a57cd6e400d854-](https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf)
319 [f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-](https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf)
320 [569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf](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
321 locations was performed with brainrender (Claudi et al., 2021).

322 **Ripples detection**

323 The LFP traces sampled at 1250 Hz were filtered using a 6th order Butterworth bandpass filter
324 between 120.0 and 250.0. Ripples were detected on CA1 LFP traces, the best channel (higher
325 ripple strength) was selected by looking at the SD of the envelope of the filtered trace, if
326 multiple SD peaks were present across space (possibly caused by sharp waves in stratum
327 radiatum and ripple activity in stratum pyramidale) we subsequently looked at the channel
328 with higher skewness, in this way we could reliably identify the best ripple channel. The

329 envelope of the filtered trace was calculated using the Hilbert transform (`scipy.signal.hilbert`).
330 Ripple threshold was set at 5 SDs. Start and stop times were calculated using a 2 SDs
331 threshold on the smoothed envelope with `window = 5` (`pandas.DataFrame.rolling`) to account
332 for ripple phase distortions. Ripple amplitude was calculated as the 90th percentile of the
333 envelope. Ripple duration was limited at > 0.015 s and < 0.25 s. Candidate ripples with starting
334 times closer than 0.05 s were joined in a single ripple with peak amplitude being the highest
335 between the candidates. We estimated power density of each candidate using a periodogram
336 with constant detrending (`scipy.signal.periodogram`) on the raw LFP trace, we checked the
337 presence of a peak > 100 Hz, candidates not fulfilling this condition were discarded, this
338 condition was meant to reduce the number of detected false positives. Ripple candidates
339 detected during running epochs were discarded, an animal was considered to be running if
340 his standardized speed was higher than the 10th percentile plus 0.06. Candidates were also
341 discarded if no behavioral data was available. Code for the detection of ripples resides in
342 'Calculate_ripples.py'.

343 **Correlation and lag analysis**

344 In each session we uniquely used ripples from the CA1 channel with the strongest ripple
345 activity, we looked at the LFP activity in all brain areas recorded in a window of 100.0 ms pre
346 ripple start and 200.0 ms post ripple start, this broad windows account for possible travelling
347 delays due to distance. For each brain area we picked the channel with higher SD of the
348 envelope of the filtered trace. For each ripple considered we calculated integral of the
349 envelope of the filtered trace (\int Ripple) and the integral of the raw LFP (ripple-induced voltage
350 deflection, RIVD). After discarding channels with weak ripple activity (envelope variance < 5),
351 we computed the pairwise pearson correlation of the envelope traces of CA1 channels
352 (`pandas.DataFrame.corr`). For the lag analysis we first identified pairs of CA1 that satisfied a
353 distance requirements. Distance threshold were set at 25% (857.29 μ m) and 75% (2126.66
354 μ m) of the totality of distances. For each ripple detected in the reference channel we identified
355 the nearest neighbour in the other channel. The analysis was repeated after dividing ripples in
356 strong (top 10% \int Ripple) and common ripples (all remaining ripples) per session. Code for the
357 correlation and lag analysis resides in 'Calculations_Figure_1.py'.

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

359 The hippocampus was divided in three section with equal number of recordings. Channels
360 with weak ripple activity (envelope variance < 5) were discarded. Sessions with recording

361 locations only in one hippocampal sections or with less than 1000 ripples in the channel with
362 strongest ripple activity were discarded as well. For each ripple detected on the reference
363 CA1 channel we identified ripples in other CA1 channels happening in a window of ± 60.0 ms,
364 this events were grouped together in a 'cluster'. If more than one event was detected on the
365 same probe we kept only the first event. 'Clusters' were subsequently divided according to
366 \int Ripple on the reference electrode in strong and common ripples. Lag maps were result of
367 averaging lags for each probe. Code for the calculations of propagation maps resides in
368 'Calculate_trajectories.py'.

369 **Ripple-associated spiking activity**

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

384 **Units selection and features calculations**

385 Clusters were filtered according to the following parameters: Waveform peak-trough ratio $<$
386 5, ISI violations < 0.5 , amplitude cutoff < 0.1 and Presence ratio > 0.1 . For an explanation of
387 the parameters see
388 [https://github.com/AllenInstitute/ecephys_spike_sorting/blob/master/ecephys_spike_sorting](https://github.com/AllenInstitute/ecephys_spike_sorting/blob/master/ecephys_spike_sorting/modules/quality_metrics/README.md)
389 [/modules/quality_metrics/README.md](https://github.com/AllenInstitute/ecephys_spike_sorting/blob/master/ecephys_spike_sorting/modules/quality_metrics/README.md) and [https://brainmapportal-live-](https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf)
390 [4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-](https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf)
391 [b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf](https://brainmapportal-live-4cc80a57cd6e400d854-f7fdcae.divio-media.net/filer_public/80/75/8075a100-ca64-429a-b39a-569121b612b2/neuropixels_visual_coding_-_white_paper_v10.pdf). Firing rate was
392 calculated on all clusters with presence ratio > 0.1 .

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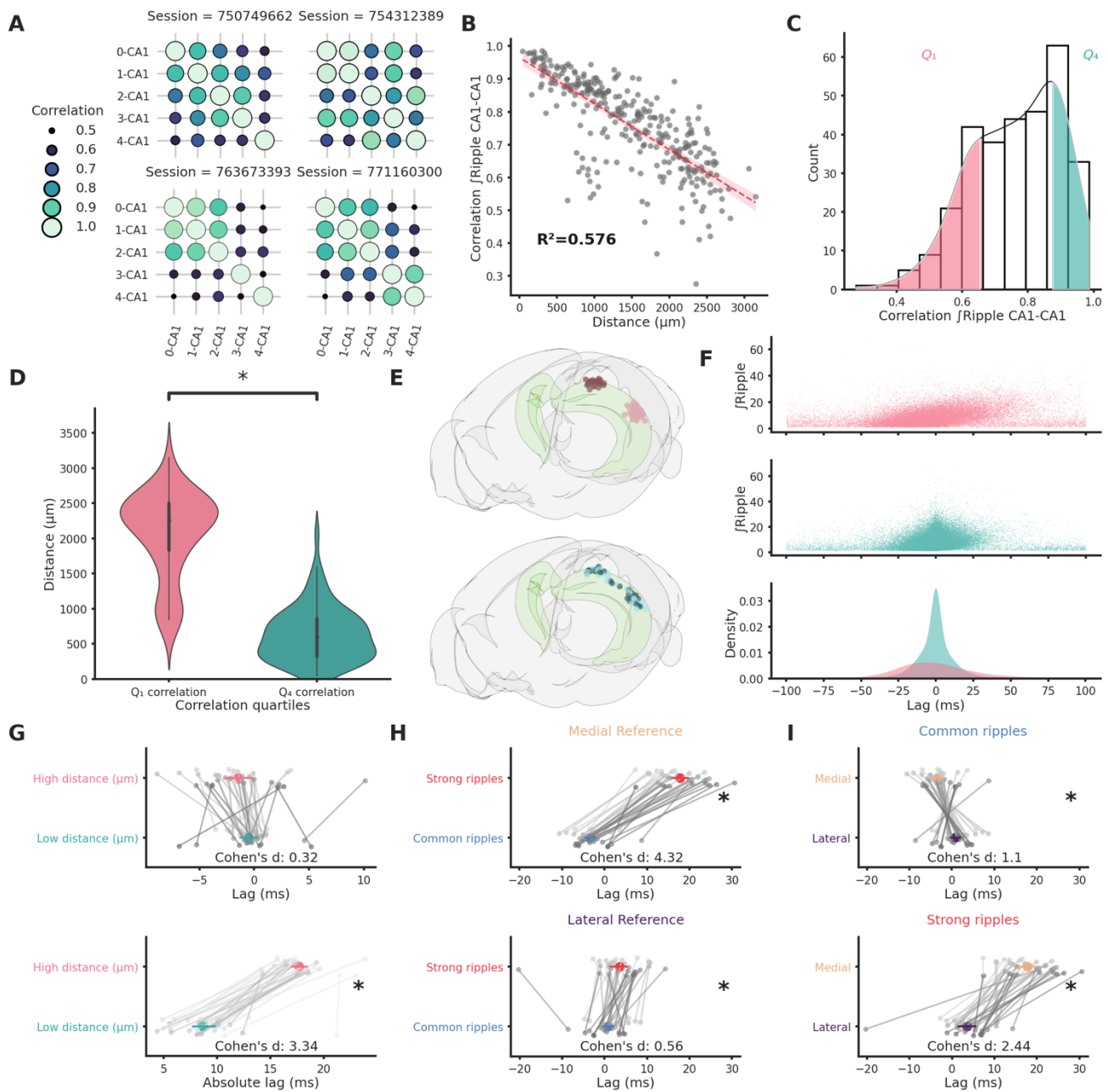
403 **Contributions**

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

406 **Data and materials availability**

407 All the code used to process the dataset is available at [https://github.com/RobertoDF/De-](https://github.com/RobertoDF/De-Filippo-et-al-2022)
408 [Filippo-et-al-2022](https://github.com/RobertoDF/De-Filippo-et-al-2022), pre-computed data structures can be downloaded at
409 [10.6084/m9.figshare.20209913](https://github.com/RobertoDF/De-Filippo-et-al-2022). All figures and text can be reproduced using code present in
410 this repository, each number present in the text is directly linked to a python data structure.
411 The original dataset is provided by the Allen Institute and available at
412 https://allensdk.readthedocs.io/en/latest/visual_coding_neuropixels.html.

