

1 **Event boundaries drive norepinephrine release and distinctive neural representations of**
2 **space in the rodent hippocampus**

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15

16 **Abstract**

17 Episodic memories are temporally segmented around event boundaries that tend to coincide with
18 moments of environmental change. During these times, the state of the brain should change
19 rapidly, or reset, to ensure that the information encountered before and after an event boundary is
20 encoded in different neuronal populations. Norepinephrine (NE) is thought to facilitate this
21 network reorganization. However, it is unknown whether event boundaries drive NE release in
22 the hippocampus and, if so, how NE release relates to changes in hippocampal firing patterns.
23 The advent of the new GRAB_{NE} sensor now allows for the measurement of NE binding with sub-
24 second resolution. Using this tool in mice, we tested whether NE is released into the dorsal
25 hippocampus during event boundaries defined by unexpected transitions between spatial contexts
26 and presentations of novel objections. We found that NE binding dynamics were well explained
27 by the time elapsed after each of these environmental changes, and were not related to
28 conditioned behaviors, exploratory bouts of movement, or reward. Familiarity with a spatial
29 context accelerated the rate in which phasic NE binding decayed to baseline. Knowing when NE
30 is elevated, we tested how hippocampal coding of space differs during these moments.
31 Immediately after context transitions we observed relatively unique patterns of neural spiking
32 which settled into a modal state at a similar rate in which NE returned to baseline. These results
33 are consistent with a model wherein NE release drives hippocampal representations away from a
34 steady-state attractor. We hypothesize that the distinctive neural codes observed after each event
35 boundary may facilitate long-term memory and contribute to the neural basis for the primacy
36 effect.

37 **Introduction**

38 Determining neurobiological mechanisms by which the hippocampus supports the formation of
39 memories for distinct episodes remains a major outstanding challenge. Norepinephrine (NE)
40 signaling is hypothesized to play a key role in organizing memory into episodes demarcated by
41 event boundaries¹. Yet, the situations in which NE is released in the hippocampus, and the
42 effects of NE on hippocampal coding, are not well understood. Here, we use the GRAB_{NE} sensor
43 and analysis of neuronal spiking dynamics to test the hypothesis that NE release occurs at event
44 boundaries and aligns with changes in neural coding that promote long-term memory.

45 Prior work suggests that NE release from the locus coeruleus (LC) may facilitate event
46 segmentation by modulating the induction threshold for synaptic plasticity²⁻¹¹, facilitating
47 reorganization of which neurons are active before and after unexpected salient events¹², and
48 changing how neurons encode their environment at the time of transmitter release¹³. NE release
49 from the LC causes immediate changes in the excitability and activity of neurons across the
50 hippocampal formation¹⁴⁻²³. Electrical stimulation of the LC acutely silences most hippocampal
51 neurons^{24,25} while simultaneously increasing firing in the subset of neurons that respond to
52 salient stimuli²⁵, an observation that motivated the hypothesis that NE sets the gain of the
53 neuronal input/output curve²⁶. Computational models predict that NE-induced changes in gain
54 should promote network shifts by lowering the activation energy for transitioning between
55 learned states/attractors²⁷⁻³². Hippocampal place fields remap³³ (change place field position),
56 with learning³⁴⁻³⁸ and also after salient changes in an animal's environment³⁹⁻⁴¹, offering an
57 attractive correlate to assess LC-induced reset⁴².

58 NE also facilitates synaptic plasticity². Plasticity-related signaling is needed for the reactivation
59 of waking spiking activity during subsequent sharp-wave ripples replay events^{34,43,44}. Neuronal

60 replay is important for memory consolidation⁴⁵ and variations in the content of replay may
61 dictate which moments are remembered and which are forgotten⁴⁶. Stimulation of dopaminergic
62 terminals from the ventral midbrain⁴⁷, as well as natural reward⁴⁸, enhances synaptic plasticity
63 and can promote reactivation. It is unknown whether moments of elevated noradrenergic release
64 similarly bias subsequent replay, though such a relationship has been predicted⁴⁹.

65 Micro-dialysis studies have revealed that NE is released in the hippocampus after exposure to
66 novel environments^{50,51}, physical restraint/handling^{50,51}, or after exposure to novel combinations
67 of familiar objects⁵². This method samples average NE concentration over a minutes-long period
68 and therefore cannot resolve whether release is related to the experimental stimuli or the
69 behaviors associated with those stimuli; for example, mice move more in novel spaces. The low
70 sampling resolution of micro-dialysis also precludes relating moment-to-moment changes in
71 neural coding with fluctuations in NE concentration. Using the recently developed GRAB_{NE}
72 sensor⁵³, which can measure NE release with sub-second resolution, hippocampal NE levels
73 were shown to increase immediately after delivering an electrical shock and decrease around
74 freezing⁵⁴. This pattern could indicate a relationship between NE around encoding and retrieval
75 events, or alternatively, may arise due to a relationship between NE release and overall levels of
76 movement or arousal, which in this case co-varied with different phases of the experiment. In
77 support of this latter interpretation, a previous study found that the firing rate of LC neurons
78 positively correlates with acceleration⁵⁵. Others have reported that LC neurons fire in response to
79 unexpected salient stimuli⁵⁶⁻⁶³, including reward prediction errors⁶⁴⁻⁶⁶. Such surprise-related
80 activity of LC neurons may cause NE release at the moments when event boundaries are thought
81 to occur, however, such a relationship is not guaranteed as NE release is also modulated at the
82 level of the axon terminal⁶⁷.

83 To better understand how hippocampal NE release dynamics relate to event boundaries and the
84 associated neuronal response, we used the GRAB_{NE} sensor to examine how NE release is related
85 to event boundaries imposed by unexpected transitions between testing environments and the
86 introduction of novel objects. We also tested how these signals are affected by moment-to-
87 moment fluctuations in behavior and reward availability, and how NE release dynamics change
88 over the course of learning. Knowing when NE is expressed, we then assessed whether these
89 moments are associated with changes in neural coding as predicted by prominent models of NE
90 function. Our findings support a model in which NE release around event boundaries scales with
91 the deviance between current and previously stored neural representations.

92 **Results**

93 To investigate the dynamics of NE release and binding in the dorsal hippocampus, the GRAB_{NE}
94 genetically encoded fluorescent indicator⁵³ was virally delivered to dorsal CA1 (Figure 1A), and
95 optic fibers were chronically implanted in C57BL6/J mice (N = 8 mice, N = 3 female)
96 unilaterally targeting the injection site. The main dependent measure was the emission intensity
97 of the NE-derived signal (experimental excitation $\lambda = 465\text{-nm}$) with corrections for mechanical
98 instability (isosbestic excitation $\lambda = 405\text{-nm}$) and photobleaching, and normalized by the mean
99 and standard deviation recorded during a 10-minute homecage baseline (see Methods); this
100 measurement will be referred to as Signal_{NE}. The Signal_{NE} derived from the GRAB_{NE} sensor was
101 validated in our hands by showing that the noradrenergic reuptake inhibitor desipramine caused a
102 significant increase in Signal_{NE} relative to vehicle injections (Figure S1A). Likewise,
103 noradrenergic $\alpha 2$ receptor antagonism with yohimbine (from which GRAB_{NE} was derived)
104 disrupted normally strong Signal_{NE} (Figure S1B).

105 **Signal_{NE} exponentially decays after transfer to a novel arena**

106 Moving between environments causes a large reorganization in which hippocampal neurons are
107 active^{33,68}. To test how NE release relates to this cause of network reorganization, Signal_{NE} was
108 measured as mice were transferred from their home cage to a novel testing arena that, over days,
109 became more familiar to the subject (Figure 1B,C). Averaging across all exposures, Signal_{NE}
110 increased immediately upon entry to the testing arena and exponentially decayed to a steady state
111 over minutes (Figure 1D). The NE dynamics may be related to the transition itself, or the
112 incidence of behaviors that occur immediately following exposure to an unfamiliar space. For
113 example, in the moments after transition, mice tended to spend more time close to the edges of
114 the environment (thigmotaxis) and tended to move more rapidly (Figure S1C). We quantified
115 how NE release relates to five potential behavioral covariates: time from arena entry,
116 acceleration, velocity, distance from edge, and time from rearing. These five behavioral variables
117 were themselves correlated (Figure S1D). Univariate analysis revealed strong, positive co-
118 modulation of Signal_{NE} with acceleration ($t(7) = 4.54, p = 0.002$) and modest positive correlation
119 with velocity ($t(7) = 2.32, p = 0.05$)(Figure S1E). Signal_{NE} also correlated with distance to the
120 edge of the environment ($t(7) = -2.37, p = 0.05$)(Figure S1E,F), and showed transient changes
121 around rearing events in a subset of animals (Figure S1E,G). Such covariation in putative factors
122 driving NE release complicates assessment of whether NE release dynamics relate to the
123 contextual transition *per se*, or whether NE is more closely associated with novelty-related
124 behaviors. The sub-second temporal resolution of the GRAB_{NE} sensors allows disambiguation of
125 these scenarios.

126 To identify the independent variable with the greatest explanatory power, we performed
127 backward stepwise regression on a non-linear model defined by the five behavioral variables of
128 interest. Time from transition was modeled with two terms: a positive term with a fast decay and

129 a negative term with a slower decay to capture decreases in NE observed after some transitions.
130 Cross-validated mean squared error (CVMSE) was calculated for the full, saturated model and
131 for a reduced model in which one of the five variables (or the intercept) has been dropped.
132 Significant decreases in model fit were only observed after dropping the time from context entry
133 independent variable (Figure 1E). Despite apparent modulation of Signal_{NE} with movement, the
134 critical factor in predicting Signal_{NE} was the time from event transition.

135 **Signal_{NE} exponentially decays after transfer to a familiar linear track**

136 LC activity and NE release have been related to reward^{65,69} and acceleration⁵⁵. The physical
137 dimensions of the testing arenas prohibited moments of high acceleration or velocity and the
138 recording sessions lacked appetitive reward conditions. We therefore sought to test whether
139 Signal_{NE} was under the control of event boundary transitions even when mice engaged in a
140 learned task in which subjects must run to receive water reward on a linear track, a standard
141 apparatus for studying hippocampal physiology.

142 Here, we considered five independent variables: time from linear track entry, acceleration,
143 velocity, distance from the edge of the track, and time from reward. As was observed in the
144 novel arena experiments, NE increased rapidly upon entry to the linear track and decayed to a
145 steady state (Figure 2 A,B). Hippocampal NE was not modulated around reward delivery
146 (signaled with an audible solenoid click) nor movement (Figure S2). The stepwise regression
147 analysis showed that removing time from entry, but no other term, significantly decreased our
148 ability to predict fluctuations in Signal_{NE} (Figure 2C). These results show that, even in the
149 context of an appetitive task that requires conditioned responses, time from transition is the
150 dominant factor in explaining hippocampal NE release.

151 **Signal_{NE} exponentially decays after introduction of a novel object**

152 In experiments that have studied event boundaries in people, the modality of the information is
153 often non-spatial (e.g. the color of a picture background^{1,70}) and LC firing has been related to
154 object sampling in the rodent⁶². Therefore, we tested whether the introduction of a novel object
155 could likewise signal an event boundary to the mouse that would be associated with a transient
156 increase in Signal_{NE}.

157 Five novel objects were consecutively introduced to the mouse, each for five minutes starting 10
158 minutes after the mouse was transferred to a familiar arena, a timeline designed to decouple
159 event boundaries related to environmental transitions from those related to object introduction
160 (Figure 3A). Mice spontaneously move to explore novel objects, and this well-characterized
161 behavior is used as a metric for intact memory⁷¹. We hypothesized that the event boundary
162 would be defined by the object's introduction, and therefore predicted that NE release would be
163 related to these moments rather than the behaviors associated with individual samples of the
164 object.

165 To address this question, a similar statistical modeling approach was adopted wherein Signal_{NE}
166 was modeled as a function of: time from object introduction, acceleration, velocity, distance
167 from edge of the environment, and whether or not the mouse was sampling the object. Upon
168 introduction, each of the five objects induced a phasic release of NE (Figure 3 B,C); NE release
169 dynamics were not systemically related to the ordinal position of the object in the sequence
170 (Figure S3 A-C). NE release was also not coordinated with individual object samples (Figure
171 S3D). Backward stepwise regression analysis revealed that the time from object introduction was
172 the only term whose absence significantly decreased CVMSE (Figure 3D). These results show
173 that changes in spatial context and introduction of salient and novel objects increase Signal_{NE},

174 thus suggesting that NE release around both types of event boundaries may organize
175 hippocampal neural activity.

176 **Novel objects do not affect Signal_{NE} around spatial context transitions**

177 As Signal_{NE} increases around novel objects and context transitions, we next tested how the
178 combination of these conditions affects noradrenergic signaling in the dorsal hippocampus. In
179 addition, mice typically initiate movement to explore novelty and we sought a scenario in which
180 mice stop to inspect something new. To achieve these goals, mice were trained to run for water
181 on a linear track and were then presented with a novel object placed midway down the track. In
182 these sessions, there was a baseline linear track period without novel objects, then mice were
183 returned to the home cage and a novel object was placed on the track (Control sessions in the
184 same subjects were run on different days without novel objects), and finally, mice were returned
185 to the linear track. Though mice reliably stopped to inspect the novel object, no difference in
186 Signal_{NE} was observed between the novel object and control conditions (Figure 4). Therefore,
187 Signal_{NE} related to the familiar context transition was not affected by the presence of novel
188 objects.

189 **Experience accelerates the decay of Signal_{NE} after spatial context transitions**

190 Prior studies have found that the effect of event boundaries on the organization of memory
191 depends on stimulus familiarity⁷² and recordings from LC neurons show rapid habituation with
192 repeated exposures^{60,62,63,73}. Therefore, we tested how the Signal_{NE} changes as a novel
193 environment becomes increasingly familiar after repeated exposure over 10 days. Comparing the
194 first and second days of testing, mice tended to display higher levels of acceleration, rear more
195 often, and spend more time close to the perimeter during first-time arena exposure (Figure S4).

196 We adopted the same regression analysis to decouple learning-related changes in behavior from
197 learning-related changes in NE release. As before, $\text{Signal}_{\text{NE}}$ was estimated as a function of time
198 from context entry, acceleration, velocity, distance from edge, and time from rearing. For each
199 subject, for each day, we derived a point estimate of a positive β -weight associated with the gain
200 in $\text{Signal}_{\text{NE}}$ due to the context transition as well as a term τ that describes the rate of decay of
201 $\text{Signal}_{\text{NE}}$ after the event boundary. The rate of $\text{Signal}_{\text{NE}}$ decay (τ ; mixed-effects linear model,
202 $t(73) = 2.31, p = 0.02$), and not amplitude (β ; mixed-effects linear model, $t(73) = 1.16, p =$
203 0.25), systematically changed as a function of the number of days of experience (Figure 5 A-C).
204 Returning the subject to their home cage was associated with an increase (β) in $\text{Signal}_{\text{NE}}$, with a
205 decay that was more rapid than that observed after 10 days of contextual habituation (Figure 5C).
206 These findings show that learning alters NE signaling dynamics, either by accelerating the rate of
207 NE clearance or by decreasing the duration in which LC neurons continue to release NE after
208 being moved into a different space.

209 **Familiarity is not the sole determinant of the decay of $\text{Signal}_{\text{NE}}$ after spatial context** 210 **transitions**

211 Mice were highly familiar with the linear track, yet $\text{Signal}_{\text{NE}}$ showed a relatively slow delay. The
212 τ_{track} was comparable to the τ_{NovelEnv} observed after 3-4 days of exposure. Moreover, there was a
213 higher baseline $\text{Signal}_{\text{NE}}$ maintained throughout the linear track sessions (Figure 2). We
214 hypothesized that the dynamics of the $\text{Signal}_{\text{NE}}$ around event transitions depend upon recent NE
215 signaling history. To equate familiarity of the context, we compared transitions to the home cage
216 from the linear track or the novel environments. For each session, $\text{Signal}_{\text{NE}}$ in the homecage was
217 modeled as a function of: context entry, acceleration, and velocity. For both linear track and
218 novel context sessions, significant decreases in model fit were only observed after dropping the

219 terms related to time from home cage entry (Figure S5). Signal_{NE} increased similarly around the
220 transition to home cage after experience in the arena or linear track (Figure 6A). However, in the
221 linear track sessions, Signal_{NE} rapidly decreased and was depressed relative to baseline for
222 several minutes. The rate of Signal_{NE} decay was faster (Figure 6B) and the NE decrease was
223 larger (Figure 6C) after linear track exposure as compared to experience in the arena. These
224 results show that recent experience changes the dynamics of Signal_{NE} around event boundaries
225 imposed by context transitions.

