

1 “Defining the synaptic mechanisms that tune CA3-  
2 CA1 reactivation during sharp-wave ripples”

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3 Paola Malerba<sup>1</sup>, Matt W. Jones<sup>2</sup>, Maxim A. Bazhenov<sup>1</sup>

4 <sup>1</sup> University of California San Diego, Department of Medicine, La Jolla 92093, USA

5 <sup>2</sup> University of Bristol, School of Physiology, Pharmacology & Neuroscience, Bristol BS8 1TD, UK

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7 Short Title: Mechanisms of ripple replay

8 Corresponding Author: Maxim Bazhenov, University of California San Diego Department of Medicine

9 9500 Gilman Drive # 7381, La Jolla, CA 92037

10 Email [mbazhenov@ucsd.edu](mailto:mbazhenov@ucsd.edu)

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## 15 **Abstract**

16 During non-REM sleep, memory consolidation is driven by a dialogue between cortex and  
17 hippocampus. The reactivation of specific neural activity sequences – replay – is believed to  
18 represent a neuronal substrate of consolidation. In the hippocampus, replay occurs during sharp-  
19 wave ripples (SWRs), short bouts of excitatory activity in area CA3 which induce high frequency  
20 oscillations in the inhibitory population of area CA1. Despite growing evidence for the functional  
21 importance of replay, its neural mechanisms remain poorly understood. Here, we develop a novel  
22 theoretical model of hippocampal spike sequence replay during SWRs. In our model, noise-induced  
23 activation of CA3 pyramidal cells triggered an excitatory cascade, which induced local ripple events  
24 in CA1. Ripples occurred stochastically in the model, with Schaffer Collaterals driving coordination,  
25 so that localized sharp waves in CA3 produced consistently localized CA1 ripples. In agreement with  
26 experimental data, the majority of pyramidal cells in the model showed low reactivation probability  
27 across SWRs, defined by the overall network connectivity. We found, however, that a small portion  
28 of pyramidal cells which had high reactivation probability across multiple SWRs owed their  
29 reactivation properties to the fine variations within network connectivity, and hence the detailed  
30 spiking dynamic within SWRs. In particular, the excitatory inputs along synaptic pathway(s) to cells  
31 and cell pairs controlled emergent single cell and cell pair reactivation. Furthermore, we found that  
32 inhibitory synaptic inputs and intrinsic cell excitability only had an influential role on the activation of  
33 CA3 pyramidal cells, but not CA1 pyramidal cells, during SWRs. Our study predicts that hippocampal  
34 replay results from a network-wide coordination of activation probability across SWRs for cells and  
35 cell pairs, which is further refined by specific synaptic strengths. This suggests a possible competition  
36 among cell assemblies for activation during SWRs, where synaptic strengths mediate the chance of  
37 dominance of a given memory over others during spontaneous SWRs.

## 38 **Author Summary**

39 During sleep, rhythmic activities in different brain regions are coordinated across multiple timescales  
40 and brain regions. The coordination of these events is important for consolidation of recently  
41 acquired memories. Sharp-wave ripples (SWRs) are one of such major sleep rhythms, seen in the  
42 hippocampal region, during which cells previously active during an awake task reactivate, in  
43 preserved order, during sleep ('replay'). Replay is thought to contribute to consolidation by enabling  
44 re-elaboration of events of the day during sleep. However, the manner in which specific spiking  
45 patterns are selected for replay remains unknown. In this study, we apply computational models to  
46 reveal mechanisms behind the generation of SWRs and to explain the factors controlling which cell  
47 sequences reactivate during SWRs. We find that different hippocampal regions have different factors  
48 that promote replay. Our study predicts that when learning changes the strength of synaptic  
49 connections during wake, it would enhance the probability of reactivation of experience-specific  
50 groups of neurons during sleep.

## 51 **Introduction**

52 Memories acquired during wakefulness continue to evolve during subsequent sleep. Sleep seems an  
53 optimal brain state for this memory consolidation: the brain is dissociated from external inputs and  
54 internal processing can be supported by sleep stage-dependent patterns of network activity, driven  
55 largely by periodic shifts in neuromodulatory tone (1, 2). During non-REM sleep, hippocampal  
56 networks show sharp-wave ripples (SWRs): short bouts of synchronized population activity (50-  
57 100ms) initiated in the CA3 area of the hippocampus with strong excitatory firing that reaches area  
58 CA1, driving fast spiking interneurons to rhythmically organize a small fraction of local pyramidal  
59 cells spiking (3-5). In CA1, local field potential (LFP) high frequency oscillations (above 150Hz in the  
60 rat, about 100Hz in humans) occur in the pyramidal layer (the ripple), while in *stratum radiatum* a  
61 strong deflection marks the effects of Schaffer Collateral input to the pyramidal cells (the sharp  
62 wave). Hippocampal SWRs can be locked to cortical slow oscillations (SO) and troughs of

63 thalamocortical spindles, in a coordination of activity across brain regions and time scales (6, 7),  
64 which is thought to orchestrate a hippocampal-neocortical dialogue mediating memory  
65 consolidation.

66 The number of SWR correlates with memory performance after sleep (8, 9), suppressing SWR  
67 compromises memory consolidation (10, 11) and increased SO power and coordination of SO and  
68 other sleep rhythms augments memory (12). Reactivation of specific neural activity patterns – replay  
69 – during slow wave sleep has been observed in both hippocampus and neocortex (13-18), and  
70 coincides with SWR (19, 20). This led to the hypothesis that coordinated sequence reactivation  
71 during precisely timed oscillations can recruit synaptic plasticity, leading to memory consolidation  
72 across brain structures (21). Within this hypothesis, understanding how replay happens in  
73 hippocampal SWR is crucial to explain sleep dependent memory consolidation.

74 CA1 pyramidal cells are not homogeneous with respect to activity during ripples, and can be sub-  
75 classified into those that spike during ripples and those that do not; these properties seem to remain  
76 stable across sleep epochs (3, 22, 23). Furthermore, recent experimental data show that comparing  
77 sleep reactivation before and after a learning experience allows identification of cells for which  
78 reactivation during SWR remains unchanged by learning and (separate) cells which show increased  
79 ripple spiking during learning and subsequent sleep (24). Together, these data support a framework  
80 in which hippocampal reactivation incorporates a relatively large set of cells which activate during  
81 ripples regardless of recent learning, and a smaller group of cells which are involved in reactivation  
82 because of experience-dependent changes in their connectivity. In the simplest scenario, the precise  
83 content of hippocampal sequence reactivation is shaped by the hippocampal synaptic circuitry, with  
84 afferents (e.g. entorhinal or thalamic) potentially eliciting a generic reactivation prompt.

85 In this work, we address a question on the mechanism of hippocampal reactivation using a  
86 biophysical network model of CA3-CA1 SWR activity, where spontaneous, localized and stochastic  
87 excitatory events in the highly recurrent CA3 network drive transient oscillations in CA1 inhibitory

88 interneurons, which in turn only leave small windows of opportunity for CA1 pyramidal cells to spike.  
89 Our model reveals a mechanism of emergent, spontaneous activation of pyramidal cells across  
90 SWRs, and predicts how learning can affect the specific reactivation of the hippocampal neurons  
91 which is seen during sleep, while global network behavior is supported by the network architecture.

## 92 **Results**

### 93 **Computational model of spontaneous, localized SPW-R activity**

94 In our previous work (25), we introduced a model of CA1 ripples in which oscillations in the LFP were  
95 due to a transient in the system dynamics (as opposed to a stable oscillatory state), imposed by fast  
96 firing of the basket cells initially synchronized by common current input (representing CA3  
97 excitation), which lost coordination in time due to the cell population heterogeneity. Here we build  
98 on that work to introduce a model of CA3-CA1 SWRs in which CA3 activity emerges spontaneously  
99 and triggers stochastic activation of the SWR events in CA3 and CA1, with the termination of ripples  
100 driven by the same de-coordination mechanism that we previously described in CA1 (25). In the new  
101 model, different subsets of cells were involved across different SWR events as observed  
102 experimentally (26).

103 This model of CA3-CA1 SWR activity is based on synaptically coupled populations of pyramidal cells  
104 and basket cells (Figure 1A). The model included highly recurrent strong excitatory AMPA receptor-  
105 mediated connections between CA3 pyramidal cells, and weak and sparse recurrent excitatory  
106 connections within CA1 pyramidal cells (27). CA3 pyramidal cells projected excitatory connections to  
107 CA1 cells, representing the Schaffer Collaterals. The CA3 network and its projections to CA1 had  
108 stochastic densities and strengths within a radius of about a third of the target network (28) (Figure  
109 1B shows a matrix the presence of synaptic connections), which is consistent with analysis of CA3  
110 pyramidal cells arborization (28). Importantly, each neuron received an independent noise current  
111 which drove occasional irregular spiking, and a baseline constant drive which was selected from a

112 distribution. Details of the computational model rationale and equations are reported in Materials  
113 and Methods.

114 **Figure 1. Computational Model of emergent, localized SPW-R activity**

115 **A.** Schematic representation of the model, showing the two main regions (CA3 and CA1) and the cell  
116 types considered (pyramidal cells and basket cells). Note that CA3 projects to CA1, but not vice-  
117 versa. **B.** Matrix representation of presence of synaptic connections in the model. Synaptic weights  
118 are not shown, hence darker tone is only indicative of local higher density of connections. Note that  
119 CA3 pyramidal cells connect to all cell types in the network. **C.** Example of SPW-R activity in the  
120 network. Top 2 plots: raster plots of cell spikes (CA3 above, CA1 below). Dots mark spikes in time of  
121 pyramidal cells (black) and interneurons (red). In CA3 sharp waves happen at different locations and  
122 show different propagation patterns in time. CA1 spiking is organized by the sharp waves in CA3, and  
123 ripples are visible as small sharp stripes of dense spiking in CA1 pyramidal cells. Bottom two plots:  
124 Local Field Potential (LFP) of the model, computed as the average of the total incoming synaptic  
125 currents across a group of pyramidal cells. Note that in CA3 we show the wide-band signal, to  
126 highlight the sharp transition occurring in the synaptic currents when a sharp wave is present in the  
127 CA3 network. At corresponding times (and locations) in the LFP of CA1 (filtered in ripple range) one  
128 can see the high frequency activity captured by the LFP signal. **D.** Zoomed-in raster plot of spiking  
129 activity in CA3 and CA1, the time window is indicated by the arrow in C. SWR activity is localized  
130 within the two regions. For each sharp wave (SPW) and each ripple (RPL) a center (or location) can  
131 be defined as the medium index among the pyramidal cells which spike during the event. The LFPs  
132 shown on the right refer to groups of cells slightly apart in the network, shown as colored rectangles in  
133 the rastergram. Note that some SWR can be seen in the LFP traces at both locations (near 11s) while  
134 others are only visible in one of the traces (about 400ms later).

135 As shown in Figure 1C, the network spontaneously organized into strong bouts of CA3 pyramidal cell  
136 spiking, which drove spiking in CA1. In CA1, interneurons organized their firing in high frequency  
137 oscillations, and a few pyramidal cells spiked within windows of opportunity left at the troughs of  
138 the lateral synaptic inhibition oscillations, thus forming a SWR event. SWRs occurred in temporal  
139 clusters punctuated by long pauses. A representation of the local field potentials (LFPs) obtained by  
140 averaging the synaptic currents impinging on subsets of pyramidal cells showed that SWR events in  
141 CA3 and CA1 were localized, and the location of the SWRs within the network changed in time. This  
142 is consistent with experimental findings that show that ripple events can be localized in space (26,  
143 29) and that CA3 pyramidal cells are known to be very active during SWR, but do not spike phase-  
144 locked to CA1 ripples (30, 31).

145 Figure 1D shows a zoomed-in version of the SWR spiking activity and LFPs in sub-regions of CA3 and  
146 CA1 which were connected by Schaffer Collaterals. Although sharp waves are typically  
147 experimentally measured in CA1 *stratum radiatum*, in the following we refer to sharp waves as the

148 bouts of excitatory activity in CA3 which lead to ripples in CA1. The general activity of the model was  
149 consistent with known properties of SWRs: ripple frequency was  $174 \pm 21.3$  Hz, ripple durations were  
150  $54 \pm 27$  ms, sharp wave durations were  $126 \pm 23$ ms and the inter-event pauses (time durations  
151 between two successive sharp waves in CA3 or ripples in CA1) showed distributions approximately  
152 exponential, which fitted to exponential functions with rates 1.08 Hz for sharp waves in CA3 and  
153 1.2Hz for ripples in CA1 (3). Within this model, we studied the spontaneous activation of CA3 and  
154 CA1 pyramidal cells across multiple ripples, in relation to their synaptic properties.