413 Figures



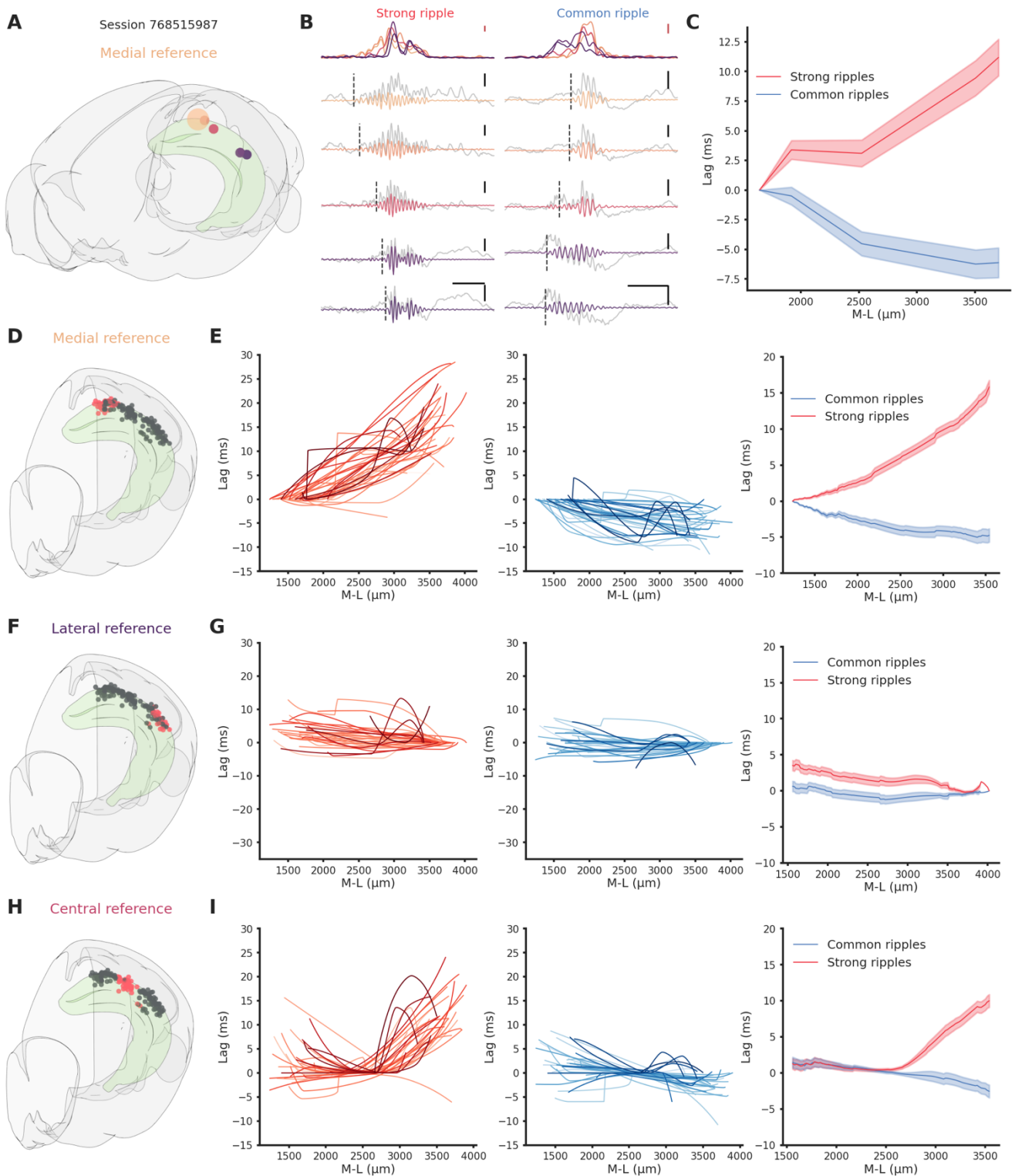
414

415 **Figure 1. Ripple strength correlation depends significantly on distance.**

416 (A) Correlation matrices showing the variability of ripple strength correlation between pairs of
 417 recording sites located in different CA1 locations in 4 example sessions. The number on the
 418 x and y axis labels indicates the probe number. Probes are numbered according to the
 419 position on the hippocampal longitudinal axis (0 is the most medial probe). (B) Scatter plot
 420 and linear regression showing the relationship between distance and correlation strength.
 421 Distance between recording sites explains 0.576% of the variability in correlation of ripple
 422 strength. (C) Ripple strength correlation distribution. Pink represents bottom 25% (Q_1) and
 423 blue top 25% (>math>Q_4</math>). (D) Violinplots showing that the top and bottom correlation quartile show

424 significantly different distance distributions (Q_1 : $2077.57 \pm 68.68 \mu\text{m}$, Q_4 : $633.56 \pm 44.02 \mu\text{m}$,
425 p -value = $4.00\text{e-}23$, Mann-Whitney U test). (E) Top: Rendering of the long distance (top) and
426 short distance (bottom) CA1 pairs, dark circles are the reference locations in each pair. (F) Top
427 and middle: scatter plots showing the relationship between ripple strength (at the reference
428 location) and lag for long distance (top, n ripples = 31855) and short distance (middle, n ripples
429 = 52858) pairs. Bottom: kernel density estimate of the lags of long distance (pink) and short
430 distance (turquoise) pairs. (G): Lag (top) and absolute lag (bottom) comparison between long
431 and short distance pairs (top: long distance = -1.47 ± 0.63 ms, Short distance = -0.51 ± 0.4
432 ms, p -value = $2.03\text{e-}01$, Student's t-test; bottom: long distance = 17.69 ± 0.38 ms, Short
433 distance = 8.69 ± 0.56 ms, p -value = $6.58\text{e-}20$, Student's t-test). (H) Lag comparison in long
434 distance pairs between common and strong ripples with reference located in the medial (top)
435 or lateral hippocampal section (bottom) (top: strong ripples = 17.83 ± 1.02 ms, common ripples
436 = -3.27 ± 0.68 ms, p -values = $2.28\text{e-}25$, Student's t-test, bottom: strong ripples = 3.62 ± 1.05
437 ms, common ripples = 0.88 ± 0.66 ms, p -values = $3.00\text{e-}02$, Student's t-test). (I) Lag
438 comparison in long distance pairs between ripples with reference located in the medial and
439 lateral section in common (top) or strong ripples (bottom) (top: medial reference = -3.27 ± 0.68
440 ms, lateral reference = 0.88 ± 0.66 ms, p -values = $4.30\text{e-}05$, Student's t-test, bottom: strong
441 ripples = 17.83 ± 1.02 ms, common ripples = 3.62 ± 1.05 ms, p -values = $4.30\text{e-}05$, Student's
442 t-test).
443

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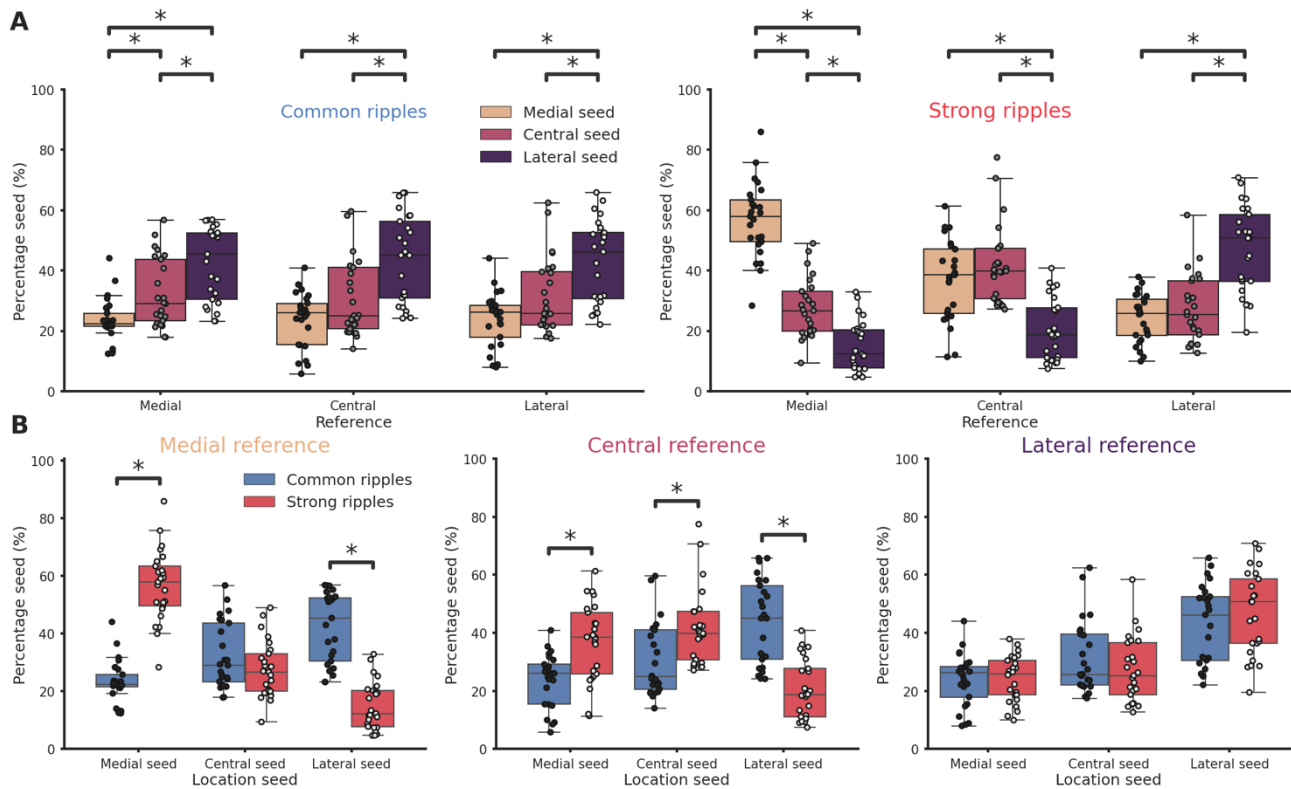


445

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

448 (A) Recording locations for session 768515987. Circles colors represents medio-lateral
449 location. Bigger circle represents the reference location. (B) Example propagation of a strong
450 (left column) and common (right column) ripple across the different recording location from
451 session 768515987, each filtered ripple is color-coded according to A. Grey traces represents

452 raw LFP signal. Dashed vertical line represents the start of the ripple. In the top row the ripple
453 envelope across all locations. Black scale bars: 50 ms, 0.5 mV. Red scale bars: 0.1 mV. (C)
454 Average propagation map of strong and common ripples in session 768515987 across the
455 medio-lateral axis. (D) Recording locations relative to E. Red circles represents the reference
456 locations across all sessions (n sessions=41), black circles represents the remaining recording
457 locations. (E) Left: Medio-lateral propagation of strong ripples, each line represents the
458 average of one session. Middle: Medio-lateral propagation of common ripples, each line
459 represents the average of one session. Right: Average propagation map across sessions of
460 strong and common ripples. Reference locations are the most lateral per session. (F) Same
461 as D. (G) Same as E. Reference locations are the most lateral per session. (H) Same as D. (I)
462 Same as E. Reference locations are the most central per session.
463