226 **CA1 spatial code takes minutes to settle after context transition**

227 Knowing the dynamics of NE after context transfer allowed us to search for changes in neural
228 activity that track this time course. Modeling studies have emphasized that NE binding should
229 increase the rate at which neural patterns change over time²⁷. Using a large open-source database
230 in which CA1 neurons were recorded as mice were transferred to novel and familiar tracks⁷⁴, we
231 found that in novel environments, the rate of decorrelation was indeed faster in the first minute
232 after transfer as compared to later in the session (Figure S6 A,B). Such a relationship was not
233 observed in a familiar space (Figure S6 C,D). Since we found strong NE release in both
234 conditions, we doubt these changes are driven by NE.

235 Next, we analyzed the rate at which the spatial map settles after inducing remapping by shifting
236 the subject from its home cage to a novel or familiar testing environment. Place fields can be
237 observed immediately after transitioning to a new environment^{75,76}, though fields can also
238 emerge and/or change throughout experience⁷⁷, and show other changes across repetition as
239 well⁷⁸. To gain an intuition for the dynamics immediately after transition, we embedded the
240 high-dimensional population firing rate vectors (mean ensemble = 253.8 neurons, range = 191-
241 363 neurons, bin size = 100-ms) into a 2D space. Color coding by position shows that the CA1

242 representational space maps the spatial layout of the environment (Figure 7A). Color coding by
243 time shows that moments immediately following the transition are associated with unusual
244 representations, which can be seen at the periphery of the representational state space (Figure
245 7B). Recognizing that single locations may have a multitude of neural representations^{79,80}, we
246 quantified the correlation of the instantaneous representation recorded at each moment relative to
247 those recorded in the same location at any other moment throughout the session. This nearest-
248 neighbor search revealed that early moments were associated with neural activity that poorly
249 correlated with activity recorded in the same location later in the session (Figure 7 C,D).
250 Representations settled into a steady state after several minutes and more rapidly in a familiar
251 environment (Figure 7 E-G). Settling involved both an increase of activity within a neuron's
252 place field and a decrease in out-of-field firing (Figure S7 A,B). To ensure this representational
253 uniqueness did not arise due to unusual behaviors during the first minutes after transfer, we
254 calculated the absolute difference in velocity ($|\Delta\text{vel}|_{\text{NN}}$) and acceleration ($|\Delta\text{acc}|_{\text{NN}}$) recorded at
255 the moments captured by the nearest-neighbor (NN) search. When comparing pairs of moments
256 with the highest representational similarity, there was no systematic relationship between time
257 after transfer and $|\Delta\text{vel}|_{\text{NN}}$ or $|\Delta\text{acc}|_{\text{NN}}$ (Figure S7 C-F). To confirm this impression, we
258 modeled the nearest-neighbor representational similarity as a function of time from transfer,
259 $|\Delta\text{vel}|_{\text{NN}}$, and $|\Delta\text{acc}|_{\text{NN}}$. Only removing time from transition significantly decreased ability to
260 predict nearest neighbor correlations (Figure S7 E,F). Similar results were found when
261 representational similarity was not conditioned on the mouse's location (Figure S7 G,H). These
262 results show that changes in representational uniqueness are more driven by time from transfer
263 than unusual movement statistics. The time course of representational stabilization qualitatively

264 matched that of NE decay in both novel and familiar environments suggesting a potential link
265 between NE release and atypical spiking behavior.

266 **No preferential reactivation of moments following transition**

267 NE binding facilitates the induction of synaptic plasticity across hippocampal subfields²⁻¹¹.
268 Another body of work has shown that reactivation of waking patterns during sharp-wave ripples
269 depends upon the same signaling pathways that mediate synaptic plasticity^{43,44}, thus motivating
270 the hypothesis that replay depends upon synaptic plasticity. Knowing when NE is likely to be
271 present, we next asked whether the moments immediately following context transition were
272 associated with enhanced reactivation. The population firing rate observed in each 100-ms bin
273 was correlated with that observed during ripples before and after experience in a novel
274 environment. These correlations were then compared to a bootstrap distribution (shuffling neural
275 activity across ripples to break patterns of synchrony) to assess the likelihood that a particular
276 firing rate vector would be observed more than expected if neurons fire independently of one
277 another across ripples. Contrary to expectations, the pattern of activity observed towards the end
278 of the session was more likely to be reactivated in the ripples that followed the experience
279 (Figure 8 A,B). We also did not observe preferential reactivation of the moments following a
280 transition in familiar environments (Figure 8 C,D), nor any evidence that the pattern of activity
281 observed on the track was present in ripples recorded prior to the experience. These results
282 suggest that enhanced NE signaling associated with context transition is not sufficient to gate
283 entry into subsequent replay.

284 **Discussion**

285 Moment-to-moment changes in extracellular NE concentration were mainly driven by the time
286 since a salient environmental change. NE release could not be explained by fluctuations in
287 spontaneous or conditioned mouse behavior. Familiarity accelerated the rate at which NE
288 decayed to baseline after transitioning between contexts, while the degree of phasic NE increase
289 at the time of transition did not systematically change with learning. In opposition to predictions
290 from models that place a central role of NE in gating the plasticity required to alter future neural
291 dynamics, we did not find any enhancement in the reactivation of neural patterns observed in the
292 moments immediately following context transition, and in fact, we observed the converse –
293 greater reactivation of the neural patterns observed later in the recording session. Analyzing the
294 dynamics of neural coding around environmental transitions, we observed that hippocampal
295 representations of space took several minutes to stabilize into a modal steady state. This time
296 course was faster in a familiar environment and qualitatively mirrored that of NE release. These
297 results support a model in which the hippocampal NE release is proportional to the deviance
298 between the current neural representation and the steady-state attractor.

299 **Potential sources dictating NE dynamics**

300 NE dynamics were well described by the sum of two exponentials, one reflecting an increase in
301 NE release around the event boundary that decays to baseline over several minutes and another
302 describing a decrease in NE release from baseline that recovers more slowly. This
303 phenomenological model was able to capture complex interactions between NE release and
304 clearance that dictate the available $\text{Signal}_{\text{NE}}$. A temporally extended input driving NE release
305 minutes after the event boundary is likely, since, in anesthetized preparations, the impulse
306 response function of NE release after LC stimulation returns to baseline within tens of seconds,
307 not minutes⁸¹⁻⁸³. Moreover, large increases in $\text{Signal}_{\text{NE}}$ returned to baseline quickly after

308 transitioning to the mouse home cage. Therefore, NE clearance can occur quickly. In the awake
309 behaving subject, however, brief optogenetic stimulation of LC produces an increase in medial
310 prefrontal NE concentration that takes minutes to decay⁵³. The mechanisms by which NE levels
311 are maintained long after LC stimulation are unknown. The LC is the sole source of NE in the
312 hippocampus and release dynamics are jointly dictated by changes in the firing of LC neurons
313 and local modulation of the LC terminals. It is possible that the LC itself receives drive long
314 after the event boundary that decreases systematically over time. Alternatively, electrotonic
315 coupling between LC neurons may underlie phasic NE release⁸⁴, and perhaps this electrical
316 coupling slowly decays after event boundaries, or LC stimulation. This latter mechanism is
317 motivated by the observation that phasic NE release is likely driven by changes in LC
318 synchrony⁸⁵⁻⁸⁷. However, single unit recordings from the LC show no increase in firing rate
319 when subjects are transferred to a familiar environment⁶¹, in contrast to the NE signal observed
320 in the current study. This dissociation suggests local control of NE release independent of
321 somatic action potentials.

322 In a synaptosome preparation, in which LC terminals located in the hippocampus are dissociated
323 from LC somata, NE is released by NMDA receptor stimulation⁶⁷, which is modulated by
324 somatostatin^{88,89} and nicotinic⁹⁰ receptors also located on the LC axon terminal. Somatostatin's
325 influence on NE release is independent of membrane depolarization⁸⁸, thus introducing the
326 possibility that the terminal depolarization may differ from the signal arriving to the post-
327 synaptic neuron. Induction of synaptic plasticity can alter the levels of spill-over glutamate^{91,92}
328 available to bind to NMDAR on LC terminals. One possible explanation for the acceleration of
329 NE decay across days of arena exposure may relate to decreases in spill-over glutamate. If decay
330 rates are dictated by glutamatergic stimulation of the LC terminal, future experiments should test

331 whether these rates differ along the longitudinal axis of the hippocampus⁹³. We predict slower
332 decay in the ventral hippocampus. A diversity of decay rates (perhaps averaged in the present
333 study) may provide more precise information about the time since an event boundary⁹⁴⁻⁹⁶.

334 We also observed significant and sustained decreases in NE release when mice were moved back
335 to their homecage whose kinetics depended upon the recent history of the subject. NE release in
336 the linear track was systematically elevated from baseline which likely creates decreased
337 subsequent noradrenergic signaling resources⁸⁶. Future studies should test whether learning after
338 transition differs in the high and low NE states.

339 **NE release is enhanced around event boundaries**

340 Event segmentation theory states that event boundaries occur at these prediction errors⁹⁷, which
341 coincide with an abrupt change, or reset, in ongoing activity⁹⁸. Event boundaries have a profound
342 influence on the organization of episodic memory. For example, memory is enhanced for the
343 events immediately following an event boundary^{99,100}. This primacy effect exists across encoding
344 modalities¹⁰¹, and in animal studies of hippocampal-dependent spatial memory^{102,103}. There are
345 also fewer serial transitions across event boundaries during free recall⁷⁰, which suggests
346 segregation of memories into discretized episodes¹⁰⁴. This segregation is particularly evident
347 when networks reorganization (reset) around the transition point, as inferred by decreased
348 correlations in multi-voxel BOLD signals¹⁰⁵⁻¹⁰⁷. NE released from LC terminals is known to
349 correlate with pupil diameter^{108,109}, thus providing an indirect (if imperfect¹¹⁰) assessment of LC
350 function in people. Around event boundaries, pupils tend to dilate¹, suggesting NE release at
351 these times.

352 Direct NE measurements in animals show enhanced release in the hippocampus around
353 conditioned and noxious stimuli, as well as following exposure to novel contexts of even
354 handling^{50-52,54,81,111}. Microdialysis studies lack the temporal resolution to dissociate whether NE
355 release is related to specific stimuli or novelty *per se* versus the associated changes in animal
356 behavior. Prior studies that have used GRAB_{NE} in the hippocampus have not attempted to
357 disambiguate these possibilities.

358 Other recording studies have found LC neuronal activity is related to movement⁵⁵, orienting
359 behaviors⁸⁷, and reward consumption⁶⁴ and NE recordings in other brain regions have found
360 correlations with these variables⁶⁵. We used two techniques to isolate NE signals related to event
361 transitions from those related to reward, movement and overall arousal. First, our statistical
362 modeling showed across a variety of testing conditions that the time elapsed after some
363 environmental change predicted NE release; translational movement, reward, and bouts of
364 exploratory behavior (rearing or object exploration) were poor predictors of Signal_{NE}. Next, we
365 developed different protocols in which exploratory behaviors either involved the initiation or the
366 interruption of movement. In neither case did we observe time-locked NE release around bouts
367 of exploration.

368 Arousal or attention also seem to be unsatisfactory explanatory cognitive constructs to explain
369 the dynamics of hippocampal NE release observed in the present study. In as much as these
370 mental states can exist or be measured in the rodent, situations in which mice systematically
371 engage in more exploration did not change the time course of NE decay after context transition
372 (Figure 4). Instead, in all cases tested, the hippocampus NE release corresponded to the time
373 elapsed from an unpredicted salient environmental change (context shift or object introduction).
374 Notwithstanding, in a subset of subjects, we did observe transient changes in NE release around

375 rearing events. Though this was not significant at the group level, we speculate that the degree of
376 NE release may be related to the nature of the information acquired during the environmental
377 sampling.

378 **The LC contribution to long-term changes in neural coding**

379 The LC influences memory formation through the co-release of dopamine^{61,69,111-115} and
380 NE^{2,54,116-119}. The modulation of late-phase synaptic plasticity, e.g. through synaptic tag-and-
381 capture mechanisms^{3,120}, has long been emphasized as the dominant role by which
382 catecholamines may gate entry of new information into long-term memory^{4,9,11,20,61,112,113,121-124}.
383 SPW-R replay is a prominent electrophysiological correlate of experience that depends on
384 plasticity-related processes^{43,44}. Since stimulation of the midbrain enhances replay⁴⁷, we
385 hypothesized that NE may also enhance future reactivation. This prediction was not correct, as
386 we did not find any evidence that the neural activity observed following context transition was
387 preferentially reactivated. In fact, we saw that *later* moments were more likely to be reactivated
388 in post-RUN ripples. This reactivation bias is likely due to the autocorrelation of the brain over
389 time in which the neurons active at any given time are more likely to continue to be active due to
390 consistencies in the external environment (or internal milieu) and the slow turn-over in proteins
391 that affect intrinsic excitability¹²⁵⁻¹²⁷. Though we did not quantify replay of the temporal
392 sequences of cell assemblies, a prior report using the same data also failed to observe enhanced
393 replay of moments following transition¹²⁸. Therefore, if a primacy effect occurs after context
394 transitions, it is unlikely to be mediated by, or reflected in, enhanced replay of these moments.
395 Others have found that LC stimulation promotes place field accumulation, but only in the present
396 of natural reward⁶⁹. NE is therefore likely to act in concert with other signals to promote long-
397 term changes in neural coding during exploration and during ripples.

398 **Changes in neural coding around event boundaries**

399 We observed that immediately after an environmental transition, the spatial representation was
400 relatively unique, and settled into a steady-state spatial code over the course of minutes. In
401 familiar spaces, the neural patterns observed in the early moments were more similar to the
402 ultimate steady state. When subjects move between environments, hippocampal place fields
403 remap which involves changes in which neurons express place fields, alterations in which
404 subsets of neurons fire together, and reorganization in the distances between the place fields of
405 simultaneously recorded neurons^{33,39}. This remapping can occur rapidly, with the reset signal
406 driven either externally – when stimuli signal changes in how subjects should behave within the
407 space^{36,129} – or internally when multiple reference frames must be simultaneously
408 maintained^{130,131}. During such rapid remapping competing ensembles “flicker” before settling
409 into a steady state^{129,132}. Manually moving subjects between environments also induces
410 remapping⁶⁸. Place fields may be observed on the first trial in a novel environment^{75,76}, but
411 previous studies have found that extended exposure modifies the hippocampal representation of
412 space in several ways: new fields may be added^{77,133}, field asymmetry changes⁷⁸, and firing
413 reliability is enhanced⁷⁶. Other changes may occur in the presence of appetitive³⁴ or aversive
414 stimuli³⁵.

415 The time course for reset around transition, in which neural activity reached its steady state,
416 qualitatively matched that of NE release. It is possible that NE perturbed neural activity away
417 from the stored attractor. The seminal work of Segal and Bloom showed that electrical LC
418 stimulation acutely silenced most hippocampal neurons^{24,25} while enhancing the firing rate of
419 those neurons that fire in response to various stimuli. In anesthetized rats, LC activation causes
420 an increase in the excitability of CA1^{23,134} and dentate gyrus²⁰ neurons, as measured by the

421 amplitude of the population spike after afferent bundle stimulation. *Ex vivo* low-frequency
422 optogenetic stimulation of LC terminals likewise causes an increase in CA1 intrinsic
423 excitability²³. These acute effects are all blocked by β -adrenergic receptor antagonists.
424 Therefore, NE-related changes in gain/excitability may cause deviations from a stored neural
425 representation.

426 Alternatively, prominent models stipulate that area CA1 could be key in the generation of a
427 memory-related surprise signal that redirects attention and drives the release of
428 neuromodulators⁴. In these models, an error signal originates from a “comparator” structure in
429 CA1^{4,135,136}. This hypothesis was motivated by the observation that CA1 neurons are activated by
430 contextual novelty¹³⁷, novel objects¹³⁸, and novel configurations of familiar objects¹³⁹.
431 Unexpected violations of a learned sequence also cause robust activation of CA1 neurons¹⁴⁰, an
432 output that may be used to signal prediction error to arousal circuits^{141,142}. This error signal may
433 drive NE release through local modulation of LC terminals, or through polysynaptic pathways
434 (e.g. via the paraventricular hypothalamus^{143,144}). We speculate that an error signal should be
435 proportional to the difference between the instantaneous and steady-state neural representation.

436 We observed relatively unique neural patterns immediately following event boundaries.
437 Computational models predict that “pattern separation” yields enhanced memory by virtue of
438 creating neural traces that are less susceptible to interference¹⁴⁵. The hippocampal activity
439 patterns observed soon after the transition provide a neural timestamp for those moments that
440 may, in turn, underlie the enhanced subsequent recall that defines the primacy effect.

441 **Limitations**

442 The main limitation of the present study is that NE and neural coding were not studied in the
443 same subjects. Future studies should combine recording modalities and causally link the changes
444 in neural activity and NE signaling through perturbation studies that up- and down-regulate NE
445 and test for changes in hippocampal coding through the lens of representational uniqueness.