### 155 **Non-uniform cell activation probability shapes distribution of ripple activation scores in** 156 **CA3 and CA1**

157 Sequential cell reactivation has primarily been demonstrated in CA1 pyramidal cells during SWRs,  
158 but fewer data are available on CA3 pyramidal cell replay (32). In our model, we first characterized  
159 sequence replay by studying the activation of each single cell across many SWRs. For this, we derive  
160 a ‘ripple activation score’ (R-activation score), given by the percent of SWRs in which a given cell  
161 spiked at least once, in the course of a 100 s simulation (schematized in Figure 2A; e.g., a R-  
162 activation score of 100% would mean that the cell spiked in every SWR event). Generating R-  
163 activation scores across many simulations (Figure 2B) revealed that, on average, cells in CA3  
164 activated across more ripples than cells in CA1. This was likely driven by the lower percentage of CA1  
165 pyramidal cells involved in any given ripple compared to the population of CA3 pyramidal cells  
166 inducing a sharp wave (which is consistent with experimental data (22, 30, 33)). The distribution of  
167 R-activation scores in both regions showed a large positive tale, and in CA1 a fast decay. This is also  
168 consistent with data suggesting that firing rates during ripples are log-normally distributed (3, 5, 34,  
169 35). One model of CA3 emergent sharp wave activity suggests that this could be related to the  
170 distribution of synaptic weights used to populate the network connectivity matrices (36).

171 **Figure 2. R-activation in CA3 and CA1 is stationary for low score cells and dynamic for high**  
172 **score cells**

173 **A.** Drawing shows the definition of R-activation score for a pyramidal cell. The total number of SWR in  
174 which a cell spikes during a 100 second simulation is found, and compared to the total number of  
175 SWR in the simulation. This fraction is expressed as a percent as the R-activation score of the cell.

176 **B.** Distribution of R-activation scores of CA3 and CA1 pyramidal cells computed across many  
177 simulations and reported as average count in any given single trial. CA1 pyramidal cells show a peak  
178 for 0% R-activation, and the mean R-activation scores for CA3 pyramidal cells is higher than CA1  
179 pyramidal cells. **C.** Curves (one per simulation) mark the probability distribution of pyramidal cells in  
180 CA3 to be spiking in any given SWR. Cells were sorted by increasing probabilities. The average  
181 probability curve (across all curves for each sorted cell index) is marked by a black solid line, while  
182 dotted black lines represent the standard deviation around the mean. **D.** Same as panel C for CA1  
183 pyramidal cells. **E.** Distributions of R-activation scores in CA3 pyramidal cells in a stationary sorting  
184 algorithm (thick line) and in the model (dotted line). Note that the stationary process and the model  
185 share the low-reactivation peak probability, but have different trends for high-reactivations: the  
186 stationary choice peaks at 60% and quickly decays to zero for higher scores, while the model does  
187 not show peaks at high R-activation values (only the low R-activation peak is present) and has a  
188 larger amount of very high R-activations. **F.** Same as panel E for CA1 pyramidal cells: again  
189 stationary choice and computational model share the low R-activation peak and the model does not  
190 show a peak for intermediate levels of R-activation.

191 The distribution of R-activation scores (Figure 2B) tells how many cells are likely to activate in a given  
192 fraction of all SWR, while the probability of spiking (Figure 2C,D) tells if a given cell is likely to  
193 activate in many or few SWRs (e.g.,  $p=1$  would mean that a cell spike in every SWR event). For each  
194 model simulation, we reported the probability of spiking in a SWR for all cells in CA3 and CA1 (in  
195 Figure 2 C-D). Since in every simulation new connectivity and heterogeneity profiles were generated  
196 (see Materials and Methods), we sorted the cells according to their spiking probability within SWRs,  
197 from lowest to highest. Then, it was possible to find an average distribution of such probabilities,  
198 and compare between CA3 and CA1 networks. In both cases, the variance around the mean  
199 increased for cells with higher SWR activation probabilities. The larger variations for high-probability  
200 cells (right side of the plots in Figure 2 C,D) suggested that all the cells fell in one of two categories:  
201 those which fired in very few ripples (the majority) and those which fired in a large fraction of ripples  
202 (above 0.6 probability).

203 Across many simulations, the rules which shaped network connectivity were fixed, but the actual  
204 specific network connections changed as they were generated probabilistically. This led to  
205 measurable variations in the properties of SWR activity, such as the total count of SWRs within

206 simulation time, and the size of ripples and sharp waves (as fraction of CA3 and CA1 pyramidal cells  
207 spiking during the event). In the following, we analyze the role of the stationary model properties:  
208 the ones that depend on the average model characteristics and do not change much across  
209 simulations (such properties included the distribution of ripple frequencies, of inter-event times, and  
210 the range of reactivation scores found across the population of pyramidal cells). We analyze  
211 separately the dynamic (or network-activity dependent) properties: those which are dependent on  
212 the specific model instantiation in a given simulation (such properties included a specific cell's  
213 spiking probability). To distinguish between the contributions of the stationary and network-activity  
214 dependent properties in shaping R-activation scores across simulations, we compared the  
215 distribution of R-activations that was found across simulations with a theoretical sampling model.  
216 This model was based on the average probability of spiking in CA3 and CA1 pyramidal cells (black  
217 lines in Figure 2 C-D). Thus, we sampled cells according to those probabilities, and we repeated the  
218 sampling 10,000 times and considered each sampling event a ripple in which the sampled cells had  
219 spiked. This sampling approach assumed that spiking in each SWR was memoryless and that the  
220 probability for a given cell to be spiking in any ripple was stationary (i.e. not changing in time within  
221 a simulation), so it was an extreme simplification of a complete computational model simulation. If  
222 the spiking of each cell across many SWRs in the complete model was independent of spiking history  
223 and activation of other cells, and only dependent on the average probability found in simulations,  
224 we should obtain in the simple theoretical model a sampling distribution of R-activation scores very  
225 similar (if not identical) to the ones in Figure 2B.

226 In Figure 2E-F we compared the stationary (sampling) distributions from the theoretical sampling  
227 model to those resulting from simulations: in both CA3 and CA1 we found that stationary R-  
228 activation (from the theoretical sampling model) showed a larger fraction of cells in the network  
229 having median R-activation scores (about 60% in CA3 and 40% in CA1) compared to the  
230 computational model, and very few cells showing very high R-activation scores (above 70% in CA3  
231 and 60% in CA1). In other words, R-activation scores in the stationary case showed two peaks, one of

232 which at median activations, while in the simulations the second peak was removed, and a larger  
233 positive tale was found instead. We concluded that specific spiking dynamics of simulations  
234 (influenced by history dependence, slow variables and specific instances of network connectivity and  
235 excitability) promoted the long tales composed by cells with very high R-activation scores.

236 This analysis suggests that ripple activation in CA3 and CA1 was built on average on the stationary  
237 properties of the network architecture and overall network state, except for few highly-activating  
238 cells, whose properties were dependent on specific instantiation of the network architecture (such  
239 as, e.g., convergence of few strong excitatory connections to a given cell). Thus, the model predicts  
240 the co-existence of a relatively rigid structure in the CA3-CA1 network which enables the emergence  
241 and general properties of SWRs, with a specific network spiking activity in a subset of highly active  
242 neurons inducing replay during SWRs.

### 243 **The influence of input on pyramidal cell R-activation**

244 The network connectivity was set randomly for each simulation, and therefore specific synaptic  
245 paths connecting cells changed from one simulation to another, influencing how the ongoing spiking  
246 activity in the whole network could contribute to the R-activation score of a given cell. Since the  
247 SWRs in the model were induced by the spontaneously emergent excitatory activity in CA3, which  
248 controlled the spike timing of CA3 pyramidal cells and competed with CA1 local inhibitory ripple  
249 activity to drive the spikes of few CA1 pyramidal cells, we next studied the R-activation of pyramidal  
250 cells in relation to their incoming inputs. We considered synaptic excitatory and synaptic inhibitory  
251 inputs, together with intrinsic cell excitability.

252 We defined the excitatory and inhibitory synaptic input ( $S^{\text{AMPA}}$  and  $S^{\text{GABA}}$ , respectively, represented in  
253 Figure 3A) for each CA3 pyramidal cell by summing the synaptic weights of all incoming connections.

254 The intrinsic excitability for each CA3 pyramidal cell corresponded to the value of model parameter  
255  $I_{DC}$ , which was assigned (and different) to every cell to introduce heterogeneity among their resting  
256 potentials (see Materials and Methods, Network model: rationale). For each input, we next analyzed

257 the distribution of the input strength across R-activation scores (Figure 3B). All inputs considered  
 258 (synaptic excitatory, inhibitory and intrinsic excitability) were on average higher for cells with higher  
 259 R-activation scores, implying that all the inputs could contribute to enhancing the R-activation  
 260 probability of a CA3 pyramidal cell.

261 **Figure 3. In CA3 and CA1, pyramidal cell R-activation scores increase with excitatory input**  
 262 **A.** Drawing of the synaptic inputs analyzed for CA3 pyramidal cells.  $S^{AMPA}$  is the sum of all incoming  
 263 AMPA connections (in black) to a CA3 pyramidal cell (labeled A) from other CA3 pyramidal cells (in  
 264 gray).  $S^{GABA}$  is the sum of all incoming GABA connections (in red) to a CA3 pyramidal cell (A) from  
 265 CA3 interneurons (in red). **B.** R-activation of CA3 pyramidal cells is related to strength of synaptic  
 266 inputs and intrinsic excitability. The bar plot shows on the x –coordinate the average R-activation  
 267 score of CA3 pyramidal cells belonging to the same score group ( $\pm 5\%$ ) and on the y-coordinate the  
 268 level of each different input ( $S^{AMPA}$ ,  $S^{GABA}$  or Intrinsic Excitability) for cells within that score group.  
 269 Error bars mark the standard error of the mean. Before grouping cells by their R-activation scores,  
 270 each input was z-scored to enable comparisons of their respective trends. Therefore, a negative y-  
 271 coordinate does not reflect a negative input, but an input below the average across the whole  
 272 network. **C.** Drawing of the synaptic inputs analyzed for CA1 pyramidal cells.  $S^{Sch}$  (from CA3 to CA1,  
 273 in green) is the sum of incoming AMPA synaptic weights from CA3 cells onto CA1 pyramidal cells.  
 274  $S^{Pre}$  (in black) for a given CA1 pyramidal cell (labeled x) finds all cells in CA3 that projects to x and  
 275 their AMPA input ( $S^{AMPA}$ , described in A). The average value of all these  $S^{AMPA}$  inputs is  $S^{Sch}$ ,  
 276 representing the how much excitatory drive the cells in CA3 which project to x in CA1 are receiving.  
 277  $S^{GABA}$  is the sum of all incoming GABA connections (in red) to a CA1 pyramidal cell (x) from CA1  
 278 interneurons (in red). **D.** R-activation of CA1 pyramidal cells is related to synaptic excitatory input. The  
 279 bar plot shows on the x –coordinate the average R-activation score of CA1 pyramidal cells belonging  
 280 to the same score group ( $\pm 5\%$ ) and on the y-coordinate the level of each different input ( $S^{Pre}$ ,  $S^{Sch}$  or  
 281 Intrinsic Excitability) for cells within that score group. Inputs were z-scored before grouping the cells  
 282 by score. Error bars mark the standard error of the mean.

283 To study role of the potential interactions among inputs in influencing cell R-activation, statistical  
 284 inference analysis was performed using multivariate linear regression (see Table 1). For CA3, it  
 285 showed significant modulation of R-activation by the three inputs (synaptic excitatory, synaptic  
 286 inhibitory and intrinsic excitability). It also emphasized that the influence of synaptic excitatory input  
 287 was captured in the interaction with the synaptic inhibitory input and with intrinsic excitability.  
 288 When considered separately, the different inputs had a similar impact on R-activation, and  
 289 combining the three inputs increased their ability to represent the R-activation data.