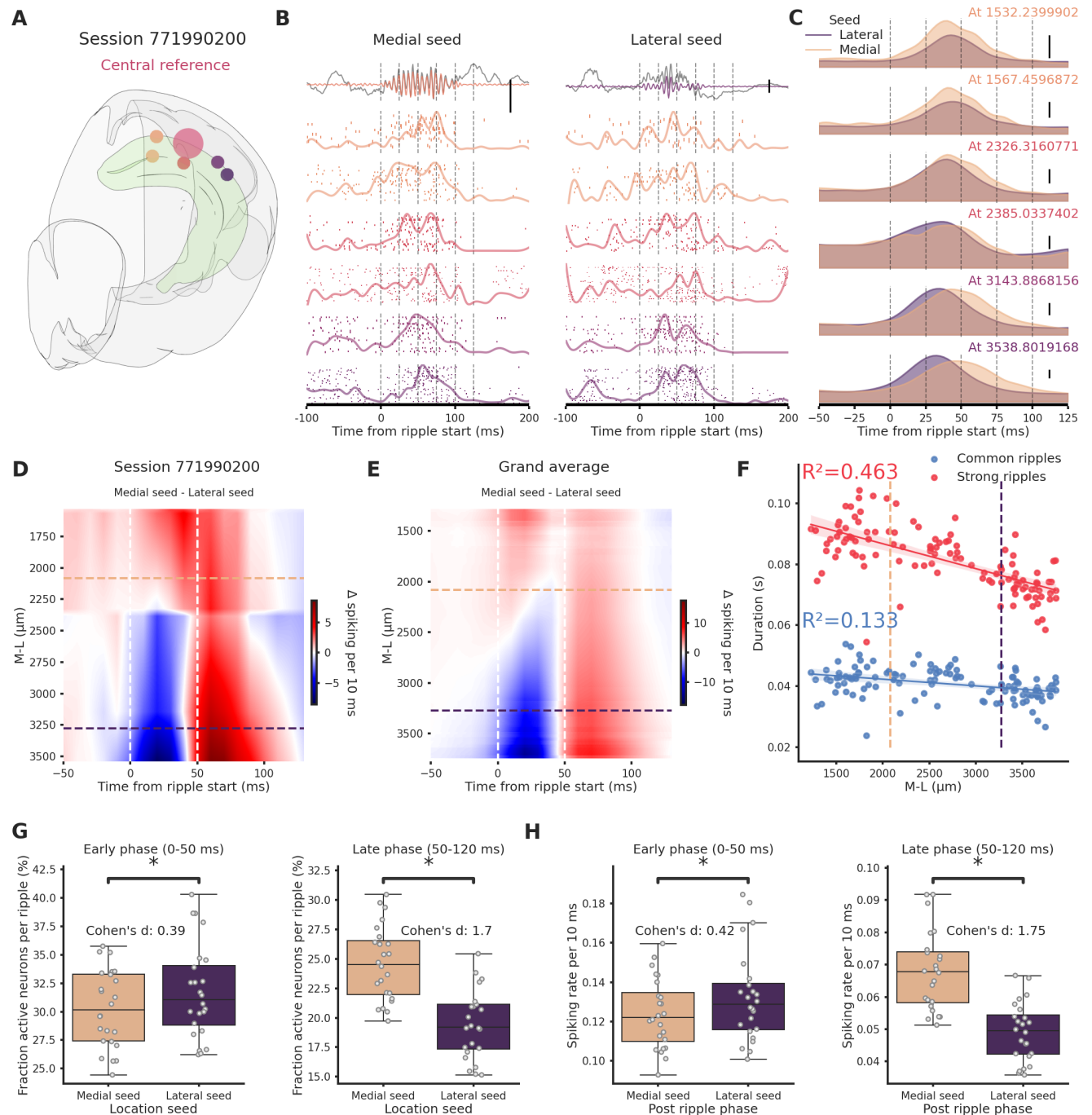


464

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

466 (A) Ripple seed location comparison between the three reference locations in common ripples
 467 (left) and strong ripples (right). Majority of common ripples seeds are located in the lateral
 468 hippocampal section regardless of the reference location (medial reference/lateral seed =
 469 42.43 ± 2.45 %, central reference/lateral seed = 43.77 ± 2.9 %, lateral reference/lateral seed
 470 = 42.83 ± 2.75 %). Strong ripples are mainly local (medial reference/medial seed = $56.78 \pm$
 471 2.48 %, central reference/central seed = 41.74 ± 2.58 %, lateral reference/lateral seed = 46.76
 472 ± 2.89 %). (B) Ripple seed location comparison between strong and common ripples using a
 473 medial (left), central (center) or lateral reference (right). Asterisks mean p < 0.05, Kruskal-Wallis
 474 test with pairwise Mann-Whitney post-hoc test.

475



476

477 **Figure 4. Ripples travelling in the medio→lateral direction show prolonged network**
478 **engagement.**

479 (A) Recording location for session 771990200. Circles colors indicate medio-lateral location.
480 Bigger circle represents the reference location. (B) Spiking activity across the hippocampal
481 M-L axis associated with a ripple generated medially (left column) or laterally (right column)
482 across the different recording location from session 771990200. Spike raster plot and
483 normalized density are plotted at each M-L location. In the top row filtered ripple, grey traces
484 represents raw LFP signal. All plots are color coded according to A. Scale bar: 0.5 mV. (C)
485 Kernel density estimates of the average spiking activity across different M-L locations and
486 between seed type. Scale bar: 5 spikes per 10 ms. (D) Interpolated heatmap of the difference

487 between medially and laterally generated ripple induced spiking activity in session 771990200.
488 Vertical dashed lines represent borders between early and late post-ripple start phases.
489 Horizontal dashed lines represent the spatial limits of the hippocampal sections. (E) Grand
490 average of the differences between medially and laterally initiated ripple induced spiking
491 activity across 24 sessions. Vertical dashed lines represent borders between early and late
492 post-ripple start phases. Horizontal dashed lines represent the spatial limits of the
493 hippocampal sections. (F) Regression plot between M-L location and ripple duration in
494 common and strong ripples. Horizontal dashed lines represent the spatial limits of the
495 hippocampal sections. (G) Average fraction of active neurons in medial (pink) and lateral
496 (purple) ripples. Early/medial seed = 0.3 ± 0.69 , early/lateral seed: 31.72 ± 0.84 , p-value =
497 $3.23e-05$, Student's t-test; late/medial seed = 24.57 ± 0.64 , late/lateral seed = 19.44 ± 0.58 ,
498 p-value = $4.09e-07$, Student's t-test. (H) Average spiking rate medial (pink) and lateral (purple)
499 ripples. Early/medial seed = 0.12 ± 0.004 , early/lateral seed = 0.13 ± 0.005 , p-value = $1.35e-$
500 04 , Student's t-test; late/medial seed = 0.07 ± 0.002 , late/lateral seed = 0.05 ± 0.002 , p-value
501 = $1.24e-12$, Student's t-test.
502