446 Another important limitation of the present study is the lack of *in vivo* calibration of the GRAB_{NE}
447 sensor. First, all measurements here are relative to baseline. Future studies should estimate how
448 emission intensities scale with NE concentration *in vivo*. Relatedly, the sensor is expressed
449 everywhere on the neuron, thus providing a read-out of a signal that may not actually be
450 available to the post-synaptic cells. Though most NE signaling occurs via “volume
451 transmission”, noradrenergic receptors do show laminar specificity¹⁴⁶ that is not honored by the
452 membrane insertion patterns of the GRAB_{NE} sensor. Finally, the sensor has fast onset ($\tau_{\text{on}} =$
453 0.09 s) and slow offset kinetics ($\tau_{\text{off}} = 1.93$ s)⁵³. Additionally, we smoothed the Signal_{NE} which,
454 combined with limitations of the sensors, impose some limitations on the rate of behavioral
455 fluctuations that may be captured in our analyses. The temporal resolution of the sensor has not
456 been calibrated against amperometry or fast cyclic voltammetry, but once such experiments have
457 been done, a deconvolution kernel may be developed to correct for binding kinetics.

458 Finally, the results have implications for a larger literature focusing on memory enhancement for
459 the events that occur after an event boundary. We define a minutes-long time window in which a
460 potential noradrenergic-dependent primacy effect may be expected, however, we did not
461 quantify learning gains as a function of time from an event boundary. Relating the present
462 observations to memory is an important future direction.

463 **Conclusion**

464 We found that the primary driver of NE release in the dorsal hippocampus is time from some
465 salient environmental change. When NE is elevated, neural activity differs from its steady state,
466 which may promote subsequent retrieval of these moments associated with relatively unique
467 neural representations. Event segmentation disturbances have been observed in a variety of
468 disorders, including: ADHD¹⁴⁷, schizophrenia¹⁴⁸, and Alzheimer's Disease¹⁴⁹ (a disease in which
469 the LC is particularly affected^{150,151}); as well as in normal cognitive decline in aging¹⁴⁹. Trauma
470 can also affect noradrenergic signaling in the hippocampus¹⁵², which affects how we respond to
471 and cope with stress¹⁵³. Future studies that relate NE release to hippocampal network
472 remapping/reset will provide important insight into the comorbid attention and memory deficits
473 associated with these disorders.

474 **Methods**

475 *Fiber photometry*

476 Subjects: C57BL/6J mice (N = 8 mice, N = 3 female) were implanted at 3-6 months-old. Data
477 was acquired for up to a year after implantation with no change in signal quality across this
478 extensive timeline. Two surgeries were performed at least two weeks apart, the first to deliver
479 the GRAB_{NE} sensor via AAV infusion and the second to implant a fiber optic stub. After viral
480 injection, animals were housed individually on a regular 12:12 h light:dark schedule and tested
481 during the light cycle. Following one week of recovery from the second surgery, mice were
482 recorded at most 5 days/week for up to a year before being euthanized with a sodium
483 pentobarbital cocktail (FatalPlus®, 300 mg/kg I.P.) and transcardially perfused with 4%
484 paraformaldehyde. All experimental procedures were performed in accordance with the National
485 Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the

486 University of New Mexico Health Sciences Center Institutional Animal Care and Use
487 Committee.

488 *Viral injections and fiber implant:* Mice were deeply anesthetized with isoflurane (1.5-2% in pure
489 oxygen) and GRAB_{NE} was delivered by injecting AAV9-hSyn-NE2h (titer: $\geq 5 \times 10^{12}$ vg/mL, WZ
490 Biosciences, MD USA)⁵³ unilaterally into the left dorsal hippocampus. Two coordinates were
491 used, both with reference from bregma: coordinate 1 (N = 2 mice) A/P: -2.3, M/L: -2.0 D/V: -1.4
492 and -1.2 from the brain surface; coordinate 2 (N = 6 mice) A/P: -2.0, M/L: -1.5 D/V: -1.3 and -
493 1.1 from the brain surface. Coordinate 1 yielded higher signal-to-noise; signals recorded from
494 both coordinates showed the same qualitative dynamics around event boundaries. In all cases,
495 the virus was injected at two depths each at a volume of 150-nL and a rate of 30 nL/min using a
496 Nanoliter 2020 Injector (WPI). At least two weeks later, fiber optic stubs (10 mm borosilicate
497 mono fiber-optic cannulas from Doric lenses; MFC_400/430-0.66_10.0mm_MF1.25_FLT) were
498 implanted at the injection site. To secure the stubs to the subject, the surface of the exposed skull
499 was covered with C&B Metabond® (Parkell, NY USA), and the sides of the exposed fiber-optic
500 cannula were coated in Unifast LC dental acrylic (SourceOne Dental, Inc, AZ USA) for stability.
501 Finally, clips (Neuralynx, AZ USA) were added to minimize motion artifact due to slippage at
502 the mating sleeve. Postoperatively, animals received a single injection of 0.1-mg/kg of
503 buprenorphine (S.C.) and again as needed for the next 1-3 days.

504 *Fiber photometry recording procedures:* Prior to the first recording session, we allowed a
505 minimum of three weeks from the viral injection procedure to allow the virus sufficient time to
506 transfect and express. Signals were captured with a LUX RZ10X processor running the Synapse
507 software (Tucker-Davis Technologies, FL). Experimental (465 nm, carrier frequency = 330 Hz)
508 and isosbestic (405 nm, carrier frequency = 210 Hz) wavelengths were combined using a

509 fluorescent MiniCube (FMC4_IE(400-410)_E(460-490)_F(500-550)_S; Doric, QC Canada) and
510 delivered to the subject with a 4-m low auto fluorescence mono fiber-optic patch cord (core =
511 400- μm ; NA = 0.57; Doric, QC Canada). Excitation intensity of the isosbestic and experimental
512 wavelengths was adjusted to equalize emission intensity, which was sampled at 1017.3 Hz.

513 Behavioral procedures

514 *Novel arena:* On the first day, mice were transferred to three novel arenas (dimensions in Figure
515 S1). First, a 10-minute homecage (HC) baseline was captured, then mice were manually
516 transferred to a novel arena (Context A) and back to their homecage for 10 minutes. This
517 procedure was performed again for Contexts B and C (HC-Context A-HC-Context B-HC-
518 Context C-HC). On following days, a 10-minute baseline period was run, followed by 10
519 minutes of exposure to Context A, and another 10 minutes in the home cage (HC-Context A-
520 HC). On Day 10, the procedure from the first day was repeated.

521 *Spontaneous Object Recognition:* On Day 0, mice were allowed to acclimate to a clean and
522 empty cage for 30 minutes. This cage had a hook-and-loop fastener for later object placement.
523 On Day 1, we recorded a 10-minute baseline in the clean and empty cage. Then, five novel
524 objects were sequentially affixed to the hook-and-loop fastener in the cage, each for five minutes
525 with no interval between objects. After the fifth object was removed, the animal remained in the
526 empty cage for another 10 minutes.

527 *Linear track:* Water-restricted mice were trained to run laps on a 1.2m linear track for water
528 reward (15 μL) which was delivered at each end of the track after mice crossed an IR sensor to
529 trigger a wall-mounted solenoid. Mice ran between 3-17 laps (mean = 8.1 laps) in 286-1500s
530 (mean = 658s). In these sessions (N = 110), there was a 10-minute homecage period before mice

531 were transferred to the linear track. Once mice stopped running for water for at least 30s, they
532 were returned to the home cage for 10 minutes. Following data acquisition, mice were given *ad*
533 *libitum* access to water in their home cage for 15 minutes and weighed to ensure no more than
534 15% loss of baseline body weight.

535 *Drug infusions:* Desipramine hydrochloride (Bio-Techne Corporation, MN USA) was injected
536 (I.P.) at a concentration of 10mg/kg (1 mg/ml) in normal saline (0.9%). Yohimbine
537 hydrochloride (Sigma Aldrich, MO USA) was injected (I.P.) at a concentration of 4-mg/kg (0.4
538 mg/ml) in normal saline. For recordings with drug injections, a 10-minute baseline was captured
539 before injections with either drug or vehicle.

540 *Signal Analysis*

541 *Estimation of Signal_{NE}:* The demuxed experimental and isosbestic signals both exhibited
542 evidence of photobleaching, though with different decay rates. Therefore, we fit a double
543 exponential to the first 10 minutes of each signal to estimate and extrapolate a mean signal which
544 was subtracted from the observed emission intensities. Next, the isosbestic was scaled to the
545 experimental signal using standard linear regression. The isosbestic was then subtracted from the
546 experimental signal, and the mean and standard deviation were calculated over the first 10
547 minutes. These values were used to normalize Signal_{NE} which is measured in terms of baseline
548 standard deviations from the baseline mean. Finally, the signal was smoothed with a Gaussian
549 kernel (1-s s.t.d.).

550 We opted against a sliding window dF/F calculation, as we did not want to impose a minutes-
551 long timescale to our analysis and we opted against divisive normalization directly to the
552 isosbestic as photobleaching dominated the fluctuations in the isosbestic signal and this rate

553 differed from that experimental signal¹⁵⁴. We adopted the mean and standard deviation from the
554 baseline period (rather than the entire session), as some of our experimental conditions (e.g.
555 desipramine infusions) dramatically changed the mean Signal_{NE} values over long periods of time.
556 We are aware that subtractive isosbestic correction (instead of divisive) may distort the relative
557 amplitudes of signals recorded early versus late into the session¹⁵⁵. These concerns are mitigated
558 here as the main decreases in emission intensity due to photobleaching occurred within the 10-
559 minute baseline period. Moreover, we observed stable responses across ~1-hr of recording (e.g.
560 see Figure 1C) and a reliable return to baseline Signal_{NE} values in the final home cage
561 recordings.

562 *Statistical modeling of Signal_{NE}*: Signal_{NE} at each moment was estimated as a function of various
563 behavioral variables which differed according to the testing paradigm.

564 In the novel arena experiments, Signal_{NE} was estimated as a function of acceleration (*acc*),
565 velocity (*vel*), normalized distance from the edge (*distedg*), time from context transfer (*t1*), and
566 time from rearing onset (*t2*), see *Equation 1*. Acceleration and velocity were calculated using a
567 second-order Kalman filter of the head location (right and left ear locations estimated with
568 DeepLabCut¹⁵⁶). Normalized distance to the edge was calculated as the distance to the nearest
569 edge divided by the maximum distance to an edge possible. In some cases, the animal could
570 extend its head beyond the wall of the arena and these values were coded as negative.

571 *Equation 1*

$$\begin{aligned} 572 \widehat{Signal}_{NE}(t) = & \beta_0 + \beta_1 acc(t) + \beta_2 vel(t) + \beta_3 distedg(t) + \beta_4 e^{-\tau_1 * t1} - \beta_5 e^{-\tau_2 * t1} \\ 573 & + \beta_6 e^{-\tau_3 * t2} - \beta_7 e^{-\tau_4 * t2} \end{aligned}$$

574 Time from transition/rearing was modeled with two terms: a positive term $\beta_{4/6}$ with a fast
575 exponential decay $\tau_{1/3}$ and a negative term $\beta_{5/7}$ with a slower exponential decay $\tau_{2/4}$. To avoid
576 degeneracy, $\tau_{1/3}$ was bounded between 0.1-0.001 and $\tau_{2/4}$ was bounded between 0.001-0.0001.
577 All β values were bound at ± 10 s.t.d. Point estimates for the 12 free parameters (β_{0-7} and τ_{1-4})
578 were calculated with MATLAB R2021b using the fmincon non-linear optimizer against a
579 regularized objective (Equation 2) defined by the mean squared error (MSE) with a penalty for
580 model complexity ($\lambda = 0.001$). Fits were robust to initial conditions.

581 *Equation 2*

582
$$\text{Objective} = \frac{\sum (\text{Signal}_{NE} - \widehat{\text{Signal}}_{NE})^2}{N} + \lambda \sum \beta^2$$

583 We performed 50/50 cross-validation, with the model trained on even days and tested on odd, or
584 vice-versa. The cross-validate mean-squared error (CVMSE) was used to assess model fit (the
585 regularization term is dropped here).

586 To assess the importance of each behavioral independent variable (and intercept), we excluded
587 all terms related to those variables in a backwards stepwise regression analysis. For example,
588 removing time from context transfer removed four terms: $\beta_4, \beta_5, \tau_1, \tau_2$. The cross-validation
589 employed here ensures that model performance should not suffer more simply due to removing
590 more free parameters, as demonstrated by the stability of the model after removing the four terms
591 related to rearing (or reward in the case of the linear track). CVMSE for the saturated and
592 reduced model was compared by computing the percent change in CVMSE.

593 *Equation 3*

$$594 \quad \Delta CVMSE = \frac{CVMSE_{reduced} - CVMSE_{saturated}}{CVMSE_{saturated}}$$

595 A similar approach was adopted for modeling $Signal_{NE}$ during novel object exposure, except we
596 included a binary indicator function for whether the mouse was sampling the object (snout
597 touching the object) and the time from event boundary, $t3$, was the time from object introduction;
598 we dropped the term related to rearing. Parameters were estimated for each subject and 50/50
599 cross-validation was done by splitting each session in half (first half training, second half test).

600 *Equation 4*

$$601 \quad \widehat{Signal}_{NE}(t) = \beta_0 + \beta_1 acc(t) + \beta_2 vel(t) + \beta_3 distedg(t) + \beta_4 objsample(t) + \beta_4 e^{-\tau_1 * t3} \\ 602 \quad - \beta_5 e^{-\tau_2 * t3}$$

603 For the linear track, we considered: velocity, acceleration, distance from edge, time from transfer
604 to the track ($t1$), and time from reward ($t4$). Parameters were estimated for each subject and
605 cross-validation was done by considering even training and odd testing days (or vice versa).

606 *Equation 5*

$$607 \quad \widehat{Signal}_{NE}(t) = \beta_0 + \beta_1 acc(t) + \beta_2 vel(t) + \beta_3 distedg(t) + \beta_4 e^{-\tau_1 * t1} - \beta_5 e^{-\tau_2 * t1} \\ 608 \quad + \beta_6 e^{-\tau_3 * t4} - \beta_7 e^{-\tau_4 * t4}$$

609 In all cases, to determine the significance of a parameter's removal, we performed Student t-test
610 on the CVMSE values (testing against h_0 CVMSE = 0) with degrees of freedom defined by the
611 number of subjects. To compare changes in parameters across days, we used a mixed-effects
612 linear model, with days of exposure defined as a fixed effect and subject as a random effect. We
613 modeled the relationship with random slopes and intercepts.

614 ***Electrophysiology***

615 *Electrophysiology subjects:* Data was downloaded from The Buzsaki Lab Databank (Project:
616 Place field-memory field unity of hippocampal neurons)¹⁵⁷. As described in Huszar et al.⁷⁴,
617 chronic recordings were performed from freely moving adult C57BL/6J mice (N = 3 mice;
618 subjID: e13_26m1, e15_13f1, e16_3m2) using high-density ASSY Int64-P32-1D or ASSY
619 Int128- P64-1D silicon probes (Diagnostic Biochips, MD USA). In these experiments, probes
620 were implanted over the right dorsal hippocampus (A/P -2.0, M/L +1.7) and lowered to the deep
621 neocortical layers, while the drive was cemented to the skull. A stainless-steel screw was placed
622 over the cerebellum for grounding and reference. Neural signals were recorded in the home cage
623 while probes were lowered into the CA1 pyramidal layer, which was identified physiologically
624 via the sharp wave polarity reversal. Neural data were amplified and digitized at 30-kHz using
625 Intan amplifier boards (RHD2132/RHD2000, Evaluation System, Intan Technologies, CA USA).
626 The complete dataset is available at <https://dandiarchive.org/dandiset/000552/0.230630.2304>. All
627 experiments were conducted in accordance with the Institutional Animal Care and Use
628 Committee of New York University Medical Center (IA15-01466).

629 *Behavioral testing:* Over weeks, mice were over-trained on a spatial alternation task in a figure-
630 eight maze (see Huszar et al. 2022, for full details). Animals were water restricted before the
631 start of experiments and familiarized with the figure-eight maze. Mice were trained to visit
632 alternate arms between trials to receive a water reward in the first corner reached after making a
633 correct left/right turn after which, a 5-s delay in the start area was introduced between trials. To
634 explore the reorganization of place tuning across different environments, the same mice were
635 introduced to novel environments after running in the familiar figure-8 maze. In the sessions
636 analyzed here (N=8), animals underwent recording sessions consisting of a ~120-min home cage

637 period, running on the familiar figure-eight maze, ~60-min home cage period, running in a novel
638 environment, followed by a final ~120-min home cage period. In some sessions, animals were
639 exposed to two distinct novel environments, with a ~60-min home cage period in between (only
640 one transition to a novel environment was chosen per session to analyze here). We considered
641 transitions to novel linear tracks (N = 3 sessions), novel figure-8 mazes (N = 3 sessions), and a
642 novel arena (N = 1 session). Mazes were placed in distinct recording rooms, or in different
643 corners of the same recording room, with distinct enclosures to ensure unique visual cues. Mouse
644 position was captured with head-mounted red LEDs.