290 **Table 1. Extract of linear regression models for R-activation of CA3 pyramidal cells vs**  
 291 **inputs (from Table S1)**

# Inputs	Inputs in Best Model	Model Equation Type	Adj. R-sq
3	AMPA,GABA,DC	quadratic, with AMPA-GABA interaction	0.249
2	AMPA,DC	quadratic, with AMPA-DC interaction	0.238

1	AMPA	Linear	0.146
1	GABA	Quadratic	0.11
1	DC	quadratic	0.0907

292 *For each possible combination of the inputs that were considered (parameters of the model for the*  
293 *statistical linear fit), we found multiple fits to R-activation of CA3 pyramidal cells. When only one input*  
294 *at a time was considered, we found linear models of linear terms and linear models of quadratic*  
295 *terms. When multiple inputs were considered, we found linear models for linear terms, interactions*  
296 *and quadratic terms. We here report the models accounting for the larger portion of the data for each*  
297 *number of inputs considered, and all the single inputs best performing models. The complete list of*  
298 *models found is reported in Table S1. The adjusted  $R^2$  terms can be interpreted as a measure of how*  
299 *much of the variance in the data is captured by a given model. As can be seen from the adjusted  $R^2$*   
300 *values, there was a high noise component in the relationship between inputs and CA3 cells R-*  
301 *activation. However, all models listed showed significant contributions of the inputs considered (by  $p$ -*  
302 *value $<0.05$  criterion).*

303 For CA1 pyramidal cells, we isolated the role of the Schaffer Collateral projections by considering  
304 only the total strength of direct synaptic connections coming to a CA1 pyramidal cell from CA3  
305 pyramidal cells ( $S^{\text{Sch}}$ ). Separately we analyzed the role of activation of the pre-synaptic CA3  
306 pyramidal cells in driving post-synaptic CA1 pyramidal cells by assigning to each CA1 pyramidal cell a  
307 value  $S^{\text{Pre}}$ , which characterized the average strength of the convergent CA3 inputs to all the CA3 cells  
308 that were projecting to a given CA1 cell. Synaptic inhibitory inputs to CA1 pyramidal cells were  
309 represented by  $S^{\text{GABA}}$ , computed by summing the synaptic weights of all GABA connections from CA1  
310 inhibitory neurons to each CA1 pyramidal cell.

311 Again, we analyzed distribution of the input strength across R-activation scores (Figure 3D). There  
312 was a clear trend towards increasing  $S^{\text{Pre}}$  and  $S^{\text{Sch}}$  for increasing R-activation of CA1 pyramidal cells,  
313 while  $S^{\text{GABA}}$  and intrinsic excitability did not show any preferential trend for increasing R-activation  
314 groups. Only for scores above 75% (very rare in the network, as can be seen in Figure 2F) it appeared  
315 that inhibitory synaptic input below the mean could favor high reactivation.

316 We then used fitting of a multivariate linear model. However, we first separated CA1 pyramidal cells  
317 in those with R-activation above and below a threshold of 55% (to satisfy the statistical requirements  
318 to perform linear model fitting). As can be seen in Figure 2F, a small portion of all available CA1  
319 pyramidal cells did show R-activation scores above 55%, so it is possible that this sub-group is less  
320 representative of the general influence of inputs on R-activation scores, compared to the set of cells

321 with R-activation scores up to 55%. In studying the large cell pool (below 55%, Table 2) we found a  
 322 contribution of all inputs (pre-synaptic excitatory input, Schaffer input, inhibitory input and intrinsic  
 323 excitability), with a tendency for Schaffer input to contribute in relationship to the pre-synaptic  
 324 excitatory input, rather than independently. When allowing for quadratic terms, the role of direct  
 325 Schaffer input was rendered null, in favor of heightened influence of pre-synaptic excitatory input  
 326 and synaptic inhibitory input. When the inputs were considered separately, both excitatory synaptic  
 327 inputs showed the highest impact on R-activation.

328 In summary, the interaction of excitatory and inhibitory inputs was significant in modulating CA1  
 329 pyramidal cells R-activation, and intrinsic excitability only increased the overall impact of the  
 330 multivariate model of a minor amount. Mechanistically, this implies that if synaptic activity could  
 331 change only one of these inputs at a given time, it would have the largest effects on R-activation by  
 332 modulating either pre-synaptic AMPA connections in CA3, or Schaffer collaterals. We point out that  
 333 the limited role of intrinsic excitability on R-activation of CA1 pyramidal cells is consistent with our  
 334 earlier findings on a model of CA1 ripple activity driven by current steps (25).

335 **Table 2. Extract of linear regression models for R-activation of CA1 pyramidal cells (below**  
 336 **55% R-activation) vs inputs (from Table S2)**

# Inputs	Inputs in Best Model	Model Equation Type	Adj. R-sq
4	AMPA-Pre,AMPA-Sch,GABA,DC	quadratic, with AMPA-Pre GABA interactions	0.161
3	AMPA-Pre,GABA,DC	quadratic, with AMPA-Pre GABA interactions	0.161
3	AMPA-Pre,AMPA-Sch,DC	Linear + AMPA-Pre AMPA-Sch interaction	0.159
3	AMPA-Pre,AMPA-Sch,GABA	Linear	0.156
2	AMPA-Pre,DC	Linear	0.158
2	AMPA-Pre,GABA	Linear	0.156
1	AMPA-Pre	Quadratic	0.154
1	AMPA-Sch	Linear	0.144
1	GABA	Linear	0.00206
1	DC	Linear	0.00491

337 *For each possible combination of the inputs that were considered (parameters of the model for the*  
 338 *statistical linear fit), we found multiple fits to R-activation of CA1 pyramidal cells. When only one input*  
 339 *at a time was considered, we found linear models of linear terms and linear models of quadratic*  
 340 *terms. When multiple inputs were considered, we found linear models for linear terms, interactions*  
 341 *and quadratic terms. The adjusted R<sup>2</sup> terms can be interpreted as a measure of how much of the*  
 342 *variance in the data is captured by a given model. As can be seen from the adjusted R<sup>2</sup> values, there*  
 343 *was a high noise component in the relationship between inputs and CA1 cells R-activation. However,*

344 *the models listed showed significant contributions of the inputs considered (by  $p$ -value<0.05 criterion).*  
345 *The complete list of models found is reported in Table S2.*

346 Overall, our analyses revealed: (a) how activation in CA3 and CA1 pyramidal cells during SWRs was  
347 controlled by synaptic excitatory inputs in both regions, and (b) the fact that inhibitory synaptic  
348 inputs and intrinsic cell excitability only had a significant influence on the R-activation of CA3  
349 pyramidal cells, but not CA1 cells. Differential impact of inhibitory and intrinsic factors in CA1 vs CA3  
350 was likely driven by the fundamentally different activity present in the two separate regions during  
351 SWR events. Spiking of CA3 pyramidal cells emerges from reverberating excitatory activity, and could  
352 be mediated by post-inhibitory rebound. Spiking in CA1 pyramidal cells is driven by Schaffer  
353 Collateral inputs, and local inhibitory signaling competes with such excitatory synaptic input to  
354 enforce spike timing of CA1 pyramidal cells during ripple oscillations.

### 355 **R-activation of cell pairs increases with shared excitatory input**

356 Having established that specific implementation of the network architecture contributed to shaping  
357 the R-activation of CA3 and CA1 pyramidal cells, we reasoned that connectivity, and in particular  
358 excitatory input, should also contribute to the R-activation of cell pairs. To extend the concept of R-  
359 activation score to cell pairs, we considered two cells and their relative order, and found in which  
360 percent of the total ripples a given cell pair spiked. Since in our definition of cell pair the order of cell  
361 spiking was considered, the R-activation scores of cell pair AB and cell pair BA were in general  
362 different. We used our R-activation score measure to group cell pairs with similar reactivation scores  
363 in the network, and studied their common synaptic inputs, as described above for single cells (in  
364 Figure 3). Below, we analyzed how activation of the cell pairs depended on the network inputs, and  
365 we separately tested CA3-CA3, CA1-CA1 and CA3-CA1 pairs.

366 **CA3-CA3 pairs:** For pairs of two CA3 pyramidal cells (Figure 4A), we defined an excitatory synaptic  
367 input quantifier  $S^{AMPA}$ , by finding all pyramidal cells in CA3 which sent synapses to both CA3 cells in  
368 the pair and considering the product of the synaptic weights from each of such cells to the cells in  
369 the pair (Figure 4A, left panel, shows a drawing of  $S^{AMPA}$ ). Analogously, the inhibitory input reaching a

370 pair of CA3 pyramidal cells was quantified by  $S^{GABA}$ , summing across all interneurons projecting to  
371 both pyramidal cells in the pair the product of the identified synaptic weights (again represented in  
372 Figure 4A, left panel). The intrinsic excitabilities of the two cells in the network were considered  
373 separately.

374 **Figure 4. Cells that co-reactivate share their input.**

375 **A. Relationship between R-activation scores and input for pairs of CA3 pyramidal cells.** Left plot:  
376 drawing and formulae introduce the synaptic AMPA and GABA inputs considered ( $S^{AMPA}$  and  $S^{GABA}$ )  
377 for any cell pair labeled (A, B). These estimates quantify the amount of excitatory and inhibitory input  
378 that cells A and B have in common. Right plot: R-activation of CA3-CA3 cell pairs is related to  
379 strength of synaptic inputs and intrinsic excitability. The bar plot shows on the x –coordinate the  
380 average R-activation score of CA3-CA3 cell pairs belonging to the same score group ( $\pm 5\%$ ) and on  
381 the y-coordinate the level of each different input ( $S^{AMPA}$ ,  $S^{GABA}$  or Intrinsic Excitability for cell A and for  
382 cell B) for cell pairs within that score group. Error bars mark the standard error of the mean. Before  
383 grouping cell pairs by their R-activation scores, each input was z-scored to enable comparisons of  
384 their respective trends. Therefore, a negative y-coordinate does not reflect a negative input, but an  
385 input below the average across the whole network. **B. Relationship between cell pair R-activation**  
386 **scores and inputs for pairs of CA1 pyramidal cells.** Left plot: drawing and formulae introduce the  
387 synaptic inputs considered. For cell pair (A, B) in CA1, excitatory AMPA input from Schaffer collateral  
388 alone is labeled  $S^{Sch}$ , while the role of the excitability of pre-synaptic cells in CA3 is considered in  
389 defining the complementary excitatory synaptic input  $S^{Pre}$ . Inhibitory synaptic input  $S^{GABA}$  is found  
390 analogously to the one for CA3-CA3 cell pairs (in panel **A**). These measures are introduced to  
391 quantify the shared synaptic inputs between cells A and B in each pair. Right plot: cell pair R-  
392 activation scores R-activation of CA1-CA1 cell pairs is related to strength of excitatory synaptic inputs,  
393 but not inhibitory synaptic inputs or intrinsic excitability. The bar plot shows on the x –coordinate the  
394 average R-activation score of CA1-CA1 cell pairs belonging to the same score group ( $\pm 5\%$ ) and on  
395 the y-coordinate the level of each different input ( $S^{Sch}$ ,  $S^{Pre}$ ,  $S^{GABA}$  or Intrinsic Excitability for cell A and  
396 for cell B) for cell pairs within that score group. Error bars mark the standard error of the mean. Before  
397 grouping cell pairs by their R-activation scores, each input was z-scored to enable comparisons of  
398 their respective trends. Therefore, a negative y-coordinate does not reflect a negative input, but an  
399 input below the average across the whole network. **C. Relationship between cell pair R-activation**  
400 **scores and inputs for pairs of CA3-CA1 pyramidal cells.** Left plot: drawing and formulae introduce the  
401 synaptic inputs considered. Excitatory (AMPA-mediated) synaptic inputs are measured as  $S^{Sch}$  (which  
402 emphasize the role of synaptic paths from cell A in CA3 to cell B in CA1) and  $S^{Pre}$  (which emphasizes  
403 the role of cells in CA3 connecting to both cell A in CA3 and cell B in CA1). Inhibitory synaptic input is  
404 found in CA3 for cell A and in CA1 for cell B, the sum of the two constitutes  $S^{GABA}$  for the (A, B) cell  
405 pair. These measures are introduced to quantify the shared synaptic inputs between cells A and B in  
406 each pair. Right plot: cell pair R-activation scores R-activation of CA3-CA1 cell pairs is related to  
407 strength of excitatory synaptic inputs, partly to inhibitory synaptic inputs, but not intrinsic excitability.  
408 The bar plot shows on the x –coordinate the average R-activation score of CA3-CA1 cell pairs  
409 belonging to the same score group ( $\pm 5\%$ ) and on the y-coordinate the level of each different input  
410 ( $S^{Sch}$ ,  $S^{Pre}$ ,  $S^{GABA}$  or Intrinsic Excitability for cell A and for cell B) for cell pairs within that score group.  
411 Error bars mark the standard error of the mean. Before grouping cell pairs by their R-activation  
412 scores, each input was z-scored to enable comparisons of their respective trends. Therefore, a  
413 negative y-coordinate does not reflect a negative input, but an input below the average across the  
414 whole network.