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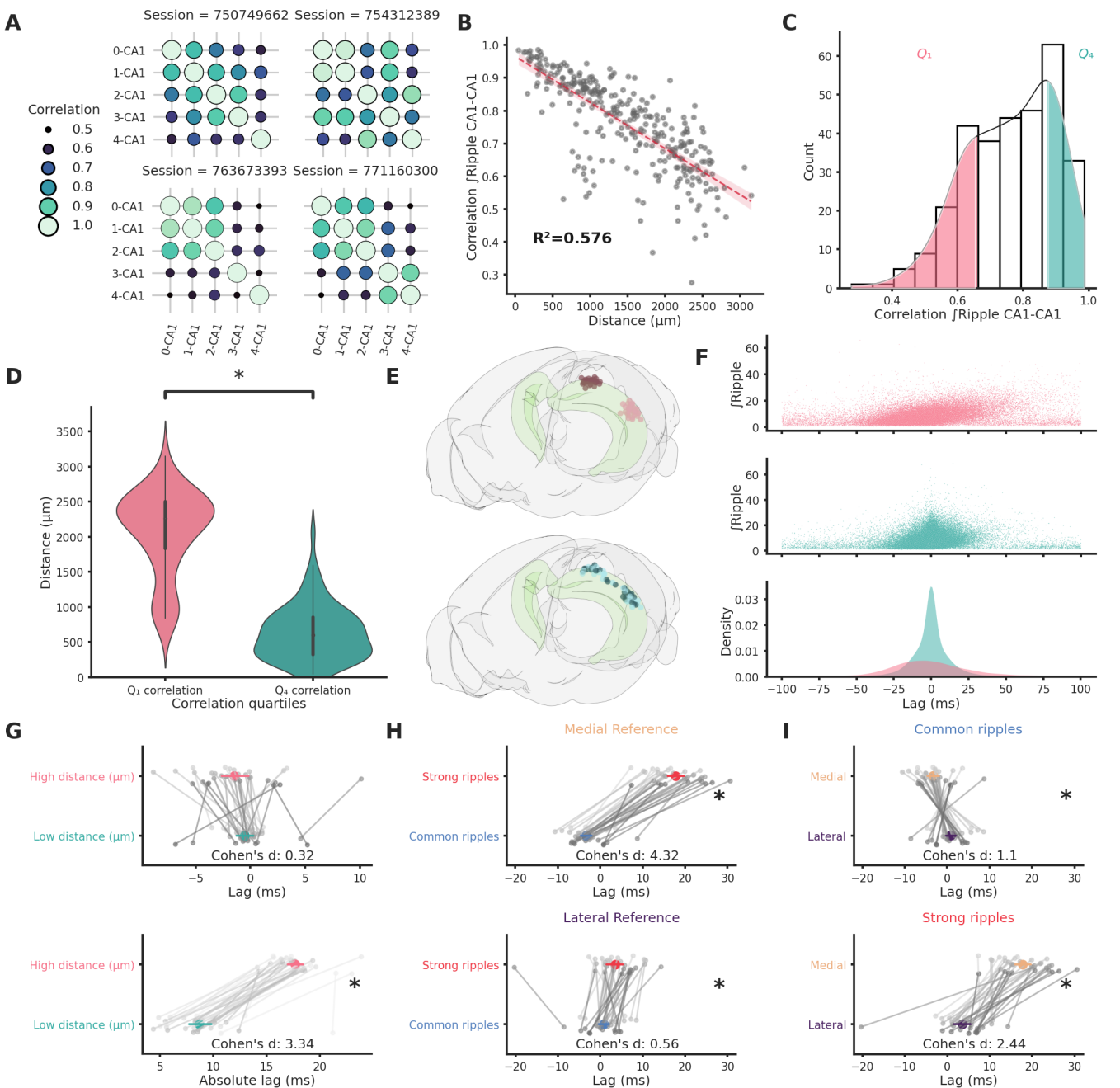
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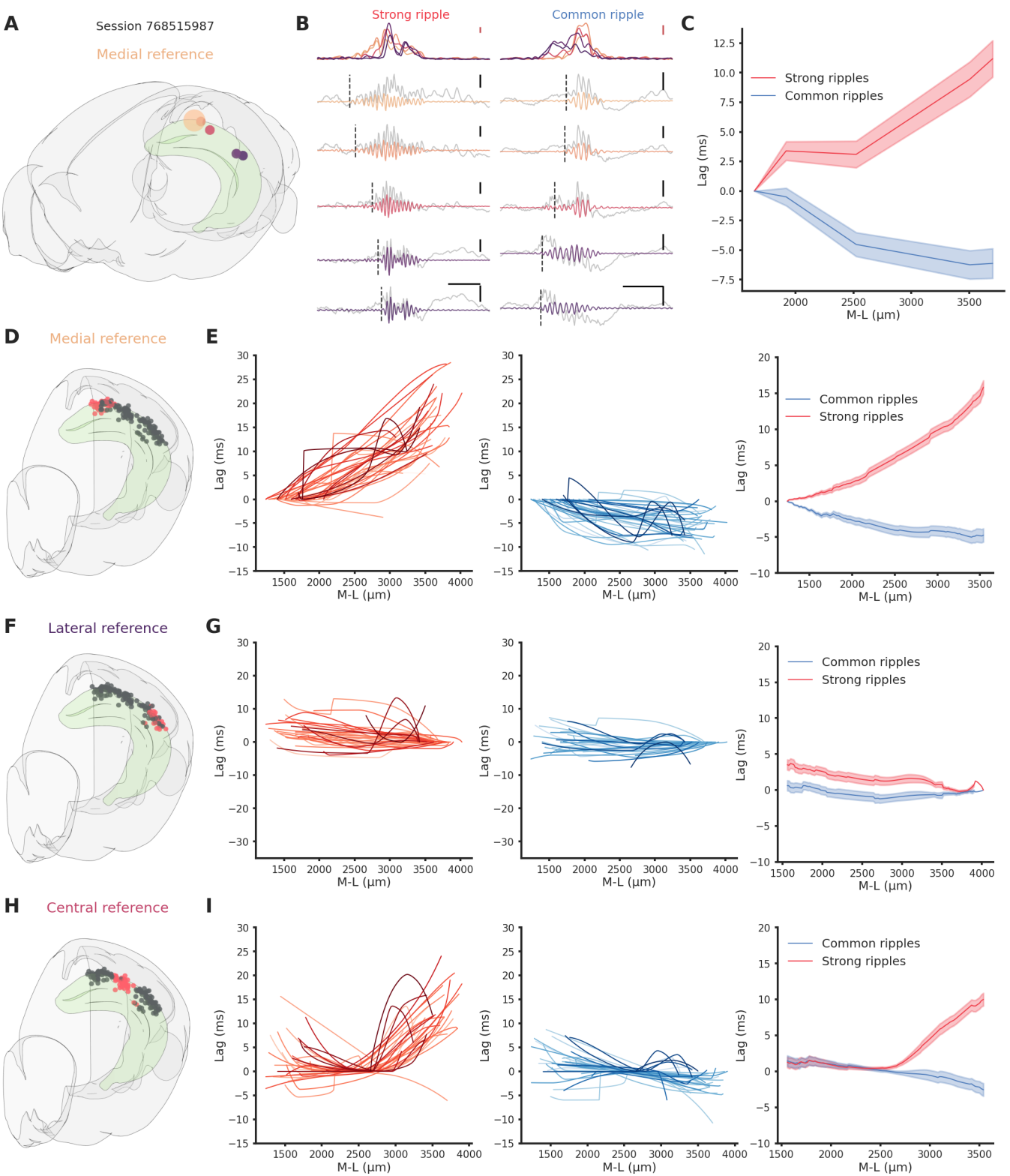
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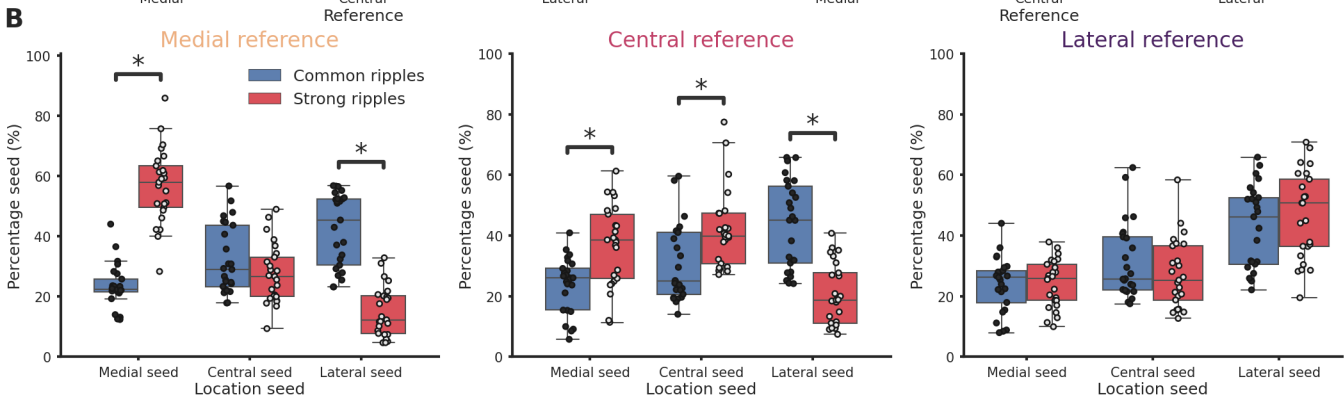