645 *Spiking analysis:* Spikes were extracted and classified into putative single units using
646 KiloSort1¹⁵⁸ and manually curated in phy¹⁵⁹. Pyramidal neurons were separated from
647 interneurons based on waveform shape and bursting statistics and only pyramidal cell spiking
648 was analyzed.

649 *ACG slope analysis:* Population firing rates were calculated in 100-ms bins by counting the
650 number of spikes observed in that period and then z-scoring over the first 1000-s after transfer.
651 All vectors within a session were correlated with one another to generate a similarity matrix of
652 Pearson R correlation values. We considered the drop-off in population firing rates vector
653 correlation over a 10-s period using a 100-s moving average with an exponent with three free
654 parameters (β , τ , c).

655 *Equation 6*

656
$$\widehat{ACG}(t) = \beta * e^{-\tau * t} + c$$

657 *Reset analysis:* At each 100-ms moment, we asked where was the subject in space, and what
658 were the 3 most similar population firing rate vectors – as assessed from the similarity matrix of

659 Pearson R values – recorded in that location (minimum occupancy = 1-s). The mean of this
660 nearest-neighbor (NN) search was saved as the measure of representational similarity of that
661 moment to all others, conditioned on the location of the mouse and smoothed with a 1-s
662 Gaussian kernel.

663 To control for movement, we additionally calculated the mean absolute difference in velocity
664 ($|\Delta vel|_{NN}$) and acceleration ($|\Delta acc|_{NN}$) for the time bins with the highest population firing rate
665 vector correlations, i.e. those identified by the nearest-neighbor search above. If low correlations
666 in our NN search were driven by unusual movements, we would anticipate this to be reflected by
667 large deviations in $|\Delta vel|_{NN}$, and $|\Delta acc|_{NN}$. Therefore, we estimated the NN correlation as a
668 function of time from transition, $|\Delta vel|_{NN}$, and $|\Delta acc|_{NN}$.

669

670 *Equation 7*

$$671 \quad NN(\widehat{t}) = \beta_0 + \beta_1 |\Delta vel|_{NN}(t) + \beta_2 |\Delta acc|_{NN}(t) + \beta_3 e^{-\tau_1 * t1} - \beta_4 e^{-\tau_2 * t1}$$

672 Cross-validation was done by withholding each session from the training dataset and reporting
673 the CVMSE for each withheld session.

674 *Place field detection:* Mouse location was binned in 1x1 cm bins and the mean normalized firing
675 of each neuron (as described above) was calculated in each location. During moments when
676 velocity exceeded 5 cm/s, the mean normalized firing rate was calculate for each bin with more
677 than 1-s occupancy. Place field bounds were defined as regions with > 5 Hz firing rate (i.e. using
678 an unnormalized firing rate threshold).

679 *Ripple detection:* Broadband LFP was bandpass filtered between 130 and 200 Hz using a fourth-
680 order Chebyshev filter, and the normalized squared signal was calculated. SPW-R maxima were
681 detected by thresholding the normalized squared signal at 5 s.t.d. above the mean, and the
682 surrounding SPW-R start and stop times were identified as crossings of 2 s.d.t. around this peak.
683 SPW-R duration limits were set to be between 20 and 200 ms. See Huzsar et al.,⁷⁴ for full details.

684 *Reactivation analysis:* For each ripple recorded within 30 minutes of the beginning of the session
685 and within 30 minutes after the session, a population firing rate vector was calculated by
686 summing the total number of spikes emitted from each unit and dividing by the duration of the
687 ripple. Next, these population firing rate vectors were correlated with those recorded on the track
688 (in 100-ms bins). To assess whether the observed Pearson R was greater than expected by
689 chance, a bootstrap null distribution was created by shifting each neuron's activity observed on
690 any given ripple to a random other ripple observed during the session, thus preserving the single-
691 cell mean ripple recruitment rate, but destroying patterns of synchrony observed across the
692 ensemble. This procedure was repeated 1000 times, so that we could ask, for each ripple, if the
693 observed Pearson R greater than 99.9% of the shuffles. We report the percentage of ripples in
694 which each moment shows significant reactivation before and after experience with a false
695 positive rate = 0.001.

696 **Declaration of Interests**

697 The authors declare no competing interests.

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703

704 References

- 705 1 Clewett, D., Gasser, C. & Davachi, L. Pupil-linked arousal signals track the temporal organization
706 of events in memory. *Nat Commun* **11**, 4007, doi:10.1038/s41467-020-17851-9 (2020).
- 707 2 Hagen, H., Hansen, N. & Manahan-Vaughan, D. beta-Adrenergic Control of Hippocampal
708 Function: Subservient to the Choreography of Synaptic Information Storage and Memory. *Cereb*
709 *Cortex* **26**, 1349-1364, doi:10.1093/cercor/bhv330 (2016).
- 710 3 Wang, S. H., Redondo, R. L. & Morris, R. G. Relevance of synaptic tagging and capture to the
711 persistence of long-term potentiation and everyday spatial memory. *Proc Natl Acad Sci U S A*
712 **107**, 19537-19542, doi:10.1073/pnas.1008638107 (2010).
- 713 4 Lisman, J. E. & Grace, A. A. The hippocampal-VTA loop: controlling the entry of information into
714 long-term memory. *Neuron* **46**, 703-713, doi:10.1016/j.neuron.2005.05.002 (2005).
- 715 5 Sajikumar, S. & Frey, J. U. Late-associativity, synaptic tagging, and the role of dopamine during
716 LTP and LTD. *Neurobiol Learn Mem* **82**, 12-25, doi:10.1016/j.nlm.2004.03.003 (2004).
- 717 6 Li, S. M., Cullen, W. K., Anwyl, R. & Rowan, M. J. Dopamine-dependent facilitation of LTP
718 induction in hippocampal CA1 by exposure to spatial novelty. *Nat Neurosci* **6**, 526-531,
719 doi:10.1038/nn1049 (2003).
- 720 7 Otmakhova, N. A. & Lisman, J. E. D1/D5 dopamine receptors inhibit depotentiation at CA1
721 synapses via cAMP-dependent mechanism. *J Neurosci* **18**, 1270-1279,
722 doi:10.1523/JNEUROSCI.18-04-01270.1998 (1998).
- 723 8 Otmakhova, N. A. & Lisman, J. E. D1/D5 dopamine receptor activation increases the magnitude
724 of early long-term potentiation at CA1 hippocampal synapses. *J Neurosci* **16**, 7478-7486,
725 doi:10.1523/JNEUROSCI.16-23-07478.1996 (1996).
- 726 9 Lemon, N., Aydin-Abidin, S., Funke, K. & Manahan-Vaughan, D. Locus Coeruleus Activation
727 Facilitates Memory Encoding and Induces Hippocampal LTD that Depends on β -Adrenergic
728 Receptor Activation. *Cereb Cortex* **19**, 2827-2837, doi:10.1093/cercor/bhp065 (2009).
- 729 10 Tsetsenis, T., Badya, J. K., Li, R. & Dani, J. A. Activation of a Locus Coeruleus to Dorsal
730 Hippocampus Noradrenergic Circuit Facilitates Associative Learning. *Front Cell Neurosci* **16**,
731 887679, doi:10.3389/fncel.2022.887679 (2022).
- 732 11 Lethbridge, R. L., Walling, S. G. & Harley, C. W. Modulation of the perforant path-evoked
733 potential in dentate gyrus as a function of intrahippocampal β -adrenoceptor agonist
734 concentration in urethane-anesthetized rat. *Brain Behav* **4**, 95-103, doi:10.1002/brb3.199
735 (2014).
- 736 12 Bouret, S. & Sara, S. J. Network reset: a simplified overarching theory of locus coeruleus
737 noradrenaline function. *Trends Neurosci* **28**, 574-582, doi:10.1016/j.tins.2005.09.002 (2005).
- 738 13 Tanila, H. Noradrenergic regulation of hippocampal place cells. *Hippocampus* **11**, 793-808,
739 doi:10.1002/hipo.1095 (2001).
- 740 14 Dahl, D. & Winson, J. Action of norepinephrine in the dentate gyrus. I. Stimulation of locus
741 coeruleus. *Exp Brain Res* **59**, 491-496, doi:10.1007/BF00261339 (1985).
- 742 15 Assaf, S. Y., Mason, S. T. & Miller, J. J. Noradrenergic modulation transmission between the
743 entorhinal cortex and the dentate gyrus of the rat [proceedings]. *J Physiol* **292**, 52P (1979).
- 744 16 Washburn, M. & Moises, H. C. Electrophysiological correlates of presynaptic alpha 2-receptor-
745 mediated inhibition of norepinephrine release at locus coeruleus synapses in dentate gyrus. *J*
746 *Neurosci* **9**, 2131-2140, doi:10.1523/JNEUROSCI.09-06-02131.1989 (1989).
- 747 17 Broncel, A., Bocian, R., Klos-Wojtczak, P. & Konopacki, J. Effects of locus coeruleus activation and
748 inactivation on hippocampal formation theta rhythm in anesthetized rats. *Brain Res Bull* **162**,
749 180-190, doi:10.1016/j.brainresbull.2020.05.017 (2020).

- 750 18 Lipski, W. J. & Grace, A. A. Activation and inhibition of neurons in the hippocampal ventral
751 subiculum by norepinephrine and locus coeruleus stimulation. *Neuropsychopharmacology* **38**,
752 285-292, doi:10.1038/npp.2012.157 (2013).
- 753 19 Brown, R. A., Walling, S. G., Milway, J. S. & Harley, C. W. Locus ceruleus activation suppresses
754 feedforward interneurons and reduces beta-gamma electroencephalogram frequencies while it
755 enhances theta frequencies in rat dentate gyrus. *J Neurosci* **25**, 1985-1991,
756 doi:10.1523/JNEUROSCI.4307-04.2005 (2005).
- 757 20 Harley, C. W. & Milway, J. S. Glutamate ejection in the locus coeruleus enhances the perforant
758 path-evoked population spike in the dentate gyrus. *Exp Brain Res* **63**, 143-150,
759 doi:10.1007/BF00235656 (1986).
- 760 21 Harley, C. W. & Sara, S. J. Locus coeruleus bursts induced by glutamate trigger delayed perforant
761 path spike amplitude potentiation in the dentate gyrus. *Exp Brain Res* **89**, 581-587,
762 doi:10.1007/BF00229883 (1992).
- 763 22 Berridge, C. W. & Foote, S. L. Effects of Locus-Coeruleus Activation on Electroencephalographic
764 Activity in Neocortex and Hippocampus. *J Neurosci* **11**, 3135-3145 (1991).
- 765 23 Bacon, T. J., Pickering, A. E. & Mellor, J. R. Noradrenaline Release from Locus Coeruleus
766 Terminals in the Hippocampus Enhances Excitation-Spike Coupling in CA1 Pyramidal Neurons Via
767 beta-Adrenoceptors. *Cereb Cortex* **30**, 6135-6151, doi:10.1093/cercor/bhaa159 (2020).
- 768 24 Segal, M. & Bloom, F. E. The action of norepinephrine in the rat hippocampus. IV. The effects of
769 locus coeruleus stimulation on evoked hippocampal unit activity. *Brain Res* **107**, 513-525,
770 doi:10.1016/0006-8993(76)90141-4 (1976).
- 771 25 Segal, M. & Bloom, F. E. The action of norepinephrine in the rat hippocampus. III. Hippocampal
772 cellular responses to locus coeruleus stimulation in the awake rat. *Brain Res* **107**, 499-511,
773 doi:10.1016/0006-8993(76)90140-2 (1976).
- 774 26 Aston-Jones, G. & Cohen, J. D. Adaptive gain and the role of the locus coeruleus-norepinephrine
775 system in optimal performance. *J Comp Neurol* **493**, 99-110, doi:10.1002/cne.20723 (2005).
- 776 27 Pfeffer, T. *et al.* Catecholamines alter the intrinsic variability of cortical population activity and
777 perception. *Plos Biol* **16**, doi:ARTN e2003453
778 10.1371/journal.pbio.2003453 (2018).
- 779 28 Cremer, A., Kalbe, F., Muller, J. C., Wiedemann, K. & Schwabe, L. Disentangling the roles of
780 dopamine and noradrenaline in the exploration-exploitation tradeoff during human decision-
781 making. *Neuropsychopharmacology* **48**, 1078-1086, doi:10.1038/s41386-022-01517-9 (2023).
- 782 29 Tervo, D. G. R. *et al.* Behavioral Variability through Stochastic Choice and Its Gating by Anterior
783 Cingulate Cortex. *Cell* **159**, 21-32, doi:10.1016/j.cell.2014.08.037 (2014).
- 784 30 Usher, M., Cohen, J. D., Servan-Schreiber, D., Rajkowski, J. & Aston-Jones, G. The role of locus
785 coeruleus in the regulation of cognitive performance. *Science* **283**, 549-554, doi:DOI
786 10.1126/science.283.5401.549 (1999).
- 787 31 Brown, E. *et al.* Simple neural networks that optimize decisions. *Int J Bifurcat Chaos* **15**, 803-826,
788 doi:Doi 10.1142/S0218127405012478 (2005).
- 789 32 Munn, B. R., Muller, E. J., Wainstein, G. & Shine, J. M. The ascending arousal system shapes
790 neural dynamics to mediate awareness of cognitive states. *Nat Commun* **12**, 6016,
791 doi:10.1038/s41467-021-26268-x (2021).
- 792 33 Kubie, J. L. & Muller, R. U. Multiple representations in the hippocampus. *Hippocampus* **1**, 240-
793 242, doi:10.1002/hipo.450010305 (1991).
- 794 34 Dupret, D., O'Neill, J., Pleydell-Bouverie, B. & Csicsvari, J. The reorganization and reactivation of
795 hippocampal maps predict spatial memory performance. *Nat Neurosci* **13**, 995-1002,
796 doi:10.1038/nn.2599 (2010).

- 797 35 Hollup, S. A., Molden, S., Donnett, J. G., Moser, M. B. & Moser, E. I. Accumulation of
798 hippocampal place fields at the goal location in an annular watermaze task. *J Neurosci* **21**, 1635-
799 1644, doi:10.1523/JNEUROSCI.21-05-01635.2001 (2001).
- 800 36 Markus, E. J. *et al.* Interactions between Location and Task Affect the Spatial and Directional
801 Firing of Hippocampal-Neurons. *J Neurosci* **15**, 7079-7094 (1995).
- 802 37 Moita, M. A., Rosis, S., Zhou, Y., LeDoux, J. E. & Blair, H. T. Putting fear in its place: remapping of
803 hippocampal place cells during fear conditioning. *J Neurosci* **24**, 7015-7023,
804 doi:10.1523/JNEUROSCI.5492-03.2004 (2004).
- 805 38 Rosenzweig, E. S., Redish, A. D., McNaughton, B. L. & Barnes, C. A. Hippocampal map
806 realignment and spatial learning. *Nat Neurosci* **6**, 609-615, doi:10.1038/nn1053 (2003).
- 807 39 Muller, R. U. & Kubie, J. L. The effects of changes in the environment on the spatial firing of
808 hippocampal complex-spike cells. *J Neurosci* **7**, 1951-1968, doi:10.1523/JNEUROSCI.07-07-
809 01951.1987 (1987).
- 810 40 Shapiro, M. L., Tanila, H. & Eichenbaum, H. Cues that hippocampal place cells encode: Dynamic
811 and hierarchical representation of local and distal stimuli. *Hippocampus* **7**, 624-642, doi:Doi
812 10.1002/(Sici)1098-1063(1997)7:6<624::Aid-Hipo5>3.0.Co;2-E (1997).
- 813 41 Leutgeb, S. *et al.* Independent codes for spatial and episodic memory in hippocampal neuronal
814 ensembles. *Science* **309**, 619-623, doi:10.1126/science.1114037 (2005).
- 815 42 Grella, S. L. *et al.* Locus Coeruleus Phasic, But Not Tonic, Activation Initiates Global Remapping in
816 a Familiar Environment. *J Neurosci* **39**, 445-455, doi:10.1523/JNEUROSCI.1956-18.2018 (2019).
- 817 43 Silva, D., Feng, T. & Foster, D. J. Trajectory events across hippocampal place cells require
818 previous experience. *Nat Neurosci* **18**, 1772-1779, doi:10.1038/nn.4151 (2015).
- 819 44 Dragoi, G. & Tonegawa, S. Development of schemas revealed by prior experience and NMDA
820 receptor knock-out. *Elife* **2**, e01326, doi:10.7554/eLife.01326 (2013).
- 821 45 Girardeau, G., Benchenane, K., Wiener, S. I., Buzsaki, G. & Zugaro, M. B. Selective suppression of
822 hippocampal ripples impairs spatial memory. *Nat Neurosci* **12**, 1222-1223, doi:10.1038/nn.2384
823 (2009).
- 824 46 Gridchyn, I., Schoenenberger, P., O'Neill, J. & Csicsvari, J. Assembly-Specific Disruption of
825 Hippocampal Replay Leads to Selective Memory Deficit. *Neuron* **106**, 291-300 e296,
826 doi:10.1016/j.neuron.2020.01.021 (2020).
- 827 47 McNamara, C. G., Tejero-Cantero, A., Trouche, S., Campo-Urriza, N. & Dupret, D. Dopaminergic
828 neurons promote hippocampal reactivation and spatial memory persistence. *Nat Neurosci* **17**,
829 1658-1660, doi:10.1038/nn.3843 (2014).
- 830 48 Singer, A. C. & Frank, L. M. Rewarded outcomes enhance reactivation of experience in the
831 hippocampus. *Neuron* **64**, 910-921, doi:10.1016/j.neuron.2009.11.016 (2009).
- 832 49 Nguyen, P. V. & Gelinas, J. N. Noradrenergic gating of long-lasting synaptic potentiation in the
833 hippocampus: from neurobiology to translational biomedicine. *J Neurogenet* **32**, 171-182,
834 doi:10.1080/01677063.2018.1497630 (2018).
- 835 50 Abercrombie, E. D., Keller, R. W. & Zigmond, M. J. Characterization of Hippocampal
836 Norepinephrine Release as Measured by Microdialysis Perfusion - Pharmacological and
837 Behavioral-Studies. *Neuroscience* **27**, 897-904, doi:Doi 10.1016/0306-4522(88)90192-3 (1988).
- 838 51 Ihalainen, J. A., Riekkinen, P., Jr. & Feenstra, M. G. Comparison of dopamine and noradrenaline
839 release in mouse prefrontal cortex, striatum and hippocampus using microdialysis. *Neurosci Lett*
840 **277**, 71-74, doi:10.1016/s0304-3940(99)00840-x (1999).
- 841 52 Moreno-Castilla, P., Perez-Ortega, R., Violante-Soria, V., Balderas, I. & Bermudez-Rattoni, F.
842 Hippocampal release of dopamine and norepinephrine encodes novel contextual information.
843 *Hippocampus* **27**, 547-557, doi:10.1002/hipo.22711 (2017).