415 In Figure 4A, right plot, we show that both excitatory and inhibitory inputs were larger for cell pairs  
 416 with higher R-activation scores. The intrinsic excitability of the first cell in the network (labeled A in  
 417 the figure) also increased with R-activation of the pair, while the intrinsic excitability of the second  
 418 cell in the pair (labeled B in the figure) decreased for higher R-activations. Intuitively, these opposite  
 419 trends can be understood if one considers that our pair R-activation score is a measure which takes  
 420 into account the order in which the two cells spiked: intrinsic excitability promotes activation of a  
 421 cell but in no connection with activity of other cells. Since for a cell pair to repeat in order across  
 422 ripples it is important that the second cell does not spike de-coupled from the synaptic paths which  
 423 connect its activity to the first cell, having high intrinsic excitability in the second cell would hinder  
 424 the R-activation of the pair.

425 Next, statistical inference analysis of the role played by the different inputs in establishing the R-  
 426 activation of cell pairs within CA3 was performed with linear regressions (Table 3). It revealed a  
 427 significant contribution of all inputs and their interactions to the R-activation of cell pairs within CA3.  
 428 When considering subgroups of inputs, excitatory synaptic input and the intrinsic excitability of the  
 429 first cell in the pair (and their interaction) could account for a large portion of the modulation of R-  
 430 activation by all inputs (and interactions). When taken separately, synaptic inputs (both excitatory  
 431 and inhibitory) still retained an impact on shaping the R-activation of cell pairs, however intrinsic  
 432 excitability of individual cells had a very small impact on R-activation of CA3-CA3 cell pairs.

433 *Table 3. Extract of linear regression models for R-activation of CA3-CA3 pyramidal cell*  
 434 *pairs vs inputs (from Table S3)*

# Inputs	Inputs in Best Model	Model Equation Type	Adj. R-sq
4	AMPA-Pre,GABA,DCa,DCb	Quadratic with all interactions	0.258
3	AMPA-Pre,GABA,DCa	Quadratic with all interactions	0.2479
3	AMPA-Pre,DCa,DCb	Quadratic with all interactions	0.244
2	AMPA-Pre,DCa	Quadratic with all interactions	0.234
1	AMPA-Pre	Quadratic	0.165
1	GABA	Quadratic	0.125
1	DCa	Quadratic	0.0658
1	DCb	Linear	0.00392

435 *For each possible combination of the inputs that were considered (parameters of the model for the*  
436 *statistical linear fit), we found multiple fits to R-activation of CA3-CA3 pyramidal cell pairs. When only*  
437 *one input at a time was considered, we found linear models of linear terms and linear models of*  
438 *quadratic terms. When multiple inputs were considered, we found linear models for linear terms,*  
439 *interactions and quadratic terms. The adjusted  $R^2$  terms can be interpreted as a measure of how*  
440 *much of the variance in the data is captured by a given model. As can be seen from the adjusted  $R^2$*   
441 *values, there was a high noise component in the relationship between inputs and cell pair R-*  
442 *activation. However, the models listed showed significant contributions of the inputs considered (by  $p$ -*  
443 *value $<0.05$  criterion). The complete list of models found is reported in Table S3.*

444 **CA1-CA1 pairs:** We extended the analysis to pairs of CA1 pyramidal cells, by introducing quantifiers  
445 of excitatory and inhibitory inputs (Figure 3). Inhibitory input  $S^{GABA}$  was calculated in the same  
446 manner as for pairs of CA3 pyramidal cells, meaning we found CA1 inhibitory interneurons projecting  
447 to both CA1 pyramidal cells in the pair, multiplied the synaptic strength and summed across all  
448 interneurons impinging on both cells in the pair (a representation is shown in Figure 4B, left panel).  
449 To quantify the excitatory synaptic inputs reaching a pair of CA1 pyramidal cells, we defined two  
450 separate inputs: one considering only the Schaffer Collateral contribution ( $S^{Sch}$ ) and one emphasizing  
451 the role of synaptic paths within CA3 ultimately reaching the cell pair in CA1 ( $S^{Pre}$ ). The inputs driven  
452 by the sole Schaffer Collaterals ( $S^{Sch}$ ) were quantified by finding cells in CA3 which projected to both  
453 cells in the pair (in CA1). The synaptic weights reaching the two cells in the pair were then summed,  
454 and these quantities were further summed across all the CA3 pre-synaptic cells found (formula and a  
455 drawing are introduced in Figure 4B left panel). The role of CA3 connectivity on the activity of a CA1-  
456 CA1 cell pair ( $S^{Pre}$ ) was quantified by assigning to each cell pair a value, found as follows. We first  
457 found paths of two subsequent synapses (di-synaptic paths, from a cell to the next, to the next)  
458 starting from one cell in CA3 and terminating on both cells of the CA1 pair (cells in the middle of the  
459 di-synaptic paths had to be CA3 pyramidal cells). These initial CA3 cells could drive spiking which  
460 impinged (in two synapses) on both cells of the CA1-CA1 cell pair. The synaptic weights along the  
461 paths found this way were combined, and further summed across all the possible di-synaptic paths  
462 from CA3 to CA1 found in the network (the formula is shown on Figure 4B, left panel). The  
463 magnitudes of intrinsic excitability for the two cells in the pair were considered separately.

464 Figure 4B in the right panel shows how the different input strength changed across R-activation  
 465 scores. Excitatory synaptic inputs, both in Schaffer Collaterals and within CA3, were higher for cell  
 466 pairs with higher R-activation scores. In contrast, inhibitory synaptic inputs and intrinsic excitability  
 467 of either cell in the pair did not show a trend with respect to cell pair R-activation. Hence, we  
 468 concluded that – consistently with what we found for the R-activation of single CA1 pyramidal cells –  
 469 only synaptic excitatory inputs could exert an effect on the R-activation of CA1 pyramidal cell pairs.  
 470 Statistical inference analysis (Table 4) showed that the synaptic excitatory inputs and their  
 471 interactions strongly affected R-activation scores of CA1-CA1 pyramidal cell pairs. Inhibitory synaptic  
 472 input and intrinsic excitability of the cells in the pair did score significantly in the model, but  
 473 increased minimally the overall ability of the model to represent R-activations. In other words,  
 474 including inhibitory inputs and intrinsic excitability added great complexity to the model without  
 475 making significant progress on the representation of R-activations as function of the inputs. Hence,  
 476 excitatory synaptic inputs greatly dominated all other deterministic inputs in shaping CA1-CA1 cell  
 477 pair R-activations.

478 **Table 4. Extract of linear regression models for R-activation of CA1-CA1 pyramidal cell**  
 479 **pairs vs inputs (from Table S4)**

# Inputs	Inputs in Best Model	Model Equation Type	Adj. R-sq
5	AMPA-Pre,AMPA-Sch,GABA,Dca,DCb	Quadratic with all interactions	0.164
4	AMPA-Pre,AMPA-Sch,GABA,Dca	Quadratic with all interactions	0.164
4	AMPA-Pre,AMPA-Sch,GABA,DCb	Quadratic with all interactions	0.163
4	AMPA-Pre,AMPA-Sch,Dca,DCb	Quadratic with all interactions	0.161
3	AMPA-Pre,AMPA-Sch,GABA	Quadratic with all interactions	0.163
3	AMPA-Pre,AMPA-Sch,Dca	Quadratic with all interactions	0.161
3	AMPA-Pre,AMPA-Sch,DCb	Quadratic with all interactions	0.16
2	AMPA-Pre,AMPA-Sch	Quadratic with all interactions	0.16
1	AMPA-Pre	Quadratic	0.106
1	AMPA-Sch	Quadratic	0.149
1	GABA	Quadratic	0.000605
1	Dca	Quadratic	0.00051
1	DCb	Quadratic	$7.81 * 10^{-5}$

480 *For each possible combination of the inputs that were considered (parameters of the model for the*  
 481 *statistical linear fit), we found multiple fits to R-activation of CA1-CA1 pyramidal cell pairs. When only*  
 482 *one input at a time was considered, we found linear models of linear terms and linear models of*  
 483 *quadratic terms. When multiple inputs were considered, we found linear models for linear terms,*

484 *interactions and quadratic terms. The adjusted  $R^2$  terms can be interpreted as a measure of how*  
485 *much of the variance in the data is captured by a given model. As can be seen from the adjusted  $R^2$*   
486 *values, there was a high noise component in the relationship between inputs and cell pair R-*  
487 *activation. However, the models listed showed significant contributions of the inputs considered (by p-*  
488 *value<0.05 criterion). The complete list of all models found is reported in Table S4.*

489 **CA3-CA1 pairs:** We finally studied whether the relationship between synaptic input and R-activation  
490 would also extend to the cell pairs that spanned the two hippocampal regions composing our  
491 network. Since SWR dynamics were organized in a CA3 excitatory event inducing inhibitory  
492 oscillations in CA1, we considered only ordered cell pairs in which the first cell was from CA3 and the  
493 second from CA1. To define quantifiers for synaptic inputs to pairs of CA3-CA1 pyramidal cells, we  
494 again looked for synaptic paths connecting both cells in the pair (showed in Figure 4C, left panel).  
495 One direct synaptic input ( $S^{Pre}$ ), considered CA3 pyramidal cells that projected synapses onto both  
496 cells in the pair, and multiplied the two synaptic weights, and summed across all found pre-synaptic  
497 cells. Another excitatory synaptic input quantifier ( $S^{Sch}$ ) was shaped to identify synaptic paths from  
498 the first cell in the pair (in CA3) to the second cell in the pair (in CA1), by finding all di-synaptic paths  
499 from the first cell in the pair to the second cell in the pair, multiplying the synaptic weights found  
500 along the paths and scaling the resulting quantity by the total excitatory synaptic input reaching the  
501 first cell in the pair (formula and drawing in Figure 4C). Since each pyramidal cell in the pair could  
502 receive inhibition only from interneurons within its same region, the inhibitory synaptic inputs to the  
503 two cells in the pair were quantified first separately following the definitions used for single cells in  
504 CA3 and in CA1, and the pair inhibitory synaptic input  $S^{GABA}$  was computed by the sum of their  
505 respective inputs. Intrinsic excitability for each cell in the pair was considered separately.

506 Once the synaptic and intrinsic deterministic inputs were found, we again plot how the input  
507 strength changed across R-activation scores (Figure 4C right panel). We found that excitatory and  
508 inhibitory inputs were higher for cell pairs with higher R-activations, while intrinsic excitability of  
509 either the first or second cell in the pair had no special trend across R-activation.

510 To describe the differential role of inputs in shaping the R-activation of CA3-CA1 cell pairs, we  
 511 derived a statistical inference analysis using multiple variable linear regressions (Table 5). We found  
 512 a strong dominance of excitatory synaptic inputs over the R-activation scores of CA3-CA1 pairs.  
 513 When considered separately, pre-synaptic and Schaffer AMPA inputs both accounted for most of the  
 514 impact of inputs on R-activation, in comparison to the effect found when considering all inputs and  
 515 all their interactions. In particular, the Schaffer input had the strongest independent impact on R-  
 516 activations. Furthermore, intrinsic excitability of either cell in the pair, while qualifying for  
 517 significance in affecting the R-activation score, again did not introduce any strong improvement on  
 518 the ability of excitatory synaptic inputs (and their interactions) to shape R-activations of CA3-CA1 cell  
 519 pairs. In summary, what was true for single CA1 pyramidal cells and CA1 cell pairs carries over to  
 520 CA3-CA1 cells pairs, emphasizing the dominant role of paths of excitatory synaptic connections over  
 521 inhibitory ones and intrinsic excitability in promoting activation of ordered cell pairs across many  
 522 SWRs.