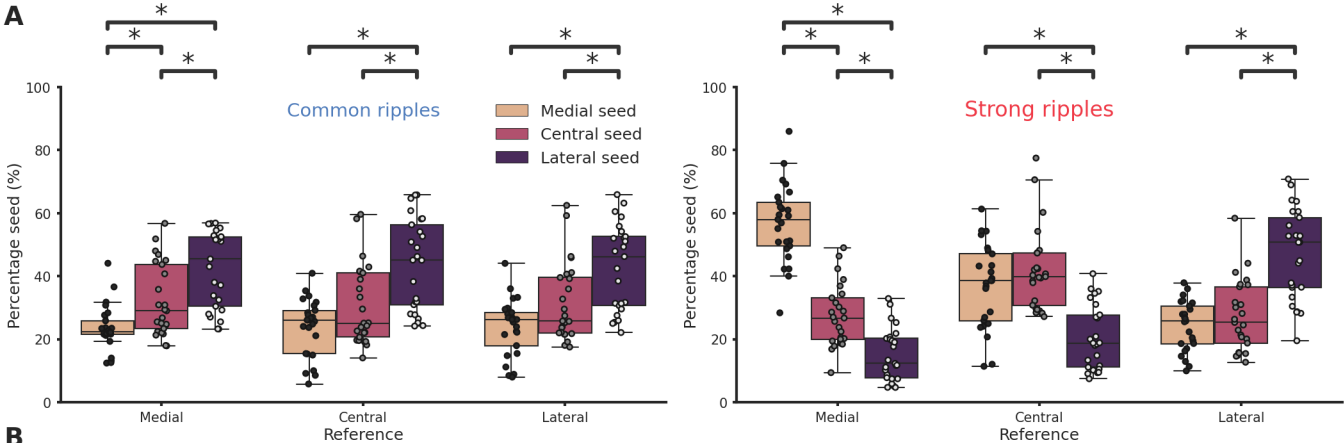
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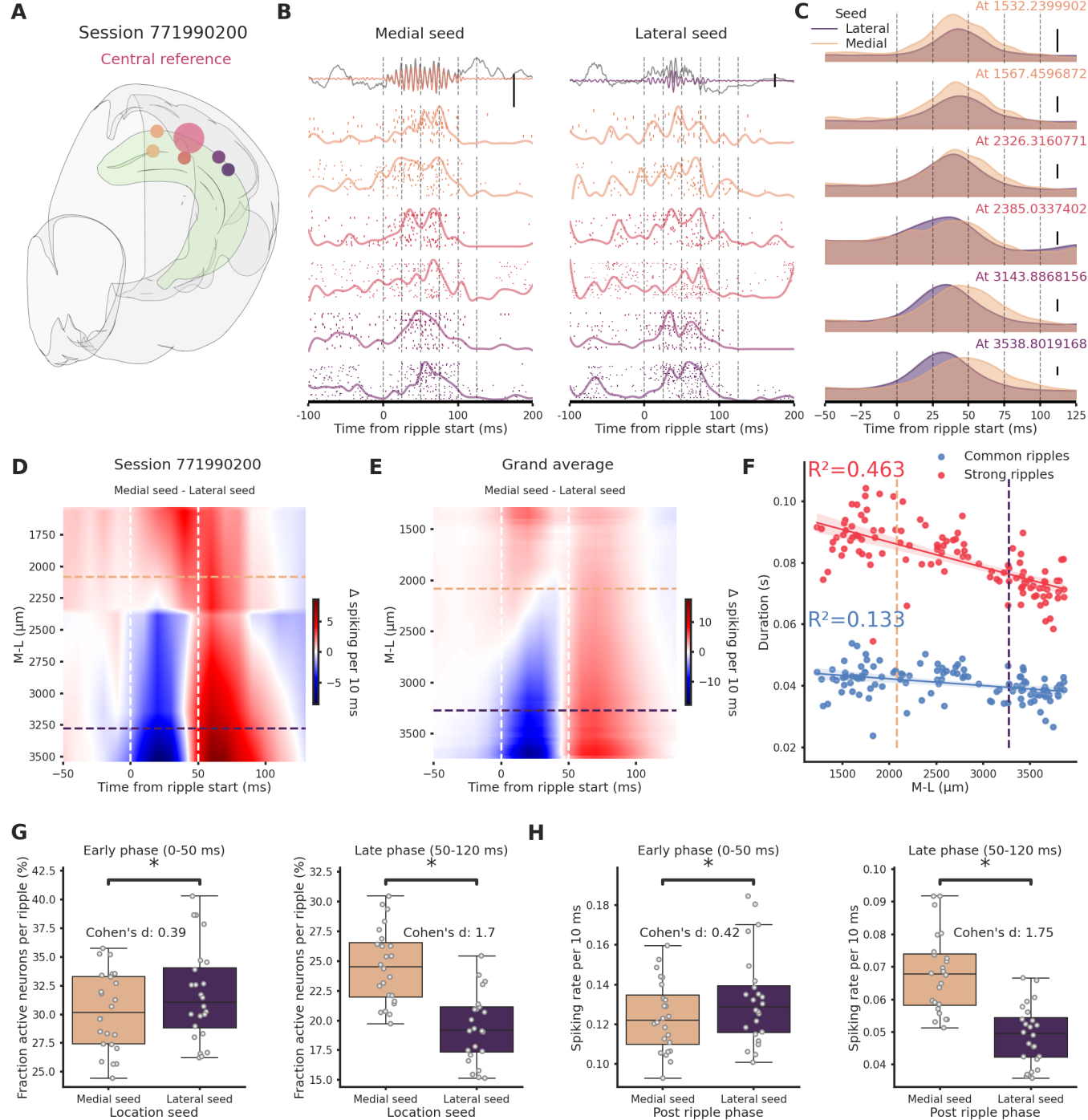
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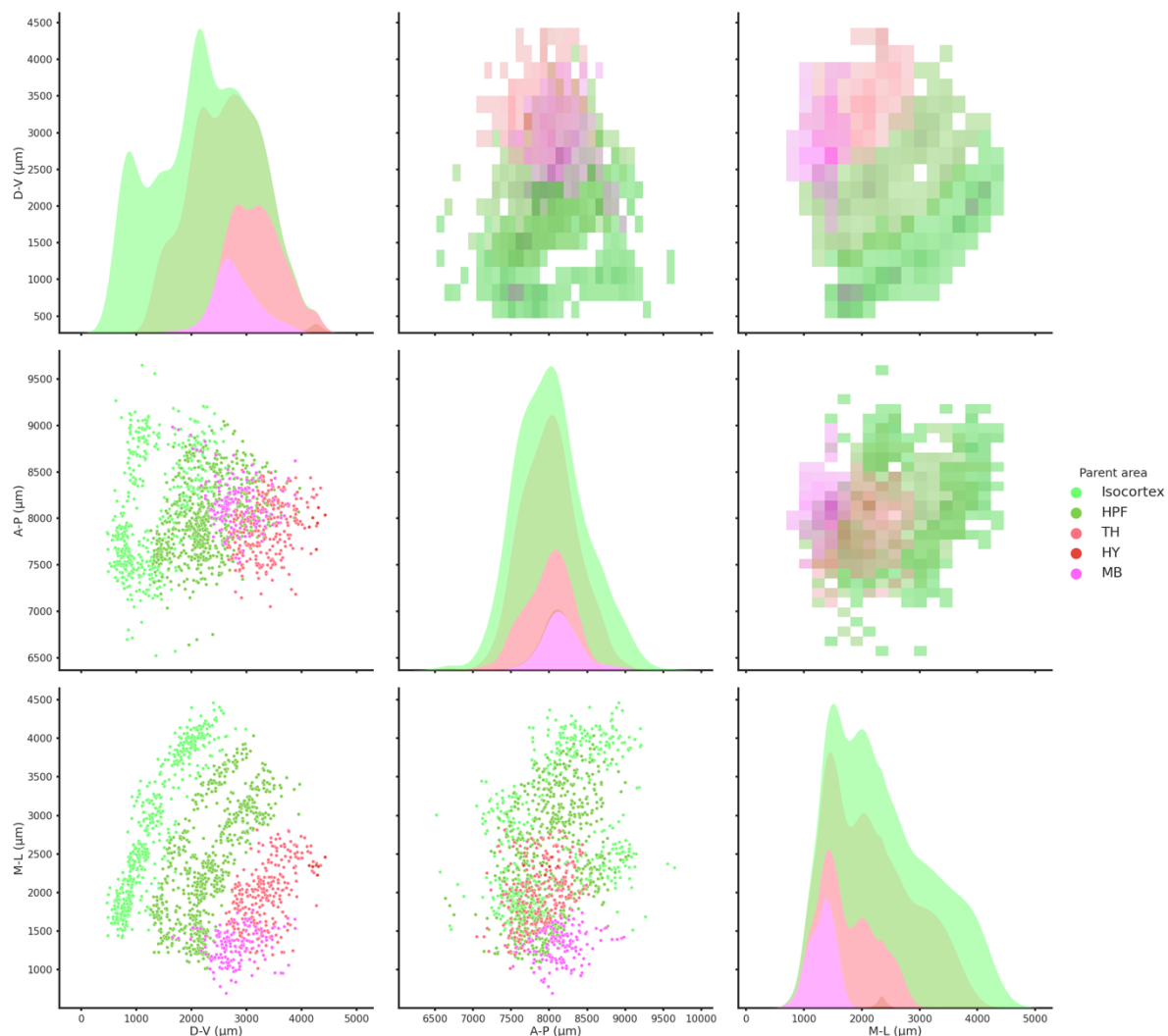