- 844 53 Feng, J. *et al.* Monitoring norepinephrine release in vivo using next-generation GRAB(NE)
845 sensors. *Neuron*, doi:10.1016/j.neuron.2024.03.001 (2024).
- 846 54 Wilson, L. R. *et al.* Partial or Complete Loss of Norepinephrine Differentially Alters Contextual
847 Fear and Catecholamine Release Dynamics in Hippocampal CA1. *Biol Psychiatry Glob Open Sci* **4**,
848 51-60, doi:10.1016/j.bpsgos.2023.10.001 (2024).
- 849 55 Xiang, L. *et al.* Behavioral correlates of activity of optogenetically identified locus coeruleus
850 noradrenergic neurons in rats performing T-maze tasks. *Sci Rep* **9**, 1361, doi:10.1038/s41598-
851 018-37227-w (2019).
- 852 56 Basu, A. *et al.* Frontal Norepinephrine Represents a Threat Prediction Error Under Uncertainty.
853 *Biol Psychiatry*, doi:10.1016/j.biopsych.2024.01.025 (2024).
- 854 57 Jordan, R. The locus coeruleus as a global model failure system. *Trends in Neurosciences* **47**, 92-
855 105, doi:10.1016/j.tins.2023.11.006 (2024).
- 856 58 Jordan, R. & Keller, G. B. The locus coeruleus broadcasts prediction errors across the cortex to
857 promote sensorimotor plasticity. *Elife* **12**, doi:10.7554/eLife.85111 (2023).
- 858 59 Foote, S. L., Astonjones, G. & Bloom, F. E. Impulse Activity of Locus Coeruleus Neurons in Awake
859 Rats and Monkeys Is a Function of Sensory Stimulation and Arousal. *P Natl Acad Sci-Biol* **77**,
860 3033-3037, doi:DOI 10.1073/pnas.77.5.3033 (1980).
- 861 60 Herve-Minvielle, A. & Sara, S. J. Rapid habituation of auditory responses of locus coeruleus cells
862 in anaesthetized and awake rats. *Neuroreport* **6**, 1363-1368, doi:10.1097/00001756-199507100-
863 00001 (1995).
- 864 61 Takeuchi, T. *et al.* Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature*
865 **537**, 357-362, doi:10.1038/nature19325 (2016).
- 866 62 Vankov, A., Herve-Minvielle, A. & Sara, S. J. Response to novelty and its rapid habituation in
867 locus coeruleus neurons of the freely exploring rat. *Eur J Neurosci* **7**, 1180-1187,
868 doi:10.1111/j.1460-9568.1995.tb01108.x (1995).
- 869 63 Sara, S. J., Vankov, A. & Herve, A. Locus coeruleus-evoked responses in behaving rats: a clue to
870 the role of noradrenaline in memory. *Brain Res Bull* **35**, 457-465, doi:10.1016/0361-
871 9230(94)90159-7 (1994).
- 872 64 Bouret, S. & Sara, S. J. Reward expectation, orientation of attention and locus coeruleus-medial
873 frontal cortex interplay during learning. *Eur J Neurosci* **20**, 791-802, doi:10.1111/j.1460-
874 9568.2004.03526.x (2004).
- 875 65 Breton-Provencher, V., Drummond, G. T., Feng, J., Li, Y. & Sur, M. Spatiotemporal dynamics of
876 noradrenaline during learned behaviour. *Nature* **606**, 732-738, doi:10.1038/s41586-022-04782-2
877 (2022).
- 878 66 Su, Z. & Cohen, J. Two types of locus coeruleus norepinephrine neurons drive reinforcement
879 learning. *bioRxiv*, doi:<https://doi.org/10.1101/2022.12.08.519670> (2022).
- 880 67 Pittaluga, A. & Raiteri, M. Release-enhancing glycine-dependent presynaptic NMDA receptors
881 exist on noradrenergic terminals of hippocampus. *Eur J Pharmacol* **191**, 231-234,
882 doi:10.1016/0014-2999(90)94153-o (1990).
- 883 68 Alme, C. B. *et al.* Place cells in the hippocampus: eleven maps for eleven rooms. *Proc Natl Acad*
884 *Sci U S A* **111**, 18428-18435, doi:10.1073/pnas.1421056111 (2014).
- 885 69 Kaufman, A. M., Geiller, T. & Losonczy, A. A Role for the Locus Coeruleus in Hippocampal CA1
886 Place Cell Reorganization during Spatial Reward Learning. *Neuron* **105**, 1018-1026 e1014,
887 doi:10.1016/j.neuron.2019.12.029 (2020).
- 888 70 DuBrow, S. & Davachi, L. Temporal binding within and across events. *Neurobiol Learn Mem* **134**
889 **Pt A**, 107-114, doi:10.1016/j.nlm.2016.07.011 (2016).
- 890 71 Ennaceur, A. & Delacour, J. A new one-trial test for neurobiological studies of memory in rats. 1:
891 Behavioral data. *Behav Brain Res* **31**, 47-59, doi:10.1016/0166-4328(88)90157-x (1988).

- 892 72 Rait, L. I., Murty, V. P. & DuBrow, S. Contextual familiarity rescues the cost of switching. *Psychon*
893 *Bull Rev* **31**, 1103-1113, doi:10.3758/s13423-023-02392-1 (2024).
- 894 73 Sara, S. J. & Segal, M. Plasticity of sensory responses of locus coeruleus neurons in the behaving
895 rat: implications for cognition. *Prog Brain Res* **88**, 571-585, doi:10.1016/s0079-6123(08)63835-2
896 (1991).
- 897 74 Huszar, R., Zhang, Y., Blockus, H. & Buzsaki, G. Preconfigured dynamics in the hippocampus are
898 guided by embryonic birthdate and rate of neurogenesis. *Nat Neurosci* **25**, 1201-1212,
899 doi:10.1038/s41593-022-01138-x (2022).
- 900 75 Hill, A. J. First occurrence of hippocampal spatial firing in a new environment. *Exp Neurol* **62**,
901 282-297, doi:10.1016/0014-4886(78)90058-4 (1978).
- 902 76 Frank, L. M., Stanley, G. B. & Brown, E. N. Hippocampal plasticity across multiple days of
903 exposure to novel environments. *J Neurosci* **24**, 7681-7689, doi:10.1523/JNEUROSCI.1958-
904 04.2004 (2004).
- 905 77 Priestley, J. B., Bowler, J. C., Rolotti, S. V., Fusi, S. & Losonczy, A. Signatures of rapid plasticity in
906 hippocampal CA1 representations during novel experiences. *Neuron* **110**, 1978-1992 e1976,
907 doi:10.1016/j.neuron.2022.03.026 (2022).
- 908 78 Mehta, M. R., Barnes, C. A. & McNaughton, B. L. Experience-dependent, asymmetric expansion
909 of hippocampal place fields. *Proc Natl Acad Sci U S A* **94**, 8918-8921,
910 doi:10.1073/pnas.94.16.8918 (1997).
- 911 79 Jackson, J. & Redish, A. D. Network dynamics of hippocampal cell-assemblies resemble multiple
912 spatial maps within single tasks. *Hippocampus* **17**, 1209-1229, doi:10.1002/hipo.20359 (2007).
- 913 80 Wood, E. R., Dudchenko, P. A., Robitsek, R. J. & Eichenbaum, H. Hippocampal neurons encode
914 information about different types of memory episodes occurring in the same location. *Neuron*
915 **27**, 623-633, doi:10.1016/S0896-6273(00)00071-4 (2000).
- 916 81 Yavich, L., Jakala, P. & Tanila, H. Noradrenaline overflow in mouse dentate gyrus following locus
917 coeruleus and natural stimulation: real-time monitoring by in vivo voltammetry. *J Neurochem*
918 **95**, 641-650, doi:10.1111/j.1471-4159.2005.03390.x (2005).
- 919 82 Mitchell, K., Oke, A. F. & Adams, R. N. In vivo dynamics of norepinephrine release-reuptake in
920 multiple terminal field regions of rat brain. *J Neurochem* **63**, 917-926, doi:10.1046/j.1471-
921 4159.1994.63030917.x (1994).
- 922 83 Park, J., Takmakov, P. & Wightman, R. M. In vivo comparison of norepinephrine and dopamine
923 release in rat brain by simultaneous measurements with fast-scan cyclic voltammetry. *J*
924 *Neurochem* **119**, 932-944, doi:10.1111/j.1471-4159.2011.07494.x (2011).
- 925 84 Aston-Jones, G., Rajkowski, J. & Cohen, J. Role of locus coeruleus in attention and behavioral
926 flexibility. *Biol Psychiatry* **46**, 1309-1320, doi:10.1016/s0006-3223(99)00140-7 (1999).
- 927 85 Noei, S., Zouridis, I. S., Logothetis, N. K., Panzeri, S. & Totah, N. K. Distinct ensembles in the
928 noradrenergic locus coeruleus are associated with diverse cortical states. *Proc Natl Acad Sci U S*
929 *A* **119**, e2116507119, doi:10.1073/pnas.2116507119 (2022).
- 930 86 Berridge, C. W. & Abercrombie, E. D. Relationship between locus coeruleus discharge rates and
931 rates of norepinephrine release within neocortex as assessed by
932 microdialysis. *Neuroscience* **93**, 1263-1270, doi:10.1016/S0306-4522(99)00276-6 (1999).
- 933 87 Aston-Jones, G. & Bloom, F. E. Norepinephrine-containing locus coeruleus neurons in behaving
934 rats exhibit pronounced responses to non-noxious environmental stimuli. *J Neurosci* **1**, 887-900,
935 doi:10.1523/JNEUROSCI.01-08-00887.1981 (1981).
- 936 88 Pittaluga, A., Bonfanti, A. & Raiteri, M. Somatostatin potentiates NMDA receptor function via
937 activation of InsP(3) receptors and PKC leading to removal of the Mg(2+) block without
938 depolarization. *Br J Pharmacol* **130**, 557-566, doi:10.1038/sj.bjp.0703346 (2000).

- 939 89 Pittaluga, A., Feligioni, M., Longordo, F., Arvigo, M. & Raiteri, M. Somatostatin-induced
940 activation and up-regulation of N-methyl-D-aspartate receptor function: mediation through
941 calmodulin-dependent protein kinase II, phospholipase C, protein kinase C, and tyrosine kinase
942 in hippocampal noradrenergic nerve endings. *J Pharmacol Exp Ther* **313**, 242-249,
943 doi:10.1124/jpet.104.079590 (2005).
- 944 90 Risso, F. *et al.* Nicotine exerts a permissive role on NMDA receptor function in hippocampal
945 noradrenergic terminals. *Neuropharmacology* **47**, 65-71, doi:10.1016/j.neuropharm.2004.02.018
946 (2004).
- 947 91 Henneberger, C. *et al.* LTP Induction Boosts Glutamate Spillover by Driving Withdrawal of
948 Perisynaptic Astroglia. *Neuron* **108**, 919-936 e911, doi:10.1016/j.neuron.2020.08.030 (2020).
- 949 92 Armbruster, M., Hanson, E. & Dulla, C. G. Glutamate Clearance Is Locally Modulated by
950 Presynaptic Neuronal Activity in the Cerebral Cortex. *J Neurosci* **36**, 10404-10415,
951 doi:10.1523/Jneurosci.2066-16.2016 (2016).
- 952 93 Poppenk, J., Evensmoen, H. R., Moscovitch, M. & Nadel, L. Long-axis specialization of the human
953 hippocampus. *Trends Cogn Sci* **17**, 230-240, doi:10.1016/j.tics.2013.03.005 (2013).
- 954 94 Bright, I. M. *et al.* A temporal record of the past with a spectrum of time constants in the
955 monkey entorhinal cortex. *Proc Natl Acad Sci U S A* **117**, 20274-20283,
956 doi:10.1073/pnas.1917197117 (2020).
- 957 95 Momennejad, I. & Howard, M. W. Predicting the future with multi-scale successor
958 representations. *bioRxiv* **449470** (2018).
- 959 96 Tiganj, Z., Gershman, S. J., Sederberg, P. B. & Howard, M. W. Estimating Scale-Invariant Future in
960 Continuous Time. *Neural Comput* **31**, 681-709, doi:10.1162/neco_a_01171 (2019).
- 961 97 Wang, Y. C., Adcock, R. A. & Egner, T. Toward an integrative account of internal and external
962 determinants of event segmentation. *Psychon Bull Rev* **31**, 484-506, doi:10.3758/s13423-023-
963 02375-2 (2024).
- 964 98 Baldassano, C. *et al.* Discovering Event Structure in Continuous Narrative Perception and
965 Memory. *Neuron* **95**, 709-721 e705, doi:10.1016/j.neuron.2017.06.041 (2017).
- 966 99 Heusser, A. C., Ezzyat, Y., Shiff, I. & Davachi, L. Perceptual Boundaries Cause Mnemonic Trade-
967 Offs Between Local Boundary Processing and Across-Trial Associative Binding. *J Exp Psychol*
968 *Learn* **44**, 1075-1090, doi:10.1037/xlm0000503 (2018).
- 969 100 Boltz, M. Temporal accent structure and the remembering of filmed narratives. *J Exp Psychol*
970 *Hum Percept Perform* **18**, 90-105, doi:10.1037//0096-1523.18.1.90 (1992).
- 971 101 Murdock, B. B., Jr. Modality effects in short-term memory: storage or retrieval? *J Exp Psychol* **77**,
972 79-86, doi:10.1037/h0025786 (1968).
- 973 102 Kesner, R. P., Chiba, A. A. & Jacksonsmith, P. Rats Do Show Primacy and Recency Effects in
974 Memory for Lists of Spatial Locations - a Reply to Gaffan. *Anim Learn Behav* **22**, 214-218, doi:Doi
975 10.3758/Bf03199922 (1994).
- 976 103 Bolhuis, J. J. & van Kampen, H. S. Serial position curves in spatial memory of rats: primacy and
977 recency effects. *Q J Exp Psychol B* **40**, 135-149 (1988).
- 978 104 Ezzyat, Y. & Davachi, L. Similarity breeds proximity: pattern similarity within and across contexts
979 is related to later mnemonic judgments of temporal proximity. *Neuron* **81**, 1179-1189,
980 doi:10.1016/j.neuron.2014.01.042 (2014).
- 981 105 Pu, Y., Kong, X. Z., Ranganath, C. & Melloni, L. Event boundaries shape temporal organization of
982 memory by resetting temporal context. *Nat Commun* **13**, 622, doi:10.1038/s41467-022-28216-9
983 (2022).
- 984 106 Sinclair, A. H., Manalili, G. M., Brunec, I. K., Adcock, R. A. & Barense, M. D. Prediction errors
985 disrupt hippocampal representations and update episodic memories. *Proc Natl Acad Sci U S A*
986 **118**, doi:10.1073/pnas.2117625118 (2021).