523 *Table 5. Extract of linear regression models for R-activation of CA3-CA1 pyramidal cell*  
 524 *pairs vs inputs (from Table S5)*

# Inputs	Inputs in Best Model	Model Equation Type	Adj. R-sq
5	AMPA-Pre,AMPA-Sch,GABA,Dca,DCb	Quadratic with all interactions (but Dca-DCb)	0.194
4	AMPA-Pre,AMPA-Sch,GABA,Dca	Quadratic with all interactions (but GABA-Dca)	0.193
4	AMPA-Pre,AMPA-Sch,GABA,DCb	Quadratic with all interactions	0.194
4	AMPA-Pre,GABA,Dca,DCb	Quadratic with interactions: AMPA-Pre & GABA, AMPA-Pre & Dca, GABA&Dca, GABA&DCb	0.192
3	AMPA-Pre,AMPA-Sch,GABA	Quadratic with all interactions	0.193
3	AMPA-Pre,GABA,Dca	Quadratic with all interactions	0.191
3	AMPA-Sch,GABA,DCb	Quadratic with all interactions (but AMPA-Sch DCb)	0.192
3	AMPA-Pre,GABA,DCb	Quadratic with all interactions	0.192
2	AMPA-Pre,GABA	Quadratic with all interactions	0.191
1	AMPA-Pre	Linear	0.174
1	DCb	Quadratic	0.00028
1	Dca	Quadratic	8.37*10 <sup>-7</sup>
1	GABA	Quadratic	0.0106
1	AMPA-Sch	Quadratic	0.168

525 *For each possible combination of the inputs considered (parameters of the model for the statistical*  
 526 *linear fit), we found multiple fits to R-activation of CA3-CA1 pyramidal cell pairs. When only one input*

527 *at a time was considered, we found linear models of linear terms and linear models of quadratic*  
528 *terms. When multiple inputs were considered, we found linear models for linear terms, interactions*  
529 *and quadratic terms. The adjusted  $R^2$  terms can be interpreted as a measure of how much of the*  
530 *variance in the data is captured by a given model. As can be seen from the adjusted  $R^2$  values, there*  
531 *was a high noise component in the relationship between inputs and cell pair R-activation. However,*  
532 *the models listed showed significant contributions of the inputs considered (by  $p$ -value<0.05 criterion).*  
533 *The complete list of all models found is reported in Table S5.*

534 Our analysis across all the possible cell pairs in this network revealed that the spontaneously  
535 emergent SWRs in our model encompassed a structured representation of single cells and ordered  
536 cell pairs across SWRs, and that such representation was synaptically driven. While the network  
537 topology was responsible for the general SWR spiking activity, the specifics of which cells received  
538 stronger excitatory synaptic inputs, especially if inputs were considered along synaptic paths which  
539 can deliver convergent excitation to a cell pair, exerted selectivity on cells and cell pairs, determining  
540 their chances for activation across multiple SWRs in time.

541 This analysis gives rise to a scenario in which the same network properties which enable the  
542 spontaneous emergence of SWRs in the CA3-CA1 architecture (high recurrence in CA3 pyramidal  
543 cells, noise-driven spiking in CA3, strong drive to inhibitory neurons in CA1 from CA3 activity) also  
544 select a small subset of cells which are most likely to reactivate in a high fraction of SWRs. In other  
545 words, our model predicts that replay arises by virtue of the same AMPA/GABA synaptic architecture  
546 which generates SWRs themselves. During sleep, the content of hippocampal replay can  
547 theoretically be selected within the hippocampal circuitry, and interact with cortical activity by  
548 carefully organized timing of SWRs compared to other ongoing oscillations. Within this architecture,  
549 memory formation mechanisms during wake (such as STDP, reward signals and awake replay) can  
550 modify the chances of specific cells to be replayed during sleep SWRs by altering the relative  
551 strengths of synaptic pathways impinging on a group of cells.

## 552 **Synaptic Plasticity can influence R-activation**

553 Our analysis so far showed a tight relationship between deterministic inputs to cell pairs in the  
554 network and their R-activation scores, which suggests that mechanisms capable of modifying such

555 deterministic inputs (such as learning) could in principle modify the R-activation of cell pairs (and  
556 hence sequences) in spontaneous SWRs. In the following, we tested whether changing inputs (as  
557 defined in the previous section) to a randomly chosen cell pair did in fact result in an increase in its  
558 R-activation score.

559 We started by randomly choosing the cell pair, labeled A and B. In a first set of simulations  
560 (representing, for example, the sleep on the night before a learning experience, marked with PRE in  
561 Figure 5) we found the R-activation score for cell pair AB, together with the deterministic synaptic  
562 inputs to AB and intrinsic excitability of A and B. Depending on the type of cell pair considered (CA3-  
563 CA3, CA3-CA1 or CA1-CA1) we chose which deterministic inputs were likely to be most impactful on  
564 the R-activation score of the cell pair, based on our finding in the previous section. We then re-  
565 scaled the strengths of all synaptic connections which contributed to the chosen inputs (and the  
566 parameter controlling intrinsic excitability where appropriate), so that in the new connectivity  
567 profile the cell pair AB would have larger inputs. We next ran a new simulation, to test how the  
568 spontaneous R-activation of the cell pair AB would change for increasing inputs. It is to note that we  
569 require that our manipulation preserved the main properties of the spontaneous SWR activity in the  
570 network within physiological bounds (i.e. the network did not show constantly firing cells, or highly  
571 rhythmically occurring SWRs).

572 **Figure 5. Increased synaptic strengths promote R-activation of randomly selected cell pairs.**  
573 **A.** One example of CA3 cell pair AB randomly chosen in a simulation. Reported on the bar plots are  
574 its R-activation score,  $S^{AMPA}$ ,  $S^{GABA}$  and the intrinsic excitability of both cell A and B separately. For  
575 each measured output, the value for the AB pair is shown next to a bar reporting the mean  $\pm$ standard  
576 deviation across all pairs of CA3 pyramidal cells (or single cells) in the same simulation. The scaling  
577 introduced in the network connectivity and intrinsic excitability increased all considered inputs from  
578 before (PRE, green) to after (POST, red). Note that the mean and standard deviations of the inputs  
579 across the network do not change from PRE to POST. The R-activation score of AB is near the mean  
580 in PRE, and larger than one standard deviation above the mean in POST. **B.** One example of CA3-  
581 CA1 cell pair AB randomly chosen in a simulation. Reported on the bar plots are its R-activation  
582 score,  $S^{Pre}$ ,  $S^{Sch}$  and  $S^{GABA}$ . For each measured output, the value for the AB pair is shown next to a  
583 bar reporting the mean  $\pm$ standard deviation of that value across all pairs of CA3-CA1 pyramidal cells  
584 in the same simulation. The scaling introduced in the network connectivity increased all considered  
585 inputs from before (PRE, green) to after (POST, red). Note that the mean and standard deviations of  
586 the inputs across the network do not change from PRE to POST. The R-activation score of AB is near  
587 the mean in PRE, and larger than one standard deviation above the mean in POST. **C.** One example

588 of CA1-CA1 cell pair AB randomly chosen in a simulation. Reported on the bar plots are its R-  
589 activation score,  $S^{Pre}$  and  $S^{Sch}$ . For each measured output, the value for the AB pair is shown next to a  
590 bar reporting the mean  $\pm$  standard deviation of that value across all pairs of CA1-CA1 pyramidal cells  
591 in the same simulation. The scaling introduced in the network connectivity increased all considered  
592 inputs from before (PRE, green) to after (POST, red). Note that the mean and standard deviations of  
593 the inputs across the network do not change from PRE to POST. The R-activation score of AB is near  
594 the mean in PRE, and larger than one standard deviation above the mean in POST.

595 Specifically, for pairs of CA3 pyramidal cells, we had previously found (Figure 4A) that excitatory and  
596 inhibitory synaptic inputs and intrinsic excitability of the first cell of the pair were larger for higher R-  
597 activating cell pairs. Hence, for a randomly chosen pair AB, we scaled synaptic connections  
598 contributing to  $S^{AMPA}(A,B)$  and  $S^{GABA}(A,B)$ , and increased the intrinsic excitability of A. The scaling was  
599 uniform across all synapses contributing to the inputs, and it was cell pair specific, because its  
600 specific value was derived by requiring that the inputs considered will increase at least one standard  
601 deviation above the network mean after scaling. As a result, a small percentage of AMPA and GABA  
602 synapses within the CA3 network was scaled (less than 0.6% of AMPA and less than 2% of GABA  
603 synapses). This led to an increase of the cell pair R-activation score from mean value of  
604 approximately 5% to about 20% (more than one standard deviation above the mean, shown in the  
605 leftmost bar plot of Figure 5A). In a total of 6 tests of randomly selected cell pairs and simulations,  
606 the change of selected inputs and excitability led to increased cell pair R-activation score, while  
607 maintaining a network activity profile well within physiological bounds. Hence, for CA3-CA3 pairs, we  
608 concluded that uniform scaling of all synapses co-impinging on a pair could promote R-activation of  
609 that pair.

610 For CA3-CA1 cell pairs, we chose to modify both excitatory ( $S^{Pre}$  and  $S^{Sch}$ ) and inhibitory ( $S^{GABA}$ )  
611 synaptic inputs, since they all showed an increasing trend for increasing R-activation of CA3-CA1  
612 cell pairs (Figure 4C). Hence, our scaling involved AMPA synapses within CA3 and from CA3 to CA1  
613 pyramidal cells, and GABA synapses within CA3 and within CA1. In one example of a randomly  
614 selected CA3-CA1 cell pair AB, shown in Figure 5B, the synaptic manipulation resulted in increased  
615 excitatory and inhibitory synaptic inputs on cell pair AB, while the mean and standard deviation of  
616 each input was not altered (the change affected less than 2% of AMPA synapses within CA3, less

617 than 0.5% of Schaffer collaterals, less than 3% of GABA synapses in CA3 and about 12% of GABA  
618 synapses in CA1). The change in synapses produced a significant increase of AB R-activation score,  
619 from ~7% to more than 30%. Among a total of 6 randomly selected CA3-CA1 cell pairs and  
620 simulations, analogous manipulations resulted in increased R-activation score for the cell pair in 4  
621 cases, while all tests showed SWR activity within physiological bounds.

622 Finally, to study the effect of synaptic scaling on the R-activation of a CA1-CA1 cell pair, we elected  
623 to modify only the excitatory synaptic inputs reaching the cell pair ( $S^{\text{Pre}}$  and  $S^{\text{Sch}}$ , defined in Figure  
624 4B), since inhibitory synaptic inputs and intrinsic excitability of either cell in the pair did not show a  
625 clear increasing trend for increasing R-activation score across CA1-CA1 cell pairs (Figure 4B). In one  
626 example of randomly selected AB CA1-CA1 cell pair (Figure 5C), both excitatory synaptic inputs  
627 increased due to our synaptic scaling procedure, and AB R-activation score grew from about 2% to  
628 above 15%. In contrast to other types of cell pairs, we found that for CA1-CA1 cell pairs the scaling of  
629 excitatory synaptic inputs very often affected the network dynamics. In a total of 11 randomly  
630 selected cell pairs and simulations which resulted in increased AB R-activation, most of them (9  
631 samples) showed an exaggerated amount of SWRs in network activity following synaptic scaling. This  
632 was likely due to the much larger fraction of excitatory synapses being modified by the scaling  
633 procedure (about 5% of all AMPA synapses between CA3 pyramidal cells, and 0.05% of Schaffer  
634 collaterals) compared to other types of cell pairs. To avoid this pitfall, we studied the  
635 complementary problem: whether reducing the input to a randomly selected CA1-CA1 cell pair  
636 would cause a reduction in the cell pair R-activation score. In a total of 7 randomly selected cell pairs  
637 and simulations, we scaled synapses within CA3 pyramidal cells and from CA3 pyramidal cells to CA1  
638 pyramidal cells to reduce the  $S^{\text{Pre}}$  and  $S^{\text{Sch}}$  on pair AB. As expected, in all tests the network activity  
639 remained physiological, and we found in 5 tests that the synaptic manipulation resulted in lower R-  
640 activation score for the selected cell pair.

641 We conclude that this artificial manipulation was effective at increasing R-activation in cell pairs as  
642 long as it did not affect a large fraction of excitatory cells (hence sending the network activity out of  
643 balance). We predict that physiological synaptic plasticity aimed to increase excitatory synaptic  
644 inputs to a CA1-CA1 cell pair which is part of a memory trace will not influence all synaptic paths  
645 leading to the pair but rather modify synapses within a specific subset of CA3 and CA1 cells (a cell  
646 assembly). The choice of which cells and synapses will be affected by learning-driven plasticity would  
647 likely depend on the specific spiking of cells during behavior. In other words, our study suggests that  
648 the reactivation of a cell assembly during ripples in CA1 really derives from the generalized  
649 reactivation of a CA3-CA1 cell assembly, which – according to our results – is established by plastic  
650 modulation of excitatory synaptic paths within CA3 and Schaffer collaterals, inhibitory synaptic paths  
651 within both CA3 and CA1, and the intrinsic excitability of CA3 pyramidal cells.

## 652 Discussion

653 In this paper, we introduced a spiking network of CA3-CA1 activity showing spontaneously  
654 emergent, localized, stochastic SWRs. Within these events, we studied the spike reactivation in CA3  
655 and CA1 during SWRs, and measured the fraction of ripples in which a cell spiked with a “ripple-  
656 activation” (R-activation) score between 0 and 100%. When compared to a stationary sampling  
657 process, we found that a relatively rigid network architecture (defined by stationary probability  
658 distributions of intrinsic and synaptic cell properties) shaped the spiking of low R-activating cells (the  
659 majority), while network dynamics (dependent on the specific implementation of the network  
660 configuration) shaped the activity of highly R-activating cells. We further found that the degree to  
661 which a cell activated across ripples was modulated by the amount of synaptic excitatory and  
662 inhibitory input received by the cell. In particular, for CA3 cells but not for CA1 cells, we found a role  
663 for intrinsic cell excitability in shaping cell activation across ripples. This observation generalized to  
664 cell pairs and synaptic paths which impinge on both cells composing the pair, meaning that a shared  
665 pathway of synaptic input could promote co-activation of cell pairs. Furthermore, we showed that

666 increasing the shared synaptic input of a cell pair could lead to increased R-activation. Together,  
667 these observations are indicative of a network-wide coordination of activation probability across  
668 SWRs for cells and cell pairs, which is further refined by specific synaptic strengths. This suggests a  
669 possible competition for R-activation among cell assemblies, where synaptic strengths mediate the  
670 chance of dominance of a given memory over others during spontaneous SWRs.