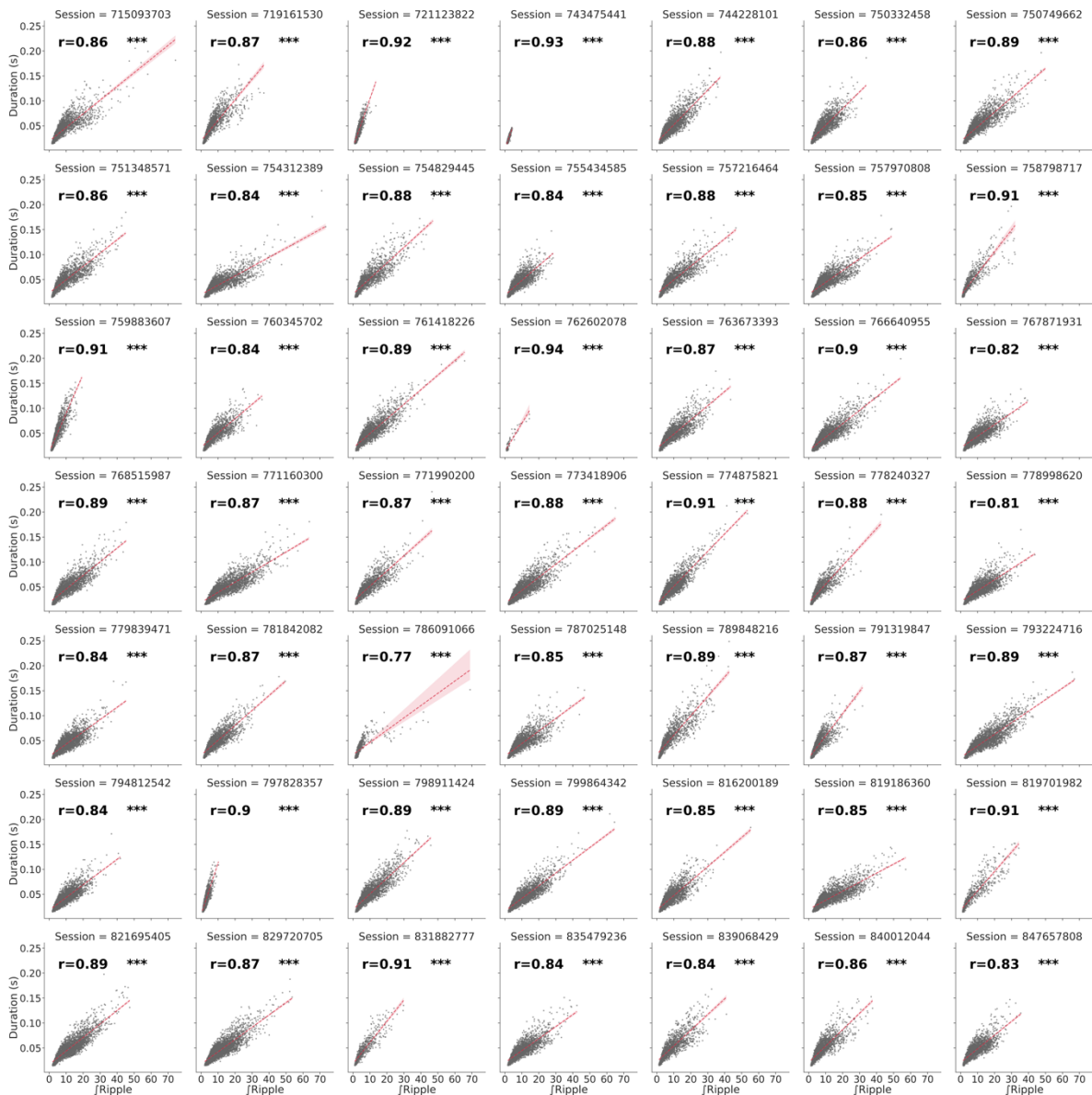


Supplementary Figures



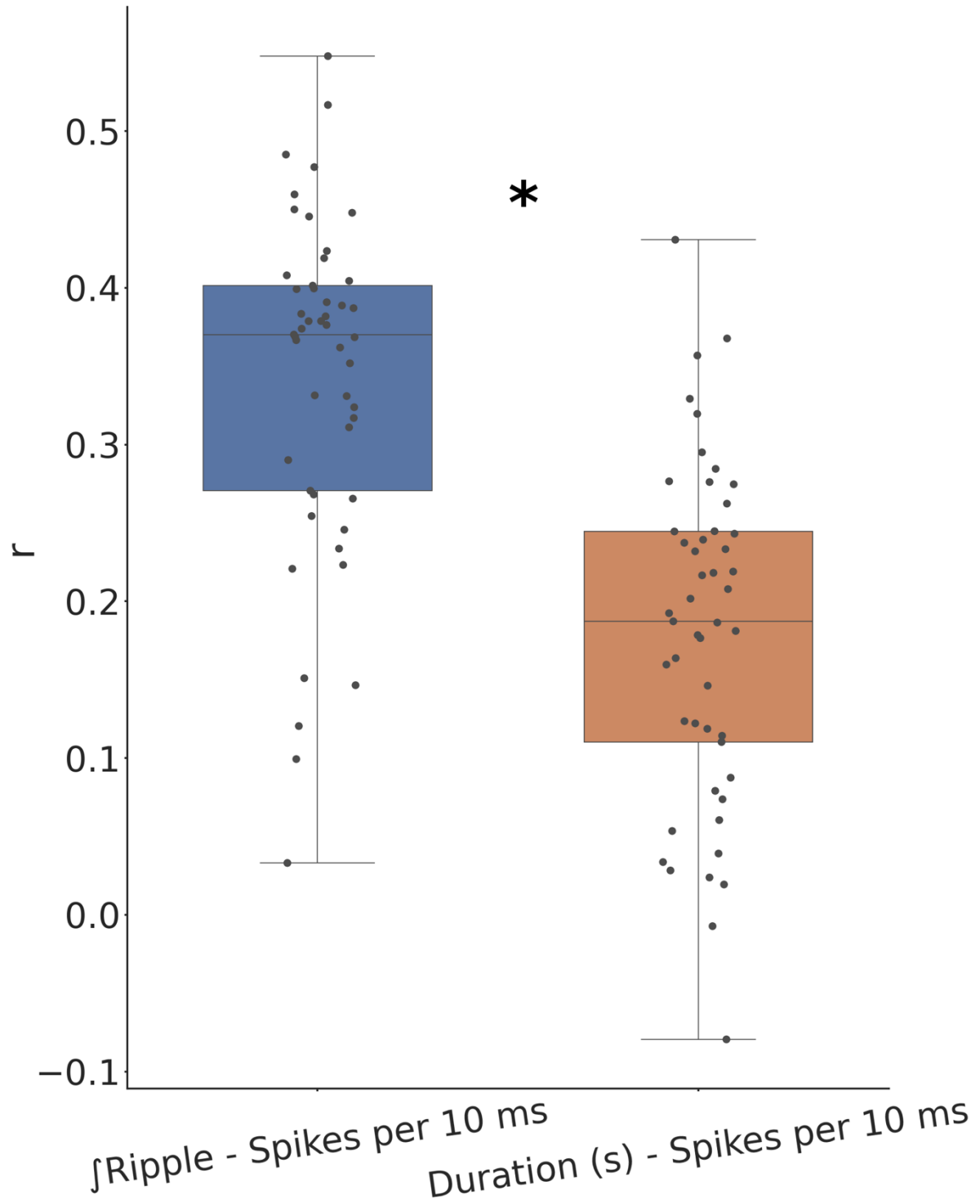
Supplementary Figure 1. Spatial coordinates of all recorded brain regions.

2D histograms (upper diagonal), scatter plots (lower diagonal) and kernel density estimate plots (diagonal) of all the recorded regions color-coded according to the Allen Institute color scheme. HPF=hippocampus, TH=thalamus, HY=hypothalamus and MB=midbrain. M-L axis is zeroed at the midline.



Supplementary Figure 2. Correlation between ripple duration and strength per session.

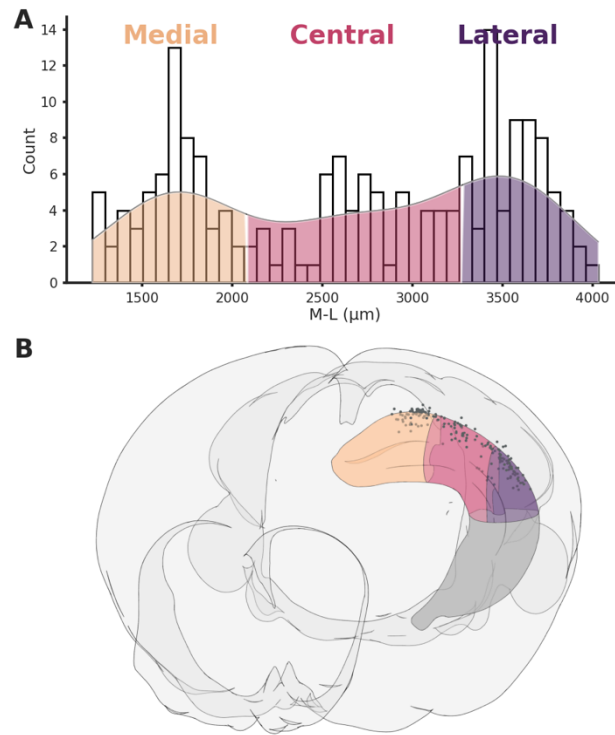
Red line represents linear regression with confidence interval of 95% estimated via bootstrap. *** means $p < 0.0005$.



Supplementary Figure 3. Comparison between correlation of ripple strength and duration with underlying spiking.

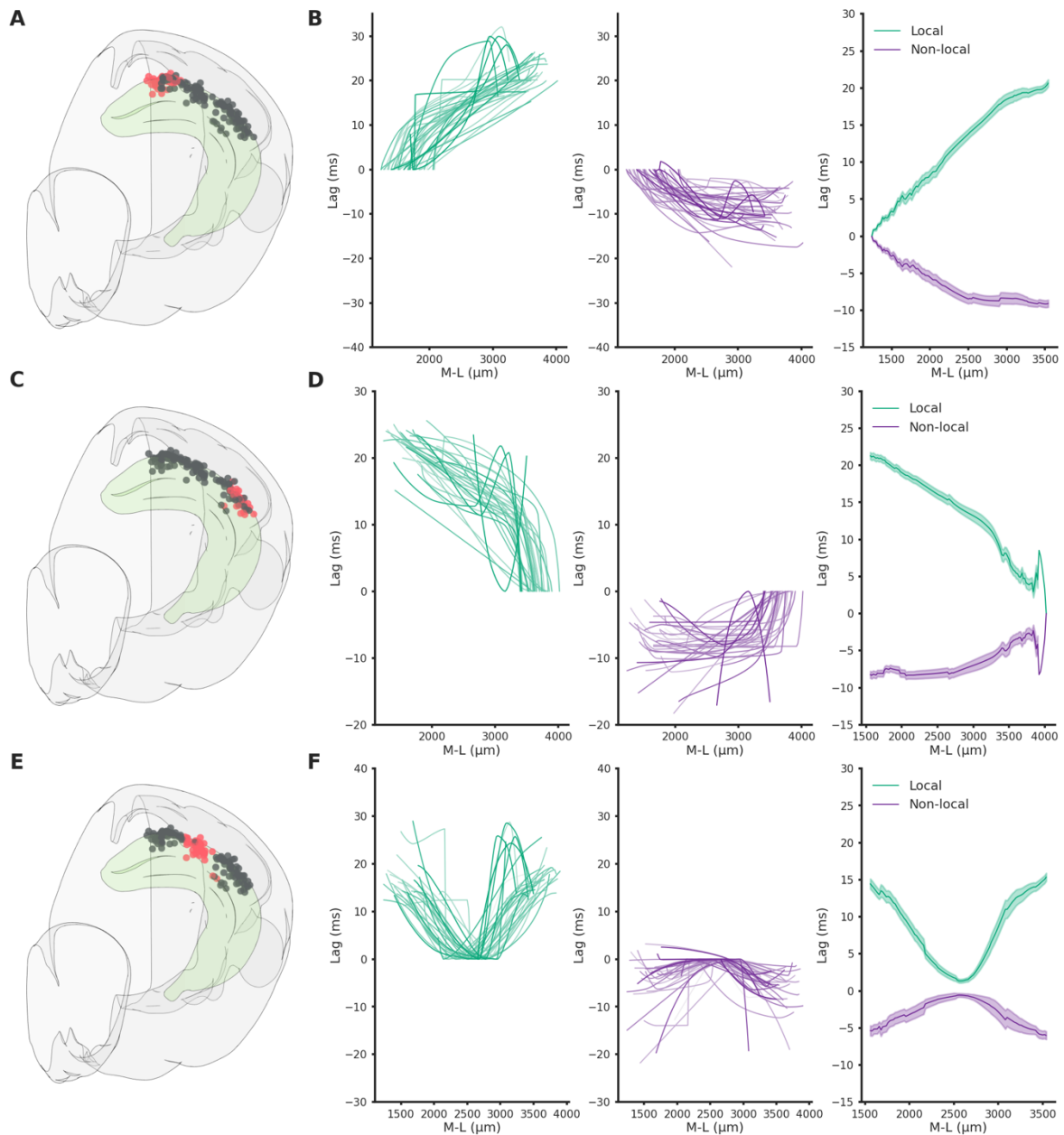
Ripple strength correlates significantly better with the underlying ripple spiking activity. * means $p < 0.0005$.

distribution of \int Ripple and RIVD z-scored per session, hippocampal regions (text in green) show the biggest responses.



Supplementary Figure 5. Hippocampal sections.

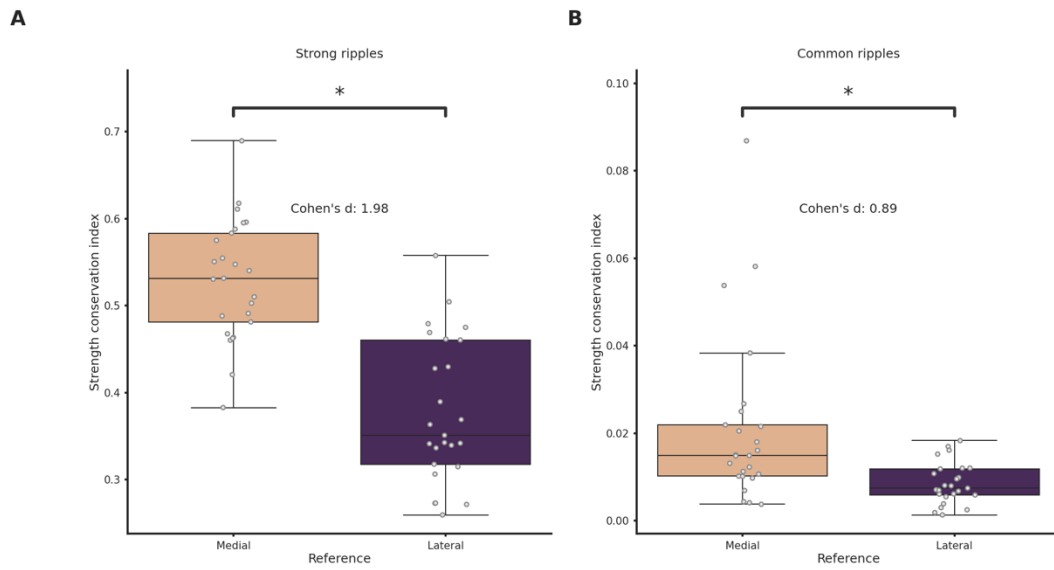
(A) Histogram showing the three sections across the M-L axis, the hippocampus was divided in order to have an equal number of recordings in each section. (B) Rendering of the 3 sections and associated recording locations (black dots).