- 987 107 Kim, G., Norman, K. A. & Turk-Browne, N. B. Neural Differentiation of Incorrectly Predicted
988 Memories. *J Neurosci* **37**, 2022-2031, doi:10.1523/JNEUROSCI.3272-16.2017 (2017).
- 989 108 Carter, M. E. *et al.* Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat*
990 *Neurosci* **13**, 1526-1533, doi:10.1038/nn.2682 (2010).
- 991 109 Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H. & Balsters, J. H. Pupil diameter
992 covaries with BOLD activity in human locus coeruleus. *Hum Brain Mapp* **35**, 4140-4154,
993 doi:10.1002/hbm.22466 (2014).
- 994 110 Megemont, M., McBurney-Lin, J. & Yang, H. D. Pupil diameter is not an accurate real-time
995 readout of locus coeruleus activity. *Elife* **11** (2022).
- 996 111 Wilmot, J. H. *et al.* Phasic locus coeruleus activity enhances trace fear conditioning by increasing
997 dopamine release in the hippocampus. *Elife* **12**, doi:10.7554/eLife.91465 (2024).
- 998 112 Tse, D. *et al.* Cell-type-specific optogenetic stimulation of the locus coeruleus induces slow-onset
999 potentiation and enhances everyday memory in rats. *Proc Natl Acad Sci U S A* **120**,
1000 e2307275120, doi:10.1073/pnas.2307275120 (2023).
- 1001 113 Chowdhury, A. *et al.* A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory
1002 linking. *Neuron* **110**, 3374-3388 e3378, doi:10.1016/j.neuron.2022.08.001 (2022).
- 1003 114 Wagatsuma, A. *et al.* Locus coeruleus input to hippocampal CA3 drives single-trial learning of a
1004 novel context. *Proc Natl Acad Sci U S A* **115**, E310-E316, doi:10.1073/pnas.1714082115 (2018).
- 1005 115 Kempadoo, K. A., Mosharov, E. V., Choi, S. J., Sulzer, D. & Kandel, E. R. Dopamine release from
1006 the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. *Proc Natl*
1007 *Acad Sci U S A* **113**, 14835-14840, doi:10.1073/pnas.1616515114 (2016).
- 1008 116 Sara, S. J. Locus Coeruleus in time with the making of memories. *Curr Opin Neurobiol* **35**, 87-94,
1009 doi:10.1016/j.conb.2015.07.004 (2015).
- 1010 117 Hämmerer, D. *et al.* Locus coeruleus integrity in old age is selectively related to memories linked
1011 with salient negative events. *P Natl Acad Sci USA* **115**, 2228-2233,
1012 doi:10.1073/pnas.1712268115 (2018).
- 1013 118 Seo, D. O. *et al.* A locus coeruleus to dentate gyrus noradrenergic circuit modulates aversive
1014 contextual processing. *Neuron* **109**, 2116-2130 e2116, doi:10.1016/j.neuron.2021.05.006 (2021).
- 1015 119 Amaral, D. G. & Foss, J. A. Locus Coeruleus Lesions and Learning. *Science* **188**, 377-378, doi:DOI
1016 10.1126/science.1118734 (1975).
- 1017 120 Frey, U. & Morris, R. G. M. Synaptic tagging and long-term potentiation. *Nature* **385**, 533-536,
1018 doi:DOI 10.1038/385533a0 (1997).
- 1019 121 O'Carroll, C. M., Martin, S. J., Sandin, J., Frenguelli, B. & Morris, R. G. Dopaminergic modulation
1020 of the persistence of one-trial hippocampus-dependent memory. *Learn Mem* **13**, 760-769,
1021 doi:10.1101/lm.321006 (2006).
- 1022 122 He, K. W. *et al.* Distinct Eligibility Traces for LTP and LTD in Cortical Synapses. *Neuron* **88**, 528-
1023 538, doi:10.1016/j.neuron.2015.09.037 (2015).
- 1024 123 Harley, C., Milway, J. S. & Lacaille, J. C. Locus coeruleus potentiation of dentate gyrus responses:
1025 evidence for two systems. *Brain Res Bull* **22**, 643-650, doi:10.1016/0361-9230(89)90084-1
1026 (1989).
- 1027 124 Frey, S., Bergado-Rosado, J., Seidenbecher, T., Pape, H. C. & Frey, J. U. Reinforcement of early
1028 long-term potentiation (early-LTP) in dentate gyrus by stimulation of the basolateral amygdala:
1029 heterosynaptic induction mechanisms of late-LTP. *J Neurosci* **21**, 3697-3703,
1030 doi:10.1523/JNEUROSCI.21-10-03697.2001 (2001).
- 1031 125 Pignatelli, M. *et al.* Engram Cell Excitability State Determines the Efficacy of Memory Retrieval.
1032 *Neuron* **101**, 274-284 e275, doi:10.1016/j.neuron.2018.11.029 (2019).

- 1033 126 Meenakshi, P., Kumar, S. & Balaji, J. In vivo imaging of immediate early gene expression
1034 dynamics segregates neuronal ensemble of memories of dual events. *Mol Brain* **14**, 102,
1035 doi:10.1186/s13041-021-00798-3 (2021).
- 1036 127 Cai, D. J. *et al.* A shared neural ensemble links distinct contextual memories encoded close in
1037 time. *Nature* **534**, 115-118, doi:10.1038/nature17955 (2016).
- 1038 128 Yang, W. *et al.* Selection of experience for memory by hippocampal sharp wave ripples. *Science*
1039 **383**, 1478-1483, doi:10.1126/science.adk8261 (2024).
- 1040 129 Jezek, K., Henriksen, E. J., Treves, A., Moser, E. I. & Moser, M. B. Theta-paced flickering between
1041 place-cell maps in the hippocampus. *Nature* **478**, 246-249, doi:10.1038/nature10439 (2011).
- 1042 130 Chung, A. *et al.* Cognitive control persistently enhances hippocampal information processing.
1043 *Nature* **600**, 484-488, doi:10.1038/s41586-021-04070-5 (2021).
- 1044 131 Pettit, N. L., Yuan, X. C. & Harvey, C. D. Hippocampal place codes are gated by behavioral
1045 engagement. *Nat Neurosci* **25**, 561-566, doi:10.1038/s41593-022-01050-4 (2022).
- 1046 132 El-Gaby, M. *et al.* An emergent neural coactivity code for dynamic memory. *Nat Neurosci* **24**,
1047 694-704, doi:10.1038/s41593-021-00820-w (2021).
- 1048 133 Monaco, J. D., Rao, G., Roth, E. D. & Knierim, J. J. Attentive scanning behavior drives one-trial
1049 potentiation of hippocampal place fields. *Nat Neurosci* **17**, 725-731, doi:10.1038/nn.3687
1050 (2014).
- 1051 134 Olpe, H. R. *et al.* Glutamate-Induced Activation of Rat Locus-Coeruleus Increases Ca1 Pyramidal
1052 Cell Excitability. *Neurosci Lett* **65**, 11-16, doi:Doi 10.1016/0304-3940(86)90112-6 (1986).
- 1053 135 Kafkas, A. & Montaldi, D. How do memory systems detect and respond to novelty? *Neurosci Lett*
1054 **680**, 60-68, doi:10.1016/j.neulet.2018.01.053 (2018).
- 1055 136 Ben-Yakov, A. & Henson, R. N. The Hippocampal Film Editor: Sensitivity and Specificity to Event
1056 Boundaries in Continuous Experience. *J Neurosci* **38**, 10057-10068,
1057 doi:10.1523/JNEUROSCI.0524-18.2018 (2018).
- 1058 137 VanElzakker, M., Fevurly, R. D., Breindel, T. & Spencer, R. L. Environmental novelty is associated
1059 with a selective increase in Fos expression in the output elements of the hippocampal formation
1060 and the perirhinal cortex. *Learn Memory* **15**, 899-908, doi:10.1101/lm.1196508 (2008).
- 1061 138 Larkin, M. C., Lykken, C., Tye, L. D., Wickelgren, J. G. & Frank, L. M. Hippocampal output area
1062 CA1 broadcasts a generalized novelty signal during an object-place recognition task.
1063 *Hippocampus* **24**, 773-783, doi:10.1002/hipo.22268 (2014).
- 1064 139 Jenkins, T. A., Amin, E., Pearce, J. M., Brown, M. W. & Aggleton, J. P. Novel spatial arrangements
1065 of familiar visual stimuli promote activity in the rat hippocampal formation but not the
1066 parahippocampal cortices: a c-fos expression study. *Neuroscience* **124**, 43-52,
1067 doi:10.1016/j.neuroscience.2003.11.024 (2004).
- 1068 140 Allen, T. A., Salz, D. M., McKenzie, S. & Fortin, N. J. Nonspatial Sequence Coding in CA1 Neurons.
1069 *J Neurosci* **36**, 1547-1563, doi:10.1523/JNEUROSCI.2874-15.2016 (2016).
- 1070 141 Vinogradova, O. S. Hippocampus as comparator: role of the two input and two output systems
1071 of the hippocampus in selection and registration of information. *Hippocampus* **11**, 578-598,
1072 doi:10.1002/hipo.1073 (2001).
- 1073 142 Kumaran, D. & Maguire, E. A. An unexpected sequence of events: mismatch detection in the
1074 human hippocampus. *Plos Biol* **4**, e424, doi:10.1371/journal.pbio.0040424 (2006).
- 1075 143 Aston-Jones, G. *et al.* Afferent regulation of locus coeruleus neurons: anatomy, physiology and
1076 pharmacology. *Prog Brain Res* **88**, 47-75, doi:10.1016/s0079-6123(08)63799-1 (1991).
- 1077 144 Kishi, T. *et al.* Topographical organization of projections from the subiculum to the
1078 hypothalamus in the rat. *Journal of Comparative Neurology* **419**, 205-222, doi:Doi
1079 10.1002/(Sici)1096-9861(20000403)419:2<205::Aid-Cne5>3.0.Co;2-0 (2000).
- 1080 145 Rolls, E. T. in *Neural models of plasticity* Ch. 13, 240-265 (Academic Press, 1989).

- 1081 146 Oleskevich, S., Descarries, L. & Lacaille, J. C. Quantified distribution of the noradrenaline
1082 innervation in the hippocampus of adult rat. *J Neurosci* **9**, 3803-3815,
1083 doi:10.1523/JNEUROSCI.09-11-03803.1989 (1989).
- 1084 147 Ryan, J. & Rogers, M. Event Segmentation Deficits in ADHD. *J Atten Disord* **25**, 355-363,
1085 doi:10.1177/1087054718799929 (2021).
- 1086 148 Zalla, T., Verlut, I., Franck, N., Puzenat, D. & Sirigu, A. Perception of dynamic action in patients
1087 with schizophrenia. *Psychiatry Res* **128**, 39-51, doi:10.1016/j.psychres.2003.12.026 (2004).
- 1088 149 Zacks, J. M., Speer, N. K., Vettel, J. M. & Jacoby, L. L. Event understanding and memory in
1089 healthy aging and dementia of the Alzheimer type. *Psychol Aging* **21**, 466-482,
1090 doi:10.1037/0882-7974.21.3.466 (2006).
- 1091 150 Braak, H., Thal, D. R., Ghebremedhin, E. & Del Tredici, K. Stages of the pathologic process in
1092 Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol* **70**, 960-969,
1093 doi:10.1097/NEN.0b013e318232a379 (2011).
- 1094 151 Theofilas, P. *et al.* Locus coeruleus volume and cell population changes during Alzheimer's
1095 disease progression: A stereological study in human postmortem brains with potential
1096 implication for early-stage biomarker discovery. *Alzheimers Dement* **13**, 236-246,
1097 doi:10.1016/j.jalz.2016.06.2362 (2017).
- 1098 152 Nisenbaum, L. K., Zigmond, M. J., Sved, A. F. & Abercrombie, E. D. Prior exposure to chronic
1099 stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a
1100 novel stressor. *J Neurosci* **11**, 1478-1484, doi:10.1523/JNEUROSCI.11-05-01478.1991 (1991).
- 1101 153 Belujon, P. & Grace, A. A. Hippocampus, amygdala, and stress: interacting systems that affect
1102 susceptibility to addiction. *Ann Ny Acad Sci* **1216**, 114-121, doi:10.1111/j.1749-
1103 6632.2010.05896.x (2011).
- 1104 154 Simpson, E. H. *et al.* Lights, fiber, action! A primer on in vivo fiber photometry. *Neuron* **112**, 718-
1105 739, doi:10.1016/j.neuron.2023.11.016 (2024).
- 1106 155 Keevers, L. J., McNally, G. P. & Jean-Richard-dit-Bressel, P. Obtaining artifact-corrected signals in
1107 fiber photometry: Isosbestic signals, robust regression and dF/F calculations. *Research Square*
1108 *Platform*, doi:<https://doi.org/10.21203/rs.3.rs-3549461/v1> (2023).
- 1109 156 Mathis, A. *et al.* DeepLabCut: markerless pose estimation of user-defined body parts with deep
1110 learning. *Nat Neurosci* **21**, 1281-1289, doi:10.1038/s41593-018-0209-y (2018).
- 1111 157 Petersen, P. C., Hernandez, M. & Buzsáki, G. (Zenodo, 2020).
- 1112 158 Pachitariu, M., Steinmetz, N., Kadir, S., Carandini, M. & Harris, K. Fast and accurate spike sorting
1113 of high-channel count probes with KiloSort. *Adv Neur In* **29** (2016).
- 1114 159 Rossant, C. *et al.* Spike sorting for large, dense electrode arrays. *Nat Neurosci* **19**, 634-641,
1115 doi:10.1038/nn.4268 (2016).

1116

1117 Figure 1

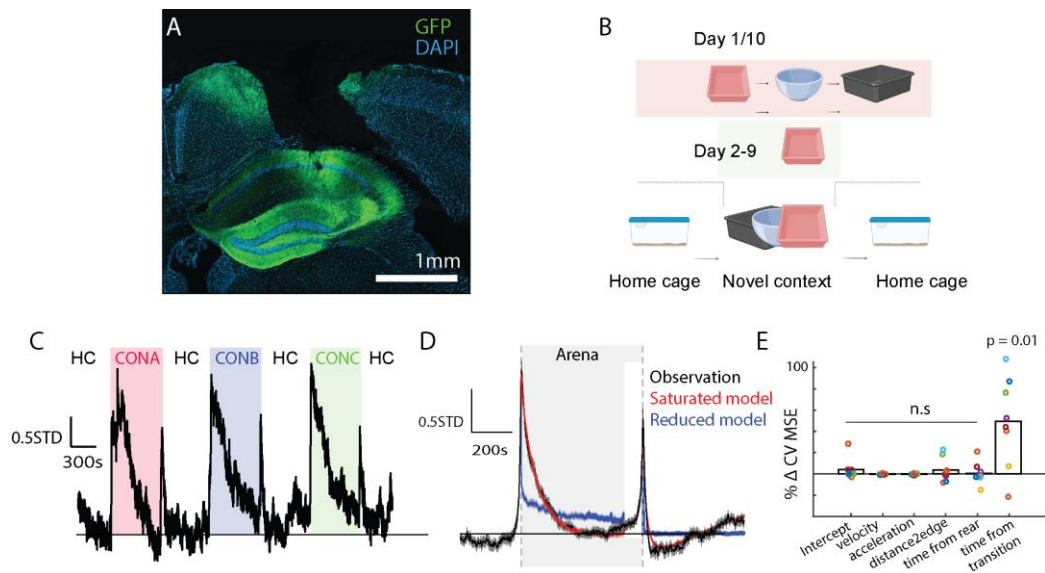


Figure 1. Time from context transition controls Signal_{NE} when mice are moved to novel arenas. A) Histological confirmation of GRAB_{NE} expression (GFP) and fiber placement over dorsal CA1. B) Schematic of experimental timeline. C) Example session showing increases in Signal_{NE} around each context and homecage (HC) transition. D) Mean Signal_{NE} measured across all transitions (black) and cross-validated prediction from the saturated model (red) or a reduced model lacking terms related to time from transfer (blue). E) Change in CVMSE due to removal of various potential behavioral variables. Only removal of the terms related to time from transition significantly decreased model performance ($t(7) = 3.30, p = 0.01$).