### 671 Model captures both generic ripple activity and potential mechanisms of learning-dependent 672 replay

673 CA1 place cells recruited during encoding of recent experience are known to reactivate together  
674 during subsequent sleep (14). Importantly, rather than displaying a uniform probability of spiking  
675 during ripples, cells can be divided in those which are active during SWRs and those which are not, a  
676 feature that persists across recordings (3, 24). The precise manner in which *in vivo* SWRs involve or  
677 exclude a specific pyramidal cell from their activity remains unknown. Our model predicts that  
678 synaptic plasticity during learning (such as, e.g., mediated by awake SWR activity (31, 37, 38)) could  
679 effectively cause the inclusion of cells coding for a novel learned task in the set of CA1 pyramidal  
680 cells which are spiking during sleep SWRs (24). Hence, we propose that SWRs frame activation of a  
681 generic representation within which spikes from the specific place cells involved in recently encoded  
682 experience are preferentially engaged, gated by recent synaptic plasticity.

### 683 Other models of SWR and hippocampal replay

684 The biophysical model of CA3-CA1 SWR activity which we propose in this study builds on a vast  
685 literature on the mechanisms of ripples and sharp waves. *In vitro* and *in vivo* studies have shown  
686 that in CA1 ripples are dominated by inhibitory phasic activity (39, 40), and basket cells spike at high  
687 frequency (39, 41) in localized groups (26). Meanwhile, pyramidal cells spike relatively rarely, phase-  
688 locked to windows of opportunity left by the ongoing oscillatory inhibitory signal (22, 33). In CA3,  
689 excitatory and inhibitory spiking is not locked to CA1 ripple waves (30), and can emerge  
690 spontaneously (39, 42) *in vitro*, while *in vivo* its initiation is still under investigation (23, 43). In the

691 search for explanatory mechanisms underlying SWRs, numerous possible strategies have been  
692 introduced. Gap junctions between CA3 pyramidal cells have been proposed to be necessary (44, 45)  
693 but experimental evidence is still not definitive for such mechanism (3, 46, 47). Models which take  
694 advantage of supra-linear summation of post-synaptic potentials among CA3 and CA1 pyramidal  
695 cells have proposed that SWRs are synaptically propagating waves, where each excitatory spike  
696 induces its own local feedback inhibitory activity (48, 49). These assume a very similar activity in CA3  
697 and CA1 during SWRs, and depend strictly on the presence of strong excitatory synapses between  
698 CA1 cells (which have been found to be very few (50)). In work by Taxidis et al. (51), AMPA and GABA  
699 receptor-mediated synaptic activity, combined with intrinsic bursting of CA3 pyramidal cells, are the  
700 basic mechanisms underlying the emergence of SWRs in a computational model which can be seen  
701 as a precursor to our model. In the model by Taxidis, SWRs have to happen rhythmically, because  
702 their initiation is crucially tied to the bursting activity in the CA3 recurrent network: that model  
703 requires that CA3 pyramidal cells spike in bursts, and do so in strong synchrony in every theta cycle.  
704 In our model, SWRs occur stochastically, with long stochastic pauses in between packets of events,  
705 consistent with *in vivo* findings (52). This physiologically realistic result arises from taking into  
706 consideration the crucial role played by background noisy activity in setting the SWR mechanism.

707 In previous work (25), we introduced a model of CA1 receiving direct current (a simplified sharp  
708 wave). In that model, ripples in CA1 were represented by transient orbits of a dynamical system in  
709 which ripple activity is initiated by a synchronizing input to interneurons, then activity winds around  
710 a fixed point inducing fast decaying oscillations, and termination is due to heterogeneity among the  
711 interneurons driving the transient orbit back to the stationary (de-synchronized) state. Here, we  
712 introduce sharp wave activity in CA3 which is an escape process. The CA3 network has strong  
713 recurrence of excitatory synapses, and CA3 pyramidal cells are in a noise-driven spiking regime,  
714 which means that spikes are driven by fluctuations in the incoming currents (including synaptic  
715 ones). This imposes a disorganized state in the network (LIA, found during slow wave sleep in the  
716 hippocampus (3)), and SWRs emerging when enough CA3 pyramidal cells spike in a small window of

717 time. This leads part of the network to organize, accumulating recruitment of other pyramidal cells  
718 and interneuron spikes until the network cannot sustain its propagation any further. This implies  
719 that sparseness in the CA3 recursive synapse architecture is also a necessary property of our model  
720 design.

721 Our model design for sharp wave activity is similar to the one introduced by Omura et al. (36), which  
722 particularly addressed the lognormal distribution of firing rates found across CA3 activity and its  
723 relationship to a specific distribution in the synaptic weights of excitatory connections in the  
724 network. In their model, hippocampal activity is isolated from external input, apart from a short-  
725 lived initial Poisson drive. Our new model is a complete CA3-CA1 spontaneous activity design, where  
726 sharp waves and ripples are built to be different phenomena, one mainly excitatory, marked by  
727 wave propagation and extending to a large portion of the excitatory population, one mainly  
728 inhibitory, rhythmic and involving a small fraction of local pyramidal cells. In our model, cells receive  
729 colored noise to represent the ongoing activity of all other inputs (for example from entorhinal  
730 cortex) present *in vivo* (53). Furthermore, we focus on how this structure is capable of supporting  
731 replay mediated by AMPA and GABA synapses, which is not addressed in Omura et al. The ability of  
732 selective connections to promote cell assembly reactivation (spontaneous and evoked) has been  
733 analyzed recently by (54) who show that synaptic strengths among cells in one assembly can  
734 promote burst-reactivation, considering both excitatory and inhibitory cells as part of the assembly.  
735 In our study, we consider spikes of pyramidal cells to represent information content and spikes of  
736 inhibitory cells to contribute to the shape of overall network dynamics (ending a sharp wave in CA3,  
737 and pacing the frequency of ripples in CA1). This idea is consistent with experimental data which has  
738 found a heightened specificity in the activation of hippocampal pyramidal cells compared to  
739 hippocampal interneurons across the various rhythmic activities which mark different phases in  
740 information processing in an *in vivo* task (55).

## 741 Summary and predictions for reactivation

742 We believe our model is the first which addresses the mechanisms of localized activity not only in  
743 CA1 (ripples), but also in CA3 (sharp waves). Our study further expands the possibilities on how  
744 hippocampal reactivation during sleep can interact with ongoing activity in cortex and other brain  
745 structures. It predicts that topologically organized input (from CA2 or directly from mossy fibers)  
746 could selectively activate a given portion of CA3 and foster reactivation which is specific to that area  
747 (a local SWR event). The spiking content which is then reactivated (the precise spike sequence) in  
748 CA3-CA1 will depend on the specific synaptic connections within CA3 and between CA3 and CA1.  
749 Such replay could then be passed downstream (through subiculum and its targets) back to cortex  
750 and other structures, in an ongoing loop aimed at changing synapses outside the hippocampus  
751 based on the content of hippocampal replay activated through selective projections from upper  
752 layers of entorhinal cortex to dentate gyrus (and hence CA3). For this overall consolidation to take  
753 place, and hence perform a share-and-transfer of information from hippocampus to cortex during  
754 slow wave sleep, ripples need to be flexible in their timing, while their content needs to be stable,  
755 but able to be evoked differentially depending on the overall input activity (replay is known to  
756 change due to auditory stimulation during sleep (32), for example). Furthermore, for consolidation  
757 to take place, SWRs need to be able to reactivate recent and past events to foster the integration of  
758 new factual events in generalized conceptual schemas which enable the animal (and humans) to use  
759 its experiences to comprehend the world surrounding it (hence, generalize). A CA3-CA1 network  
760 which is too rigid, too rhythmic, or too dependent on few supra-linear connections in its specific  
761 SWR activity, will find it harder to support flexible spiking to mediate consolidation across a night of  
762 sleep.

## 763 **Materials and Methods**

### 764 **Network Model: rationale**

765 We started with our previously developed (25) network of CA1 pyramidal and basket cells and  
766 constructed a network of pyramidal and basket cells to represent CA3 activity, then built Schaffer  
767 Collaterals projecting CA3 pyramidal cells to CA1 pyramidal cells and interneurons. We used  
768 equations of the adaptive exponential integrate and fire formalism (56, 57), which can show bursting  
769 activity (like CA3 and CA1 pyramidal cells (58)) or fast-spiking activity (like basket cells (58))  
770 depending on their parameters (57). CA3 pyramidal cells were allowed a stronger tendency to burst  
771 in response to a current step input by having a less strong spike frequency adaptation than CA1  
772 neurons (58). For simplicity, all cells belonging to the same population had the same parameters  
773 (specified in the following section). To introduce heterogeneity among cells in the network, every  
774 cell received a different direct current term (selected from a normal distribution)), and every cell  
775 received an independent Ornstein–Uhlenbeck process (OU process) (59), which can be thought of as  
776 a single-pole filtered white noise, with cutoff at 100Hz. This noisy input was added to take into  
777 account the background activity of the cells which we did not explicitly model in the network. The  
778 standard deviation of the OU process controlled the size of the standard deviation in sub-threshold  
779 fluctuations of cell voltages, and was a parameter kept fixed within any cell type. Once the  
780 parameter tuning was in effect, the cells (even when disconnected from the network) were showing  
781 fast and noisy sub-threshold voltage activity, and their spikes were non-rhythmic, driven by  
782 fluctuations in the noise input they received, which is called a noise-driven spiking regime, rather  
783 than a deterministic spiking regime, and is representative of *in vivo* conditions (60-62).

784 Cells were arranged within a one-dimensional network in CA3 (see Figure 1A), and connectivity  
785 within CA3 was characterized by each cell reaching other cells within a third of the network around  
786 them (Figure 1B), which is consistent with anatomical estimates (28). For pyramidal to pyramidal  
787 cells connections, the probability of synaptic contact within this radius of one third was higher for

788 neurons closer to the pre-synaptic cell and decayed for neurons further away. Details of all network  
 789 connections are introduced in the Network Model: connectivity section. Intuitively, the highly  
 790 recurrent connections between pyramidal cells in CA3 had a gradient in density that resulted in a  
 791 convergence/divergence connectivity fairly uniform across all CA3 pyramidal cells, which represents  
 792 the overall homogeneity of CA3 pyramidal cells arborization within the region Overall, this  
 793 connectivity represents the highly recurrent pyramidal connections in CA3 without introducing  
 794 special hubs of increased excitatory recurrence in any specific location in the network.

### 795 **Network Model: equations and parameters**

796 We model SWR activity in the hippocampus using a network of 240 basket cells and 1200 pyramidal  
 797 cells in CA3, 160 basket cells and 800 pyramidal cells in CA1. The ratio of excitatory to inhibitory  
 798 neurons is known to be approximately 4 (58) and since in our model we did not introduce any of the  
 799 numerous hippocampal interneuron types but for basket cells, we apply that ratio to the pyramidal  
 800 to basket cell network. This ratio also favored the ability of the network to support a background  
 801 disorganized spiking regime, where excitatory and inhibitory currents were able to balance each  
 802 other (53). For each neuron, the equations are

$$C \dot{v} = -g_L(v - E_L) + g_L \Delta \exp\left(\frac{(v - V_t)}{\Delta}\right) - w + I(t)$$

$$\tau_w \dot{w} = a(v - E_L) - w$$

$$v(t) = V_{thr} \Rightarrow v(t + dt) = V_r, w(t + dt) = w(t) + b$$

$$I(t) = I_{DC} + \beta \eta_t + I_{syn}(t)$$

$$\tau d\eta_t = -\eta_t dt + dW_t$$

$$I_{inp}(t) = I_{max} \left(1 + \exp\left(-\frac{t - t_{on}}{k}\right)\right)^{-1} \left(1 + \exp\left(\frac{t - t_{off}}{k}\right)\right)^{-1}$$

803 CA1 cells parameters are reported in (25), and CA3 cells parameters were as follows. Pyramidal cells  
 804 parameters: C (pF) = 200;  $g_L$  (nS) = 10;  $E_L$  (mV) = -58; A = 2; b (pA) = 40;  $\Delta$  (mV) = 2;  $\tau_w$  (ms) = 120;  $V_t$

805 (mV) = -50;  $V_r$  (mV) = -46;  $V_{thr}$  (mV) = 0. Interneurons parameters: C (pF) = 200;  $g_L$  (nS) = 10;  $E_L$  (mV) = -  
806 70; A = 2; b (pA) = 10;  $\Delta$  (mV) = 2;  $\tau_w$  (ms) = 30;  $V_t$  (mV) = -50;  $V_r$  (mV) = -58;  $V_{thr}$  (mV) = 0.