Supplementary Figure 6. Spatio-temporal lag maps of locally and not locally generated ripples

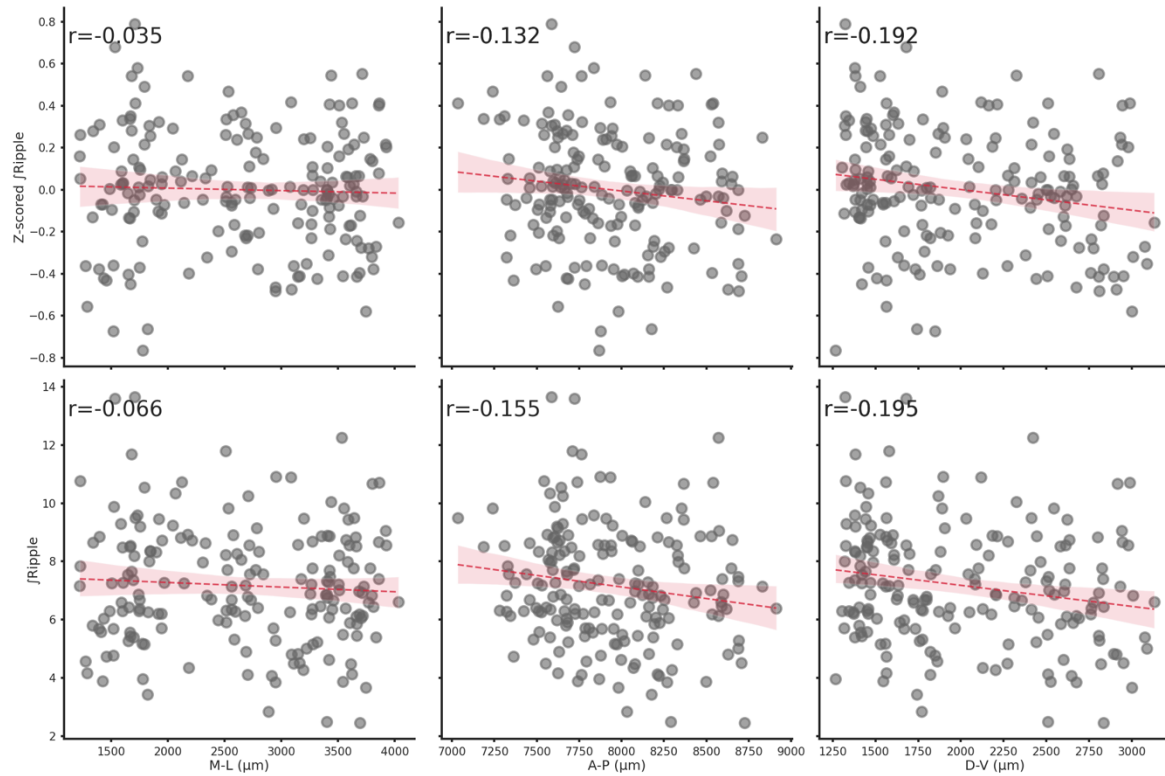
Spatio-temporal profiles are symmetrical, strong indication of similar propagation speed regardless of seed position. (A) Recording locations relative to (B). Red circles represents the reference locations across all sessions (n sessions=41), black circles represents the remaining recording locations. (B) Left: Medio-lateral propagation of locally generated ripples (generated in the reference section), each line represents the average of one session. Middle: Medio-lateral propagation of non-locally generated 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. (C) Same as A. (D) Same as B. Reference locations are the most lateral per session. (E) Same as A. (F) Same as B. Reference locations are the most central per session.



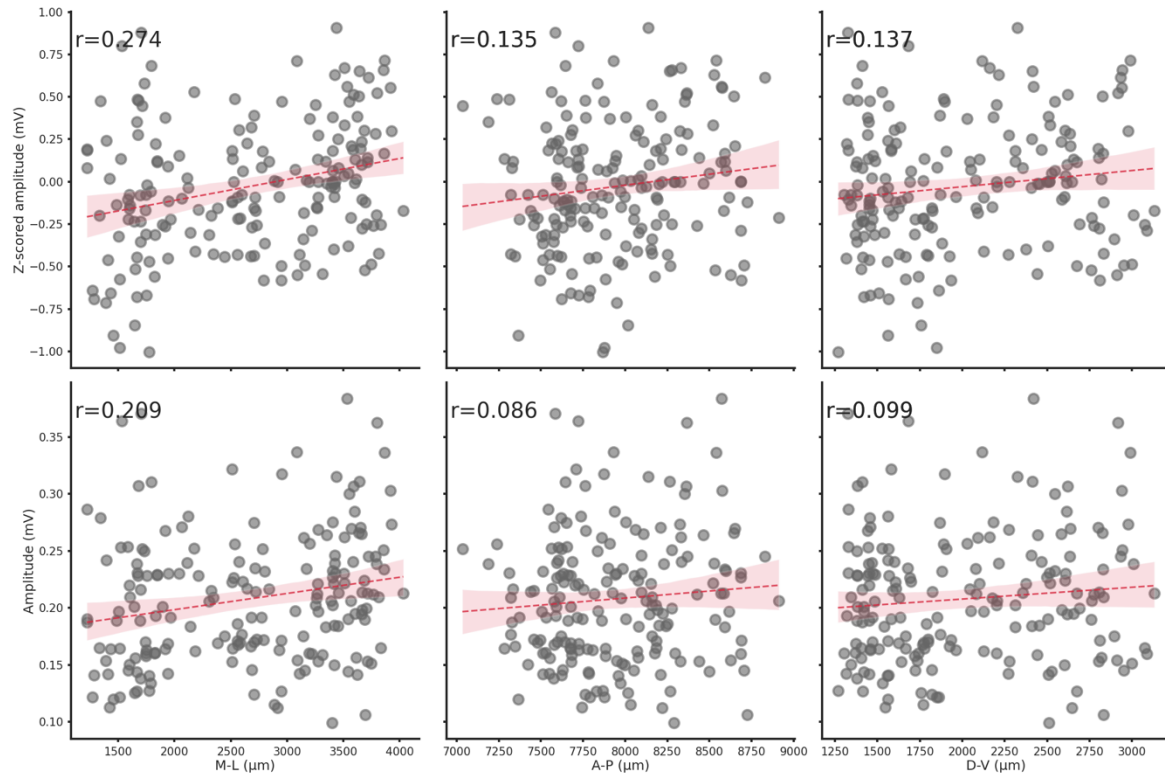
Supplementary Figure 7. Strength conservation in medially and laterally generated ripples.

(A) Strength conservation index in strong ripples grouped by reference location. Ripples generated in the lateral section shows significantly lower strength conservation ($p=7e-09$, Student's t-test). (B) Strength conservation index in common ripples grouped by reference location.



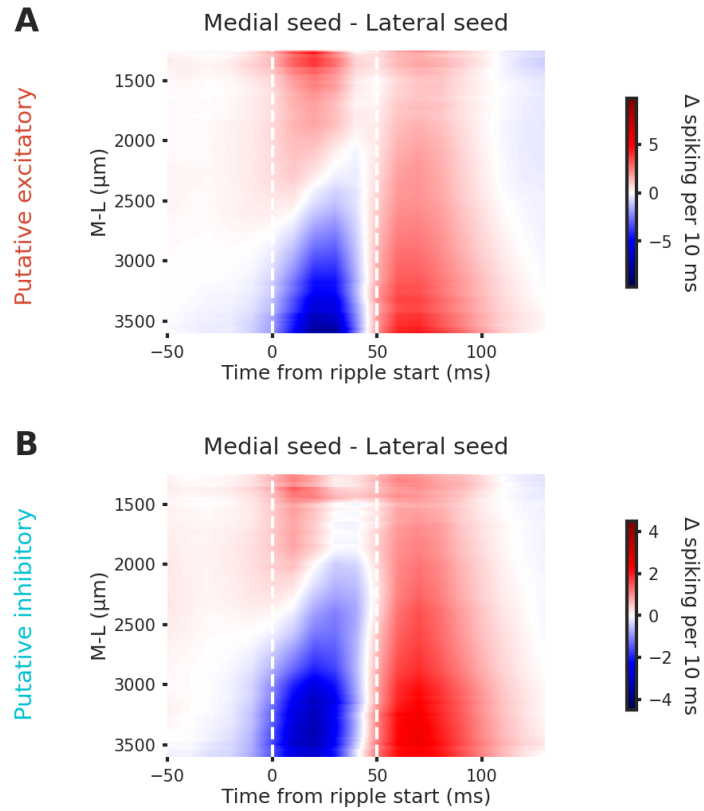
Supplementary Figure 8. Spatial location does not influence \int Ripple.

Relationship between Z-scored \int Ripple (top row) or \int Ripple (bottom row) and each spatial axis (M-L, A-P or D-V). Spatial location has a negligible effect on \int Ripple.