1118 Figure 2

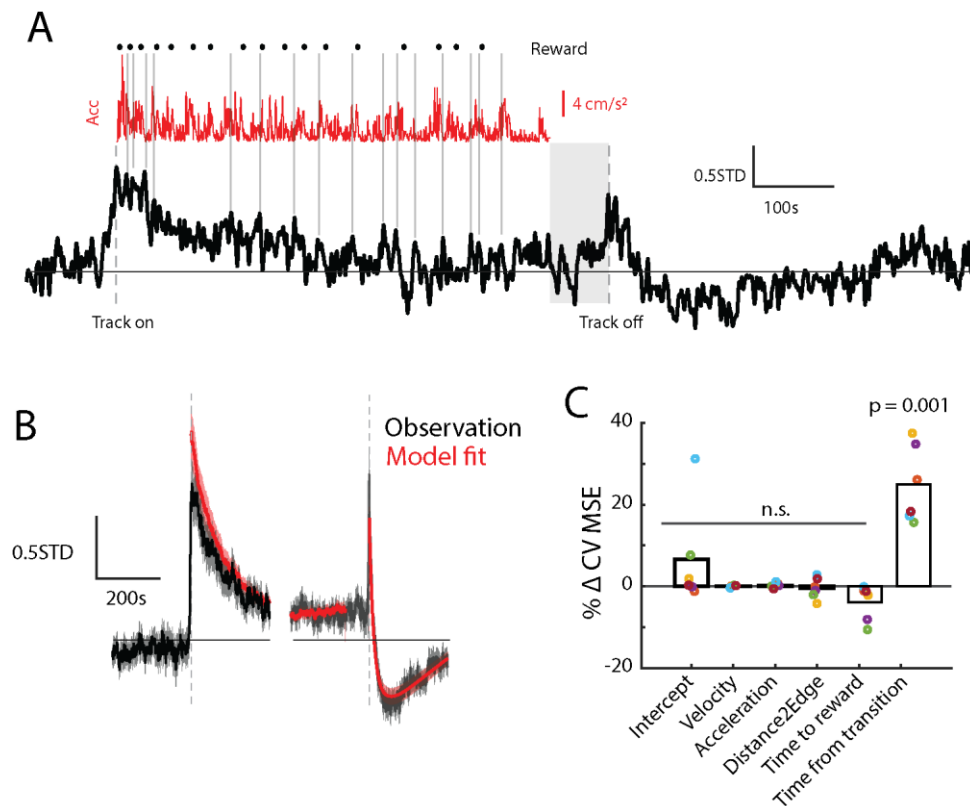


Figure 2. Time from context transition controls Signal_{NE} when mice are moved to a linear track. A) Example session showing Signal_{NE} (black) aligned with acceleration (red) and reward delivery (•). Vertical gray lines show that local peaks in Signal_{NE} do not align to bouts of acceleration nor reward timing. Shaded area shows last 60s before removing from track during which Signal_{NE} was not modeled. B) Mean Signal_{NE} measured across all linear track transitions (black) and cross-validated prediction from the saturated model (red). C) Change in CVMSE due to removal of various potential behavioral variables. Only removal of the terms related to time from transition significantly decreased model performance ($t(7) = 7.20, p = 0.0008$).

1120 Figure 3

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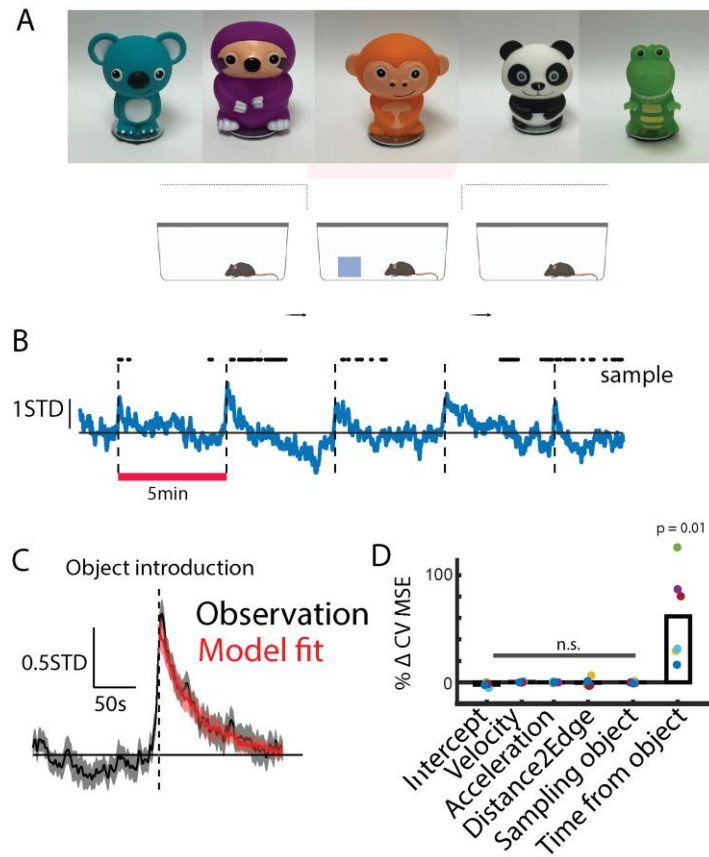


Figure 3. Time from object introduction controls $Signal_{NE}$ A) Photographs of five novel objects presented to the mouse. B) Example session showing $Signal_{NE}$ (black) aligned object introduction (dashed line) and object sampling (\bullet). C) Mean $Signal_{NE}$ measured across all object presentations (black) and cross-validated prediction from the saturated model (red). D) Change in CVMSE due to removal of various potential behavioral variables. Only removal of the terms related to time from object introduction significantly decreased model performance ($t(5) = 3.54, p = 0.017$).

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1123 Figure 4

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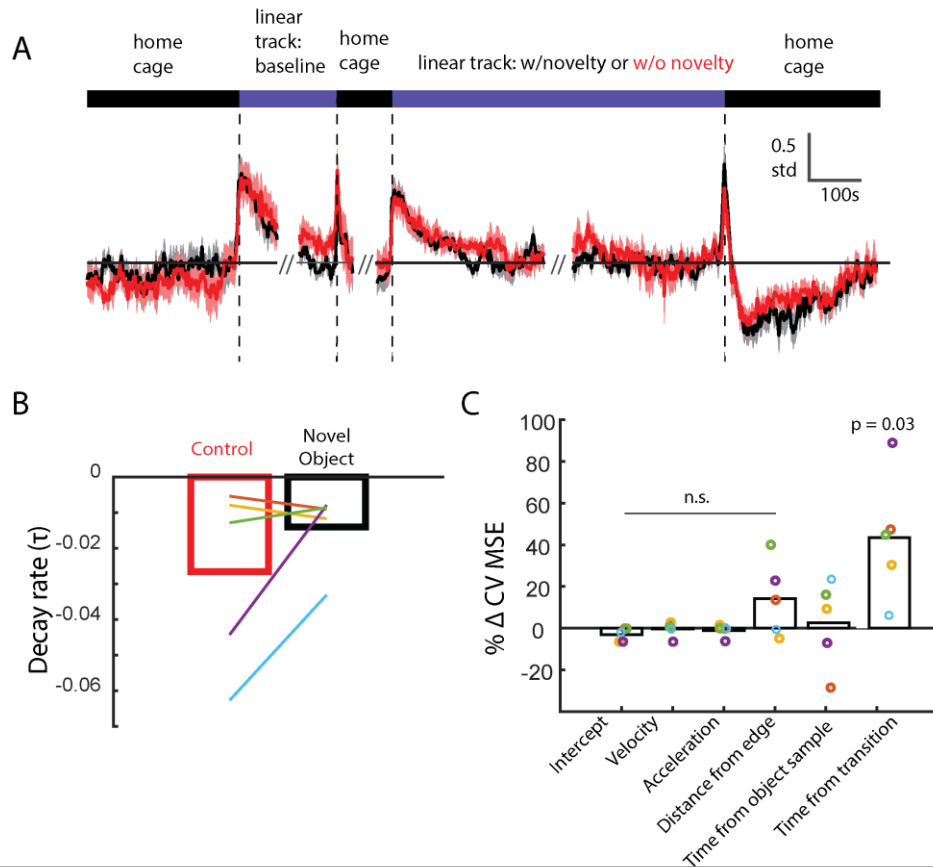


Figure 4. Novel objects do not affect NE dynamics after transfer to a familiar linear track. A) Mean Signal_{NE} across experimental sessions when the track was baited with a novel object (black); control sessions were run without new objects (red). B) Estimated τ describing Signal_{NE} decay after moving to the linear track did not change in the presence of a novel object ($t(4) = 1.47, p = 0.22$). C) Change in CVMSE due to removal of various potential behavioral variables. Only removal of the terms related to time from linear track transfer significantly decreased model performance ($t(5) = 3.22, p = 0.03$).

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1126 Figure 5

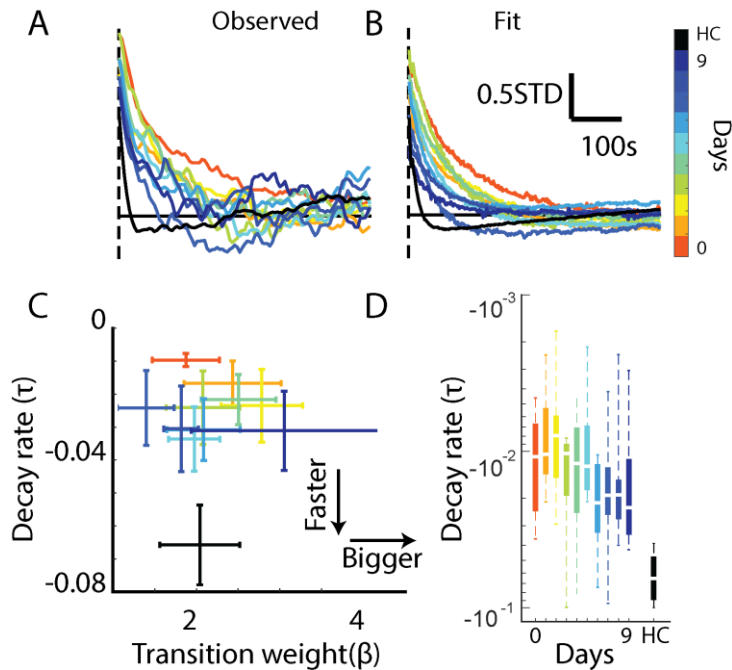
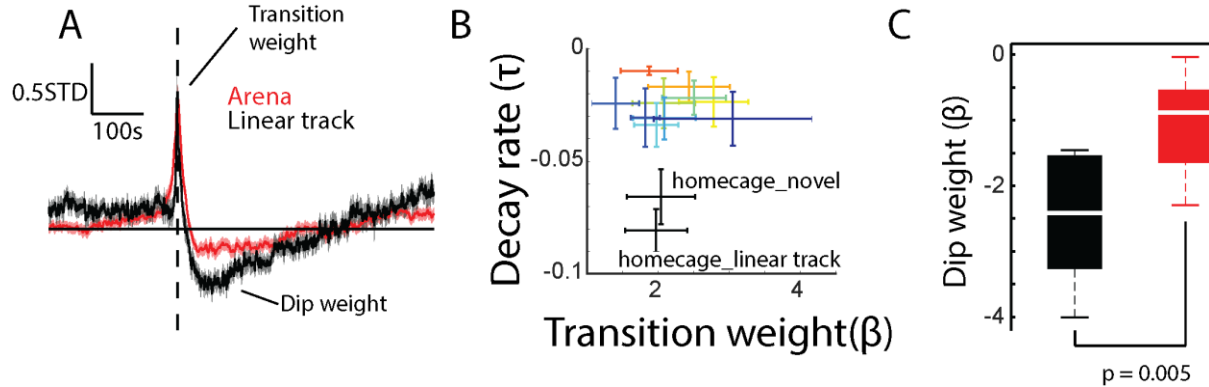


Figure 5. Experience accelerates Signal_{NE} decay after context transition. A) Mean Signal_{NE} plotted as a function of time from context transition (dashed line) and color coded by number of days of experience. Black trace shows Signal_{NE} recorded after transitioning back to the home cage (HC). B) Estimated Signal_{NE} derived from the saturated model. C) Parameter estimates for the magnitude (β) and decay rate (τ) of Signal_{NE} after context transition color-coded by days of experience. D) Decay rate (τ) after transfer to the arena hastens over days of exposure (mixed-effect linear model; $t(73) = 2.31, p = 0.02$) and is most rapid during transfer to the HC (*Day N vs HC, all $p \leq 0.01$*).

1128 Figure 6



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Figure 6. Signal_{NE} is depressed relative to baseline after periods of sustained elevation. A) Mean Signal_{NE} recorded after moving mice back to the home cage from the arena (red) or the linear track (black). B) Same data as Figure 5C with the addition of parameter estimates for the behavior of Signal_{NE} after transition to home cage from the linear track. C) The decrease in Signal_{NE} was significantly larger after transitioning mice to the home cage from the linear track as compared to from the novel arenas ($t(5) = 3.74, p = 0.005$)

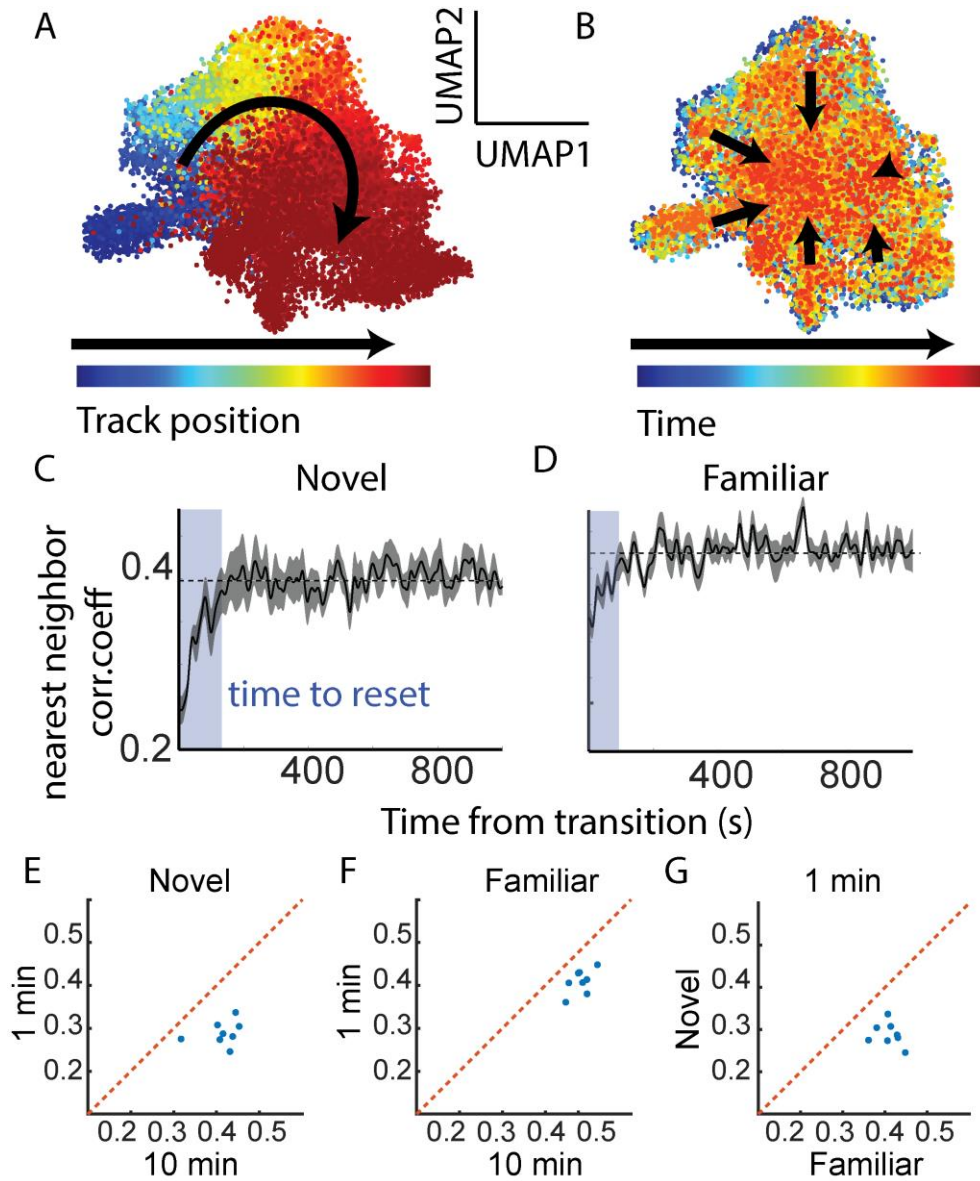
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1133 Figure 7

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Figure 7. CA1 spatial code takes minutes to stabilize after context transition in novel and familiar spaces. A) Example UMAP embedding of population firing rate vectors (100-ms), color-coded by where the mouse was physically located on a linear track when the data was recorded. B) Same embedding color coded by time from context transfer. C) Representational similarity (Pearson R) of the observed population firing rate vector at each moment in a novel environment relative to the mean of the next 3 most similar vectors recorded in the same location. D) Same as Panel C recorded in a familiar environment. E) In a novel environment, the patterns recorded in the first minute were less correlated than those observed 10 minutes into the session ($t(7) = 8.05, p = 0.00009$) F) Same as Panel E recorded in a familiar environment ($t(7) = 8.20, p = 0.00008$). G) Initial representations were more correlated to their nearest neighbors in a familiar environment as compared to those recorded in a novel environment ($t(7) = 7.58, p = 0.0001$).