807 The coefficients establishing noise size were  $\beta = 80$  for pyramidal cells,  $\beta = 90$  for interneurons. DC  
808 inputs were selected from Gaussian distributions with mean 24 (pA) and standard deviation 30% of  
809 the mean for pyramidal cells in CA3, mean 130 (pA) and standard deviation 30% of the mean for CA3  
810 interneurons, mean 40 (pA) and standard deviation 10% of the mean for CA1 pyramidal cells and  
811 mean 180 (pA) and standard deviation 10% of the mean for CA1 interneurons.

812 Synaptic currents were modeled with double exponential functions, for every cell  $n$  we had  
813 
$$I_{syn}(t) = \sum_{j=1}^{160} g^{j \rightarrow n} s^{j \rightarrow n}(t)(v_n - E_i) + \sum_{j=1}^{800} g^{j \rightarrow n} s^{j \rightarrow n}(t)(v_n - E_e),$$

814 where  $E_i = -80$  mV and  $E_e = 0$  mV, and  $s^{j \rightarrow n}(t) = \sum_{t_k} F \left( e^{H\left(\frac{t-t_k}{\tau_D}\right)} - e^{H\left(\frac{t-t_k}{\tau_R}\right)} \right)$ , where  $t_k$  are all  
815 the spikes of pre-synaptic cell  $j$ .

816 In this equation,  $F$  is a normalization coefficient, set so that every spike in the double exponential  
817 within parentheses peaks at one, and  $H(\cdot)$  is the Heaviside function, ensuring that the effect of each  
818 pre-synaptic spike affects the post-synaptic current only after the spike has happened. The time  
819 scales of rise and decay (in ms) used in the model were as follows (25, 51, 63, 64). For AMPA  
820 connections from pyramidal cells to pyramidal cells:  $\tau_R = 0.5$ ,  $\tau_D = 3.5$ . For AMPA connections from  
821 pyramidal cells to interneurons:  $\tau_R = 0.5$ ,  $\tau_D = 3$ . For GABA<sub>A</sub> connections from interneurons to  
822 interneurons:  $\tau_R = 0.3$ ,  $\tau_D = 2$ . For GABA<sub>A</sub> connections from interneurons to pyramidal cells:  $\tau_R = 0.3$ ,  $\tau_D =$   
823 3.5.

## 824 **Network Model: connectivity**

825 The CA3 network was organized as a one-dimensional network. For connections from a CA3  
826 pyramidal cell to the other CA3 pyramidal cells, we first considered a radius (of about one third of  
827 the network) around the presynaptic cell, and the probability of connection from the presynaptic cell

828 to any cell within such radius was higher for cells with indices nearby the presynaptic cell and  
829 reduced progressively with cell index distance (28). Specifically, we used a cosine function to shape  
830 the probability within the radius, and parameterized how fast with index distance the probability  
831 had to decay by using a monotonic scaling of the cosine phase: if  $x$  was the index distance within the  
832 network,  $y = \arctan(kx)/\arctan(k)$  imposed the decay probability  $p(y) = P\cos(4y)$ , where  $P$  was the  
833 peak probability and  $k=2$  was a parameter controlling the decay of connection probability with  
834 distance within the radius. An analogous structure underlaid the probability of CA3 pyramidal cells to  
835 connect to inhibitory interneuron in CA3 and for Schaffer Collaterals to connect a CA3 pyramidal cell  
836 to CA1 pyramidal cells (28). To balance the relationship between feed-forward excitation from  
837 pyramidal cells to interneurons and feedback inhibition from interneurons to pyramidal cells,  
838 probability of connection from a presynaptic basket cell to a cell within a radius (about 1/3 of the  
839 network size) was constant at 0.7, for GABA<sub>A</sub> connections to both CA3 pyramidal cells and  
840 interneurons. Within CA1 connectivity was all-to-all, with the caveat that synaptic weights which  
841 were sampled at or below zero caused a removal of a given synapse. As a result, most synapses  
842 between CA1 pyramidal cells were absent, consistently with experimental findings (50). To introduce  
843 heterogeneity among synaptic connections, synaptic weights for all synapse types were sampled  
844 from Gaussian distributions with variance ( $\sigma$ ) given by a percent of the mean ( $\mu$ ). Parameters used in  
845 the simulations were (we use the notation Py3 and Py1 to denote pyramidal cells in CA3 and CA1,  
846 respectively and analogously Int3/Int1 for interneurons). Py3->Py3:  $\mu = 34$ ,  $\sigma = 40\%\mu$ ; Int3->Int3:  $\mu =$   
847  $54$ ,  $\sigma = 40\%\mu$ ; Py3->Int3:  $\mu = 77$ ,  $\sigma = 40\%\mu$ ; Int3->Py3:  $\mu = 55$ ,  $\sigma = 40\%\mu$ ; Py3->Py1:  $\mu = 34$ ,  $\sigma = 10\%\mu$ ;  
848 Py3->Int1:  $\mu = 320$ ,  $\sigma = 10\%\mu$ ; Int1->Int1:  $\mu = 3.75$ ,  $\sigma = 1\%\mu$ ; Py1->Int1:  $\mu = 6.7$ ,  $\sigma = 1\%\mu$ ; Int1->Py1:  $\mu$   
849  $= 8.3$ ,  $\sigma = 1\%\mu$ ; Py1->Py1:  $\mu = 0.67$ ,  $\sigma = 1\%\mu$ . It is to note that the mean ( $\mu$ ) declared was normalized  
850 by the total number of cells before the variance to the mean was introduced in the distribution.  
851 Since the CA3 and CA1 networks are of different sizes, a direct comparison of the parameter values  
852 or their magnitude across regions would not account for the effective values used in the simulations.  
853

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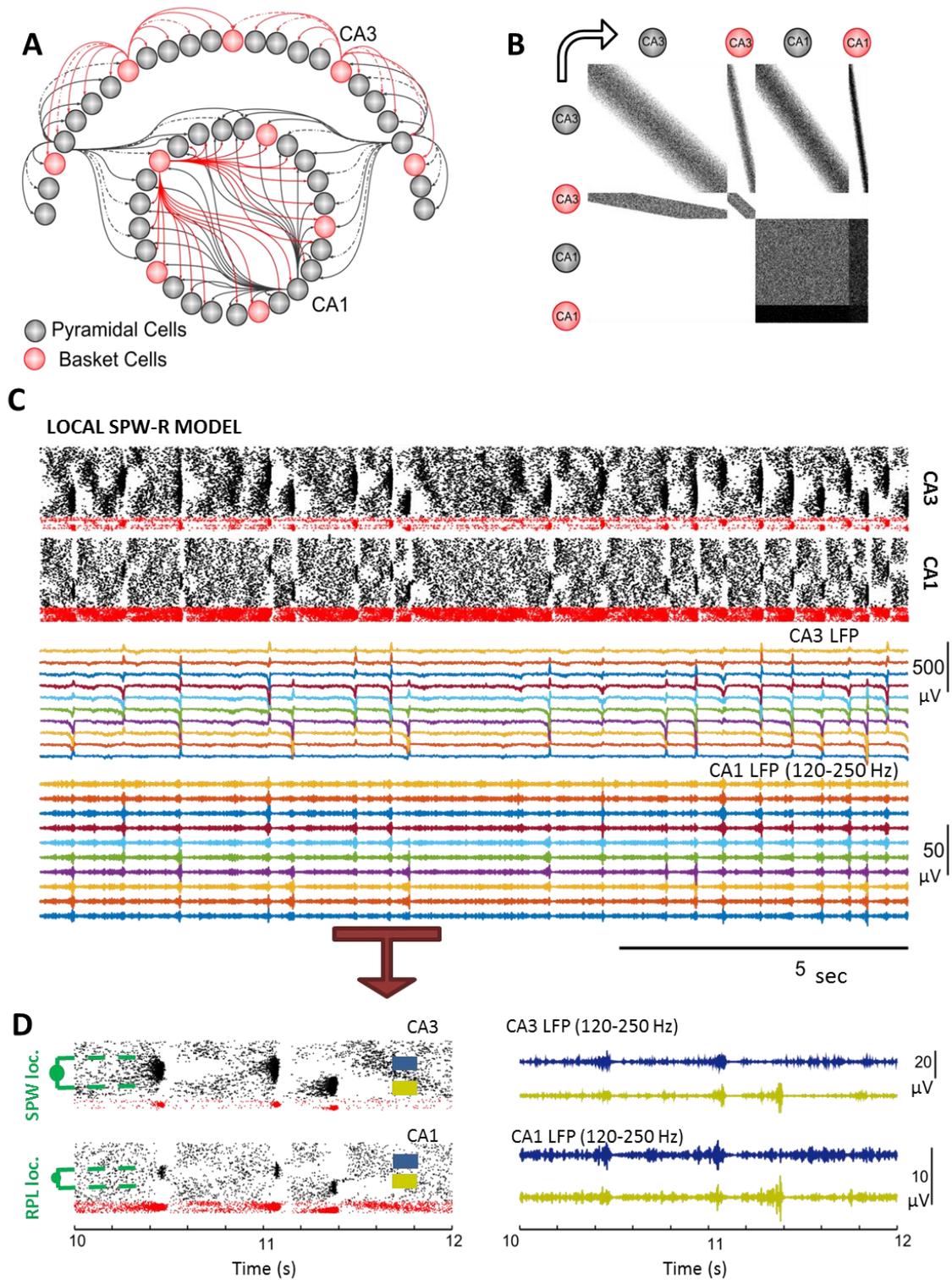
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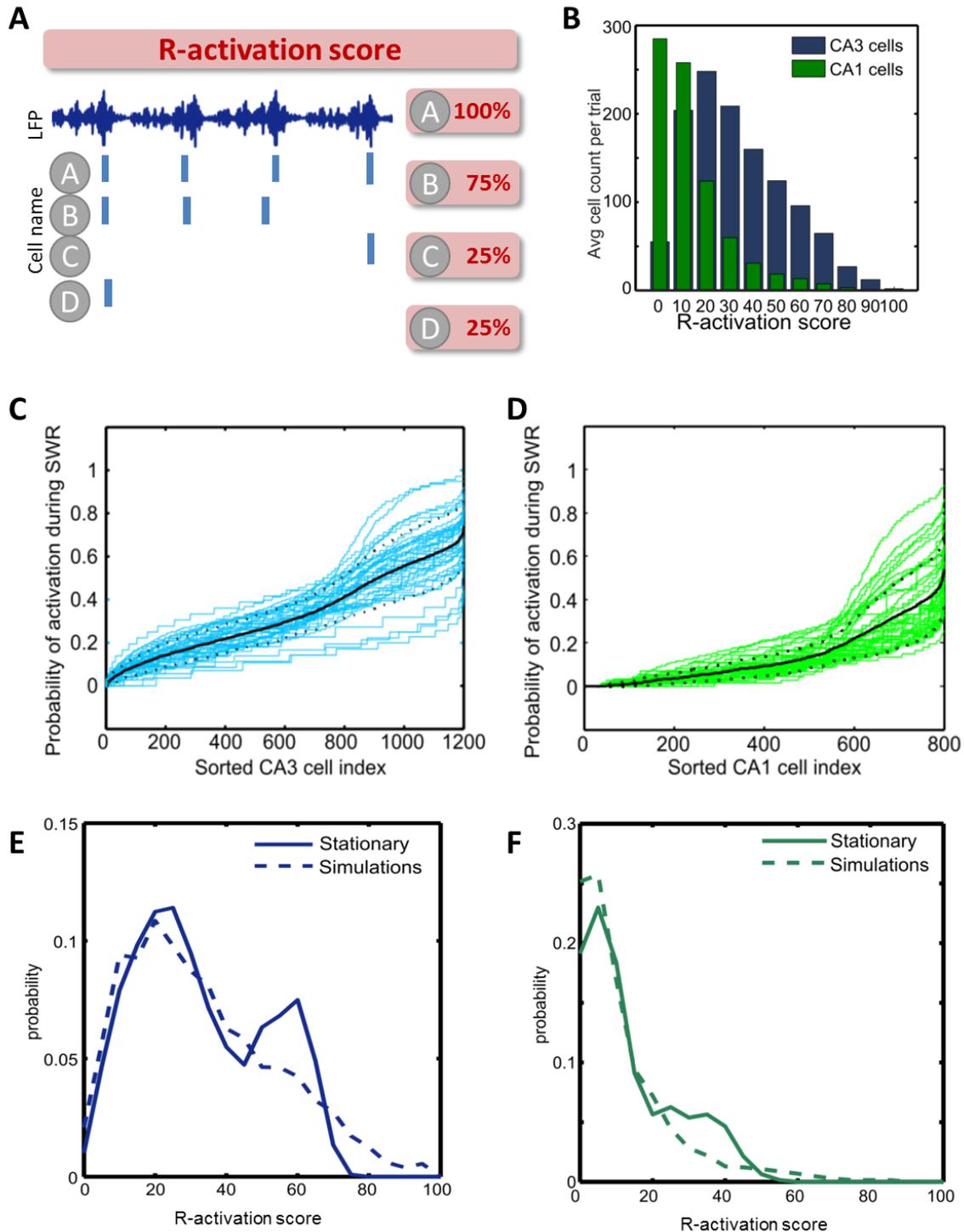
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- 1010