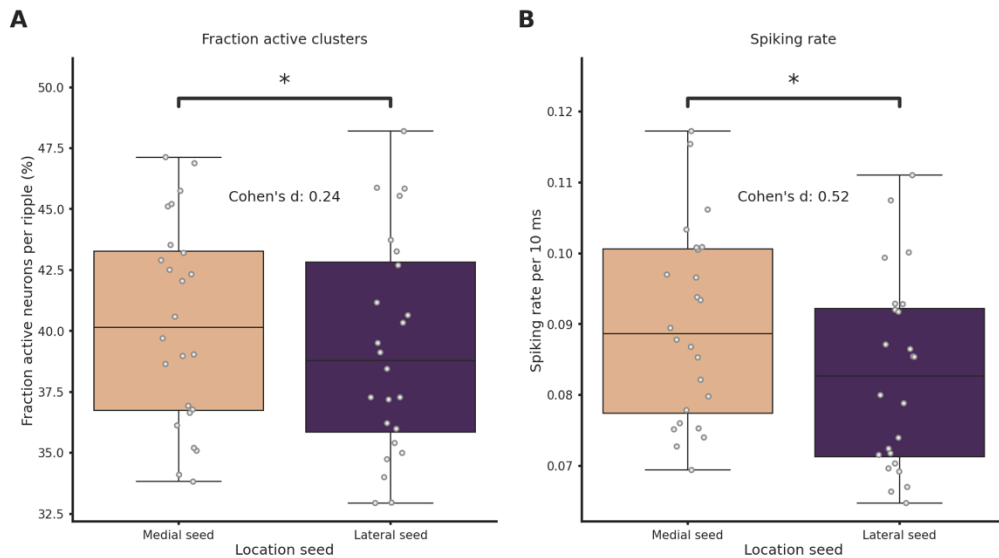
Supplementary Figure 9. Spatial location does not influence ripple amplitude.

Relationship between Z-scored amplitude (top row) or amplitude (bottom row) and each spatial axis (M-L, A-P or D-V). Spatial location has a negligible effect on ripple amplitude.



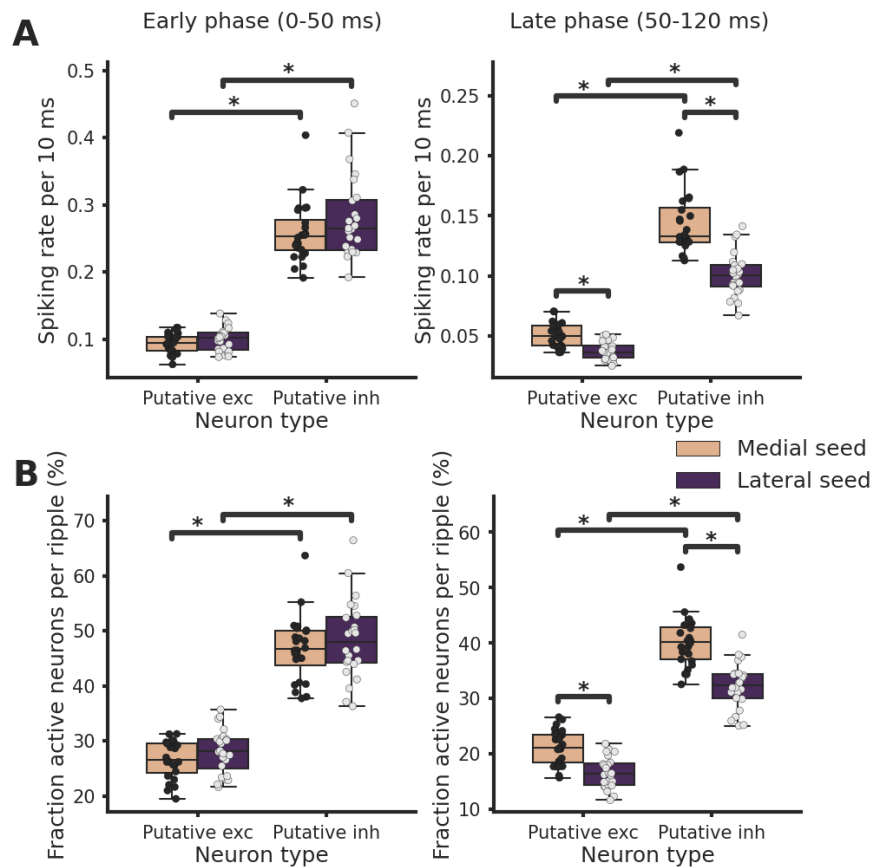
Supplementary Figure 10. Putative excitatory and inhibitory neurons show similar spiking patterns in lateral and medial ripples.

Grand average of the differences between medial and lateral ripples induced spiking activity in putative excitatory (A) and inhibitory neurons (B).



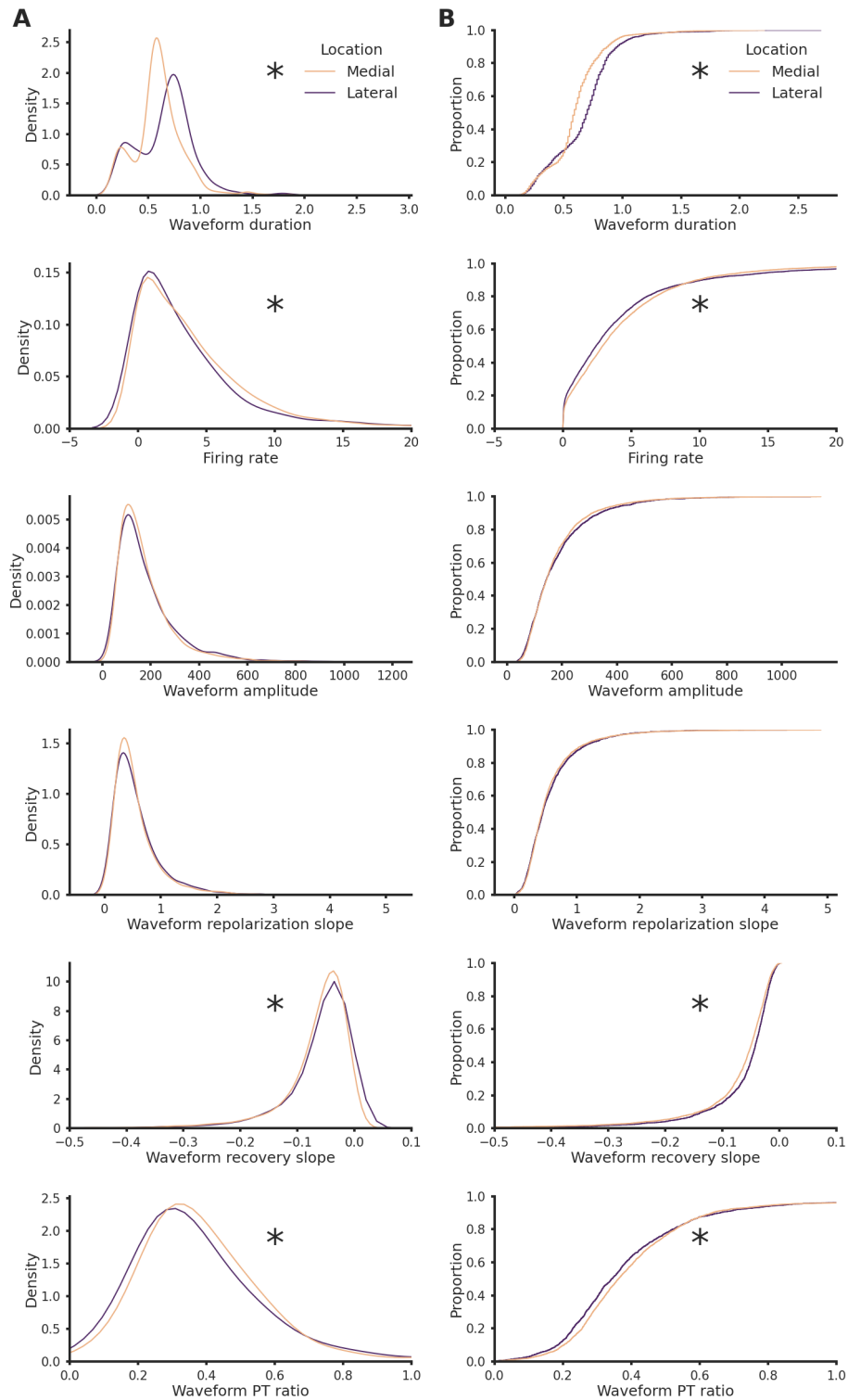
Supplementary Figure 11. Spiking rate and fraction of active neurons are significantly higher in medial ripples

(A) Fraction of active neurons per ripple grouped by ripple seed location. (Medial seed= $40.0 \pm 1.0\%$, lateral seed= $39.0 \pm 1.0\%$, p-value= $9.52e-05$, Student's t-test). (B) Average spiking rate grouped per ripple grouped by ripple seed location (Medial seed= $9.0 \pm 0.0\%$, lateral seed= $8.0 \pm 0.0\%$, p-value= $5.20e-10$, Student's t-test). Asterisks mean $p < 0.05$, Student's t-test.



Supplementary Figure 12. Spiking rate and fraction of active neurons are increased in the late phase post-ripple start in medial ripples both in putative excitatory and inhibitory neurons.

(A) Average spiking rate in early (left) and late (right) phase post-ripple start grouped by ripple seed location and putative neuron identity. Asterisks mean $p < 0.05$, ANOVA with pairwise Tukey post-hoc test. (B) Fraction of active neurons per ripple in early (left) and late (right) phase post-ripple start grouped by ripple seed location and putative neuron identity. Asterisks mean $p < 0.05$, ANOVA with pairwise Tukey post-hoc test.



Supplementary Figure 13. Units features in medial and lateral sections

(A) Kernel density estimate plot of waveform duration (p-value=1.64e-33), firing rate (p-value=6.41e-01), waveform amplitude (p-value=5.48e-01), waveform

repolarization slope (p-value=4.09e-01), waveform recovery slope (p-value=1.13e-10) and waveform peak-through ratio (p-value=5.42e-05) grouped by hippocampal section. Asterisks mean $p < 0.05$, Mann-Whitney U test. (B) Cumulative distribution plot of waveform duration (p-value=0.00e+00), firing rate (p-value=9.26e-03), waveform amplitude (p-value=9.09e-02), waveform repolarization slope (p-value=6.90e-02), waveform recovery slope (p-value=1.58e-10) and waveform peak-through ratio (p-value=2.27e-05) grouped by hippocampal section. Asterisks mean $p < 0.05$, Kolgomorov-Smirnov test.