1011 **Figures**



1012  
1013 **FIGURE 1**

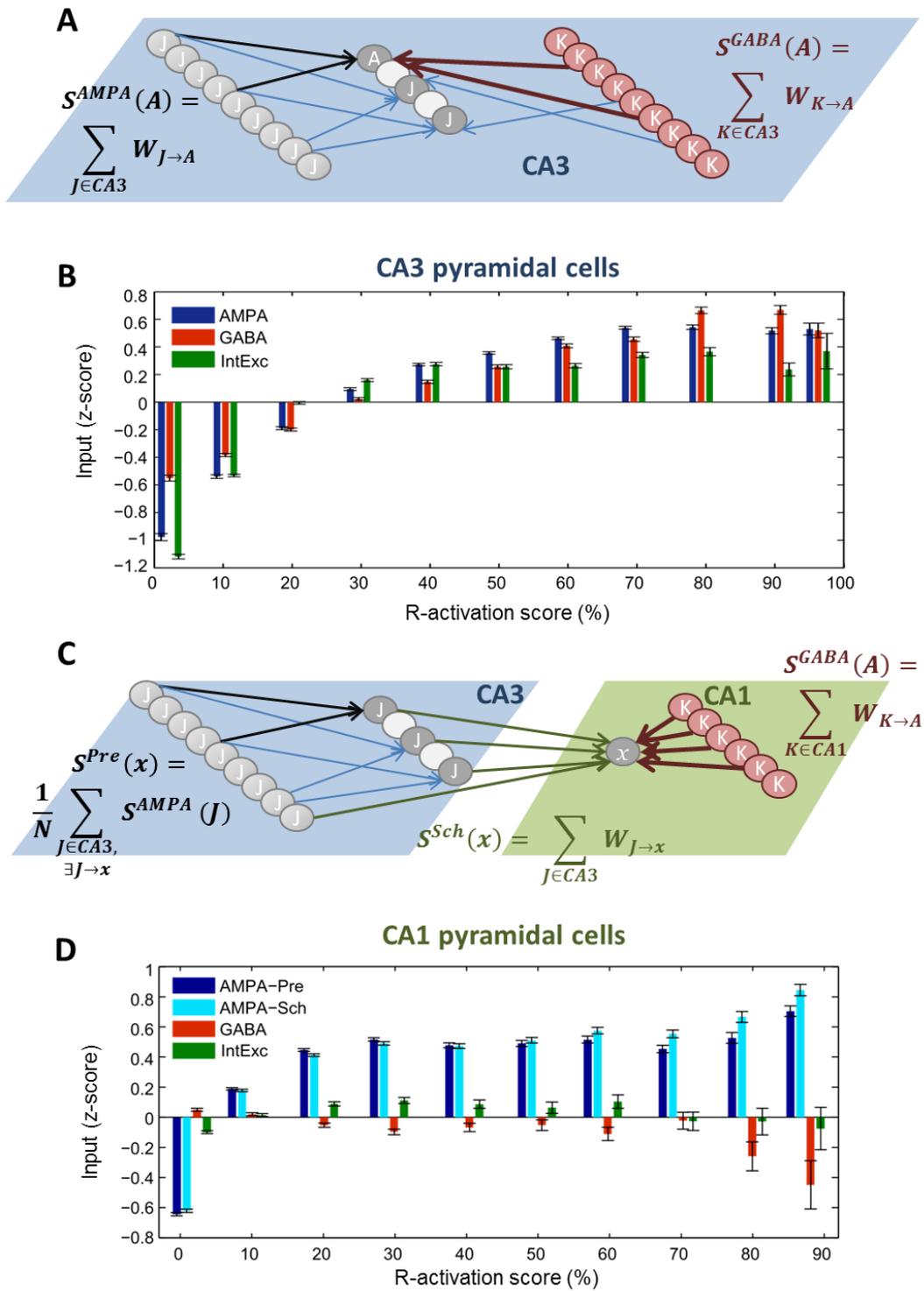
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1016 **FIGURE 2**

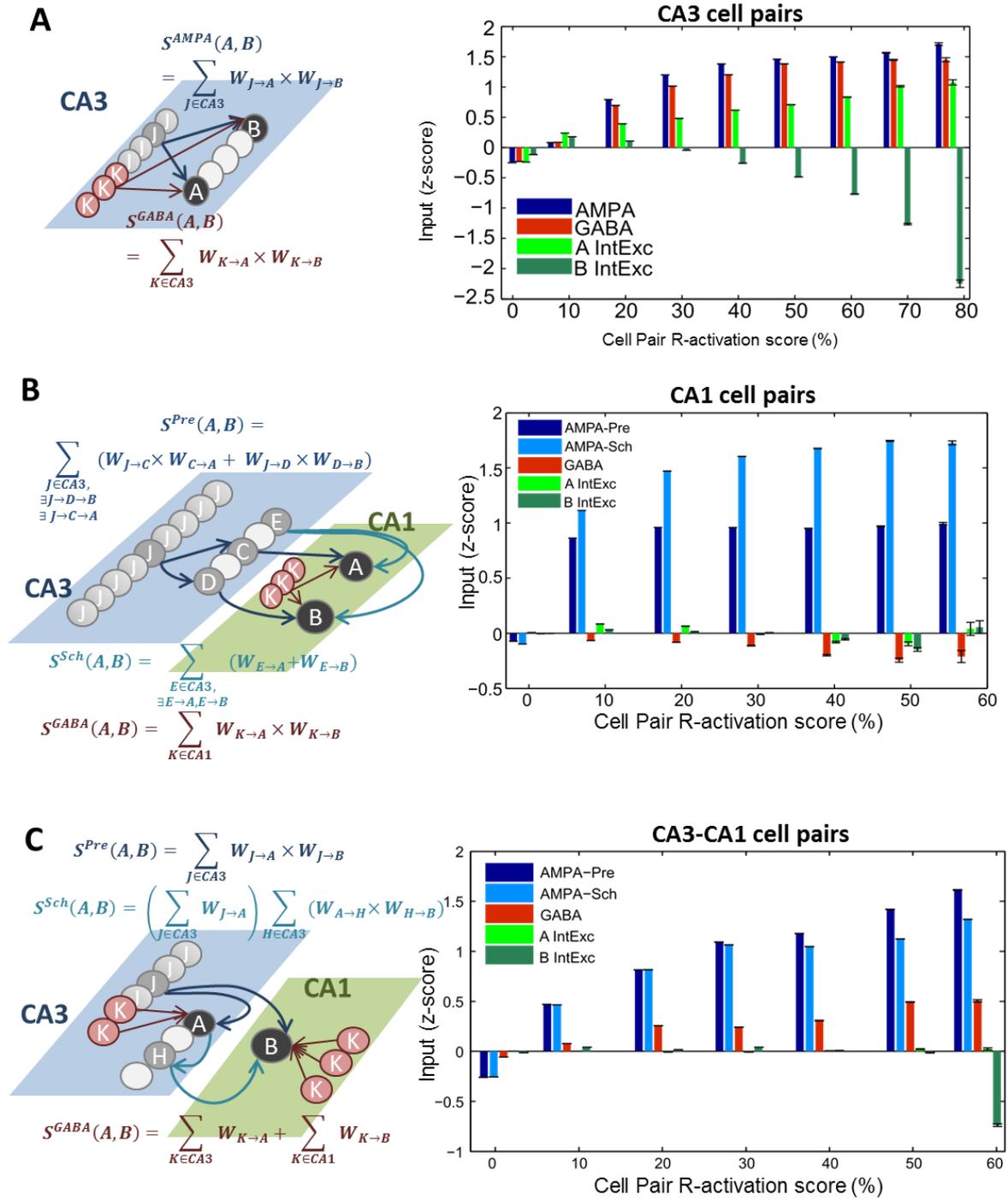
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1019 **FIGURE 3**

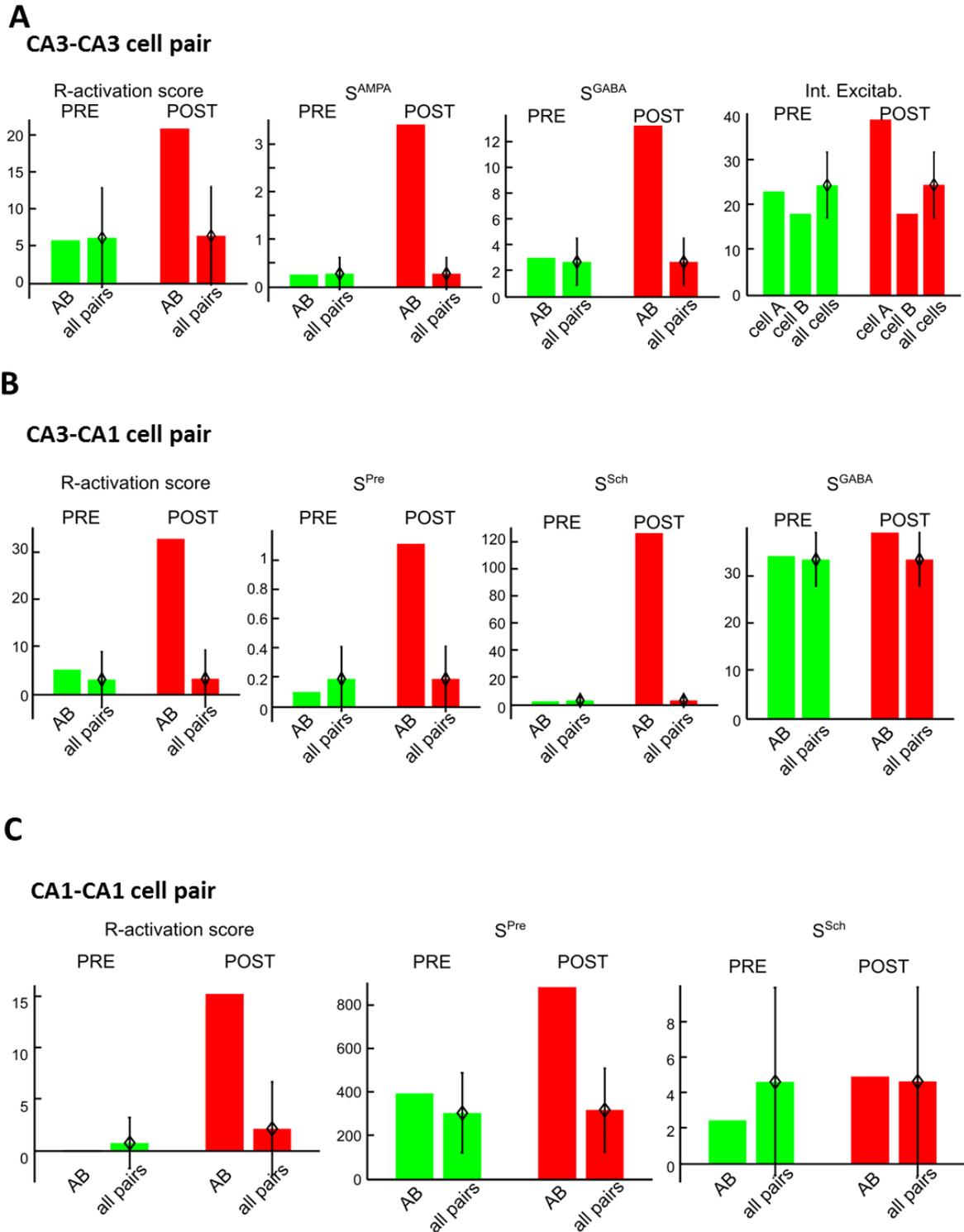
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1022 **FIGURE 4**

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1025 **FIGURE 5**