1139 Figure 8

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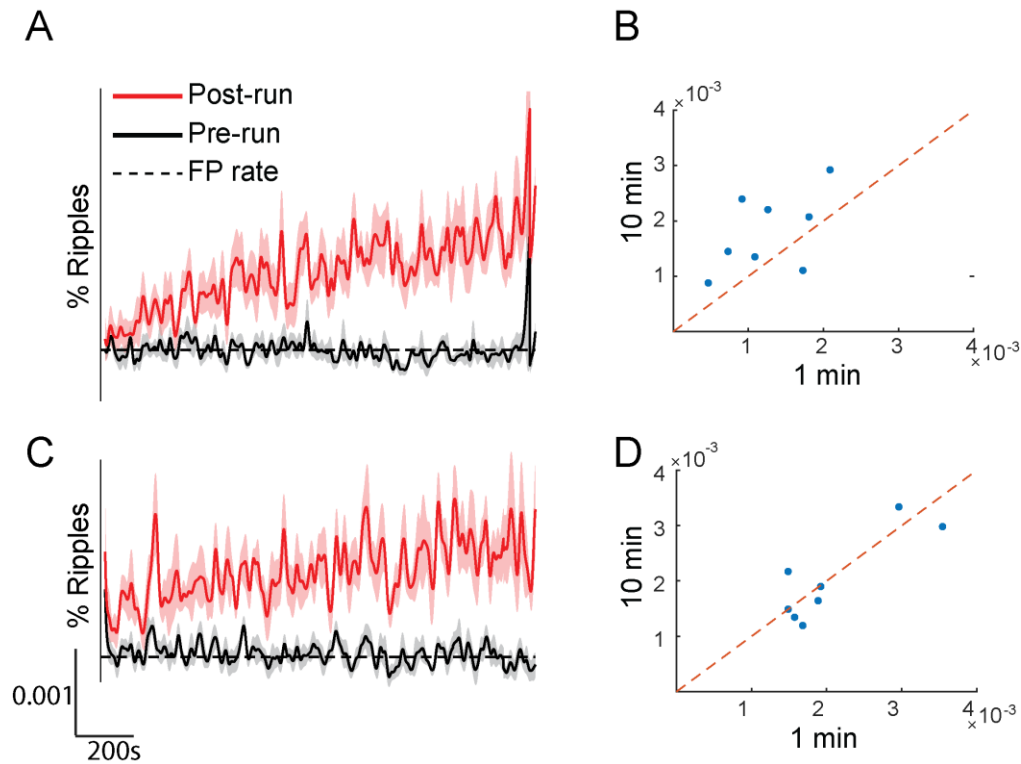
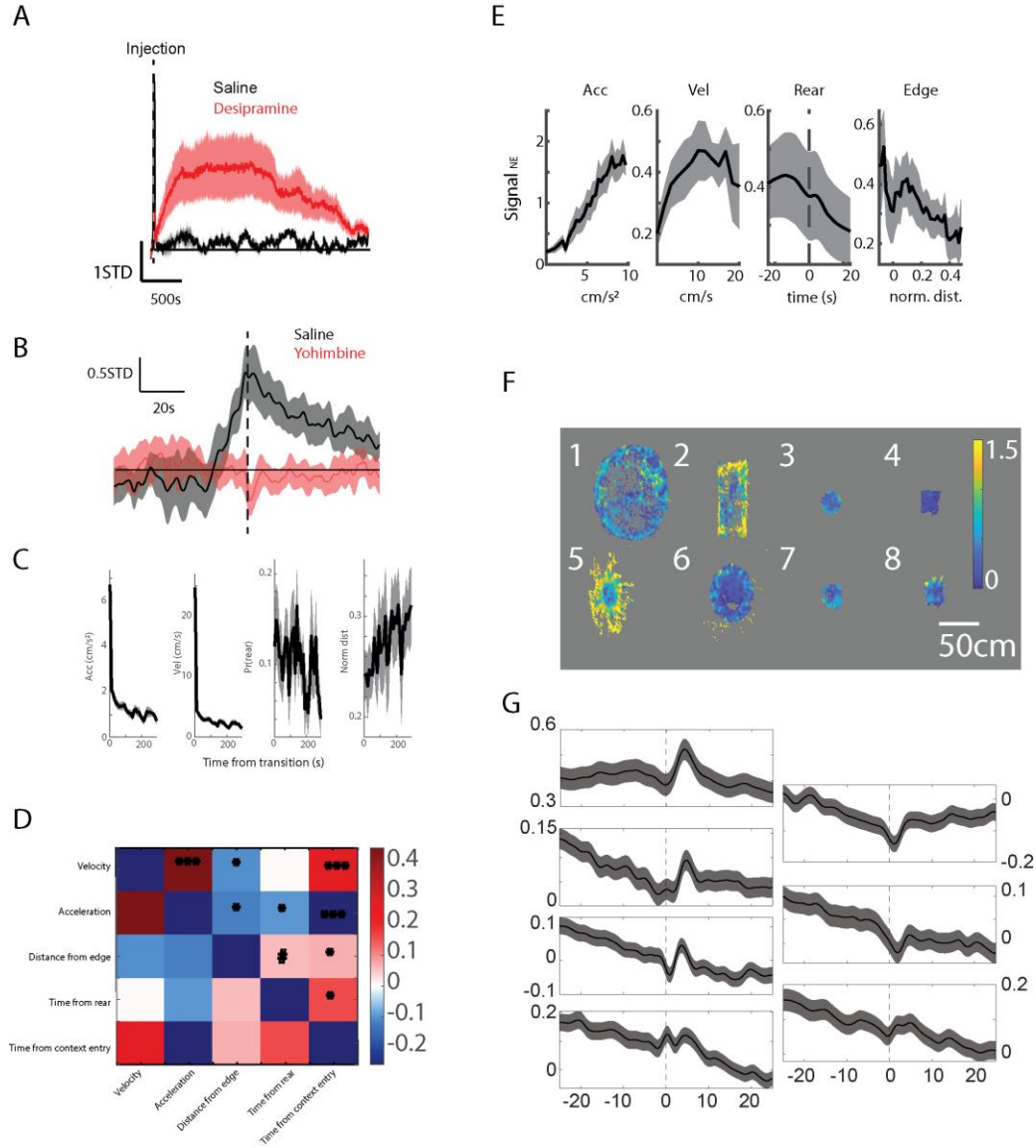


Figure 8. Moments immediately after transition are not preferentially replayed. A) Percentage of ripples recorded before (black) and after (red) experiencing a novel environment that showed significant reactivation of each moment after transition. Dashed line shows false positive (FP) rate. B) Moments recorded 10-11 minutes after novel context transition were more likely to be reactivated than those recorded 0-1 minutes after transition ($t(7) = 2.46$, $p = 0.04$). C) Same as Panel C showing reactivation rates as a function of time after transition to a familiar environment. D) There is no difference in reactivation rate for early vs late moment in a familiar environment ($t(7) = 0.40$, $p = 0.70$).

1141 **Supplemental Figures**

1142



1143 **Figure S1.** Validation of GRAB_{NE} sensor and behavioral correlates of Signal_{NE}. A) Signal_{NE}

1144 increases after injection of desipramine. B) The normal increase in Signal_{NE} after context

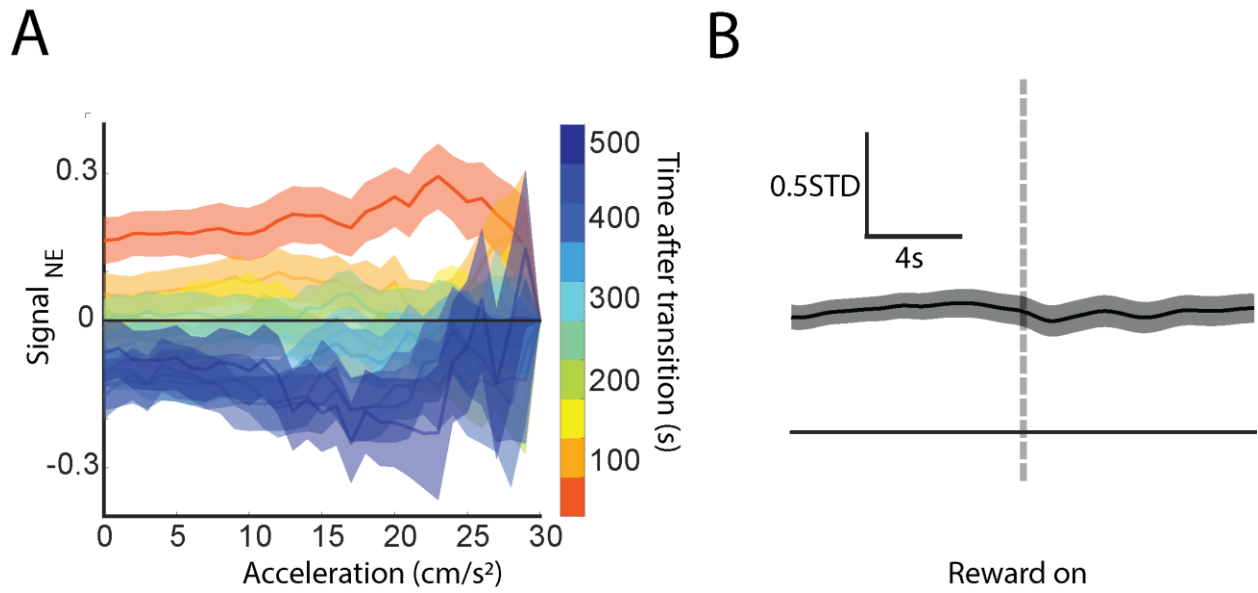
1145 transition is eliminated after injection with yohimbine. C) Fluctuations in behavior as a function

1146 of time after context transition. D) Time series correlations (Pearson R) in independent

1147 behavioral variables used to predict Signal_{NE}. E) Signal_{NE} plotted as a function of different

1148 behavioral variables. F) Signal_{NE} plotted as a function of mouse position in each of the novel
1149 arenas. G) Signal_{NE} plotted for each mouse as a function of time around rearing (data for one
1150 subject was not available).

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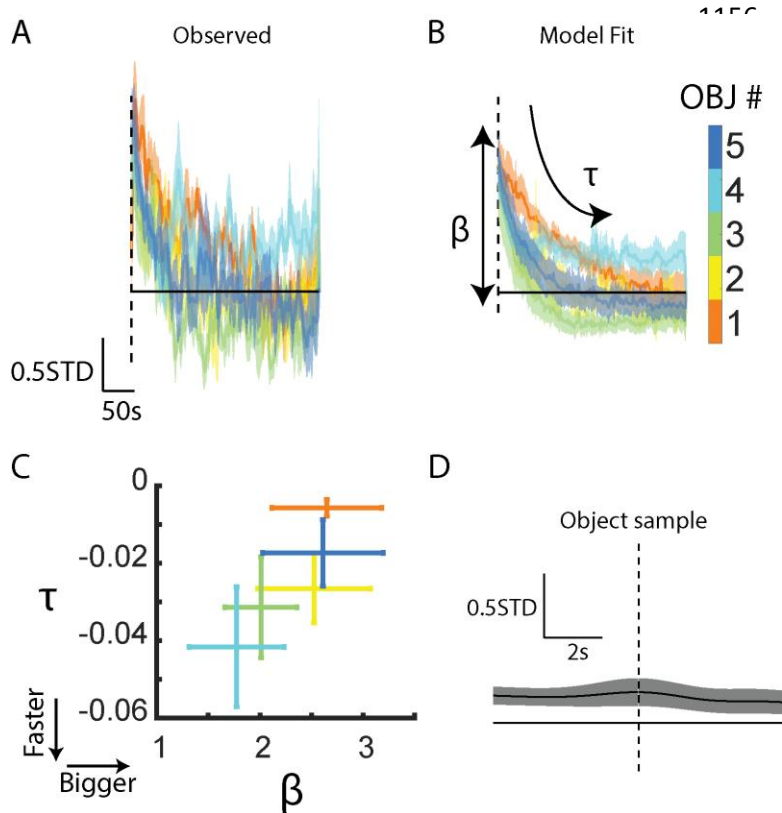


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1153 **Figure S2.** No change in Signal_{NE} due to acceleration nor reward delivery on a linear track. A)

1154 Mean Signal_{NE} plotted as a function of acceleration conditioned on time after transition. B) No

1155 change in Signal_{NE} after reward delivery (dashed line).



1165

1166 **Figure S3.** Signal_{NE} is related to object introduction, not sampling. A) Observed mean Signal_{NE}
1167 around each object's introduction. B) Estimated fits derived from the saturated model. C) Mean
1168 \pm SEM point estimates for the increase (β) and decay (τ) in Signal_{NE} around introduction of each
1169 object. D) Mean observed Signal_{NE} around each object sample.

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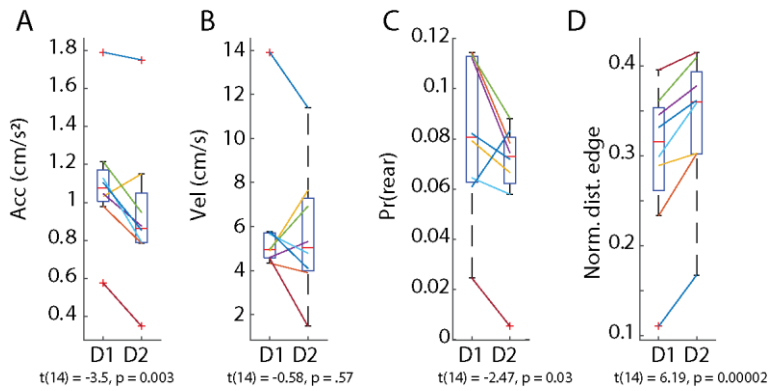
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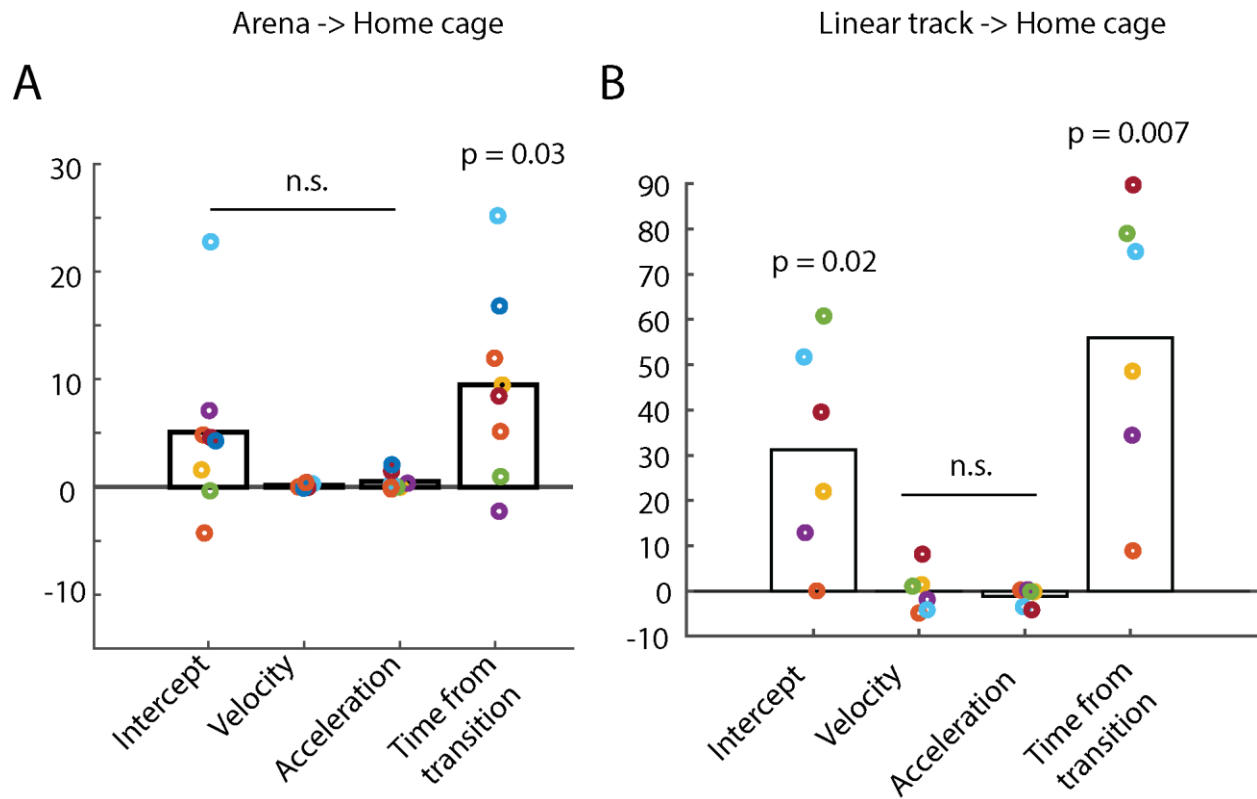
1178 **Figure S4.** Change in behavior across days. Change in A) acceleration, B) velocity, C)

1179 propensity to rear, and D) distance to the edge across day 1 (D1) and day 2 (2) in the novel arena.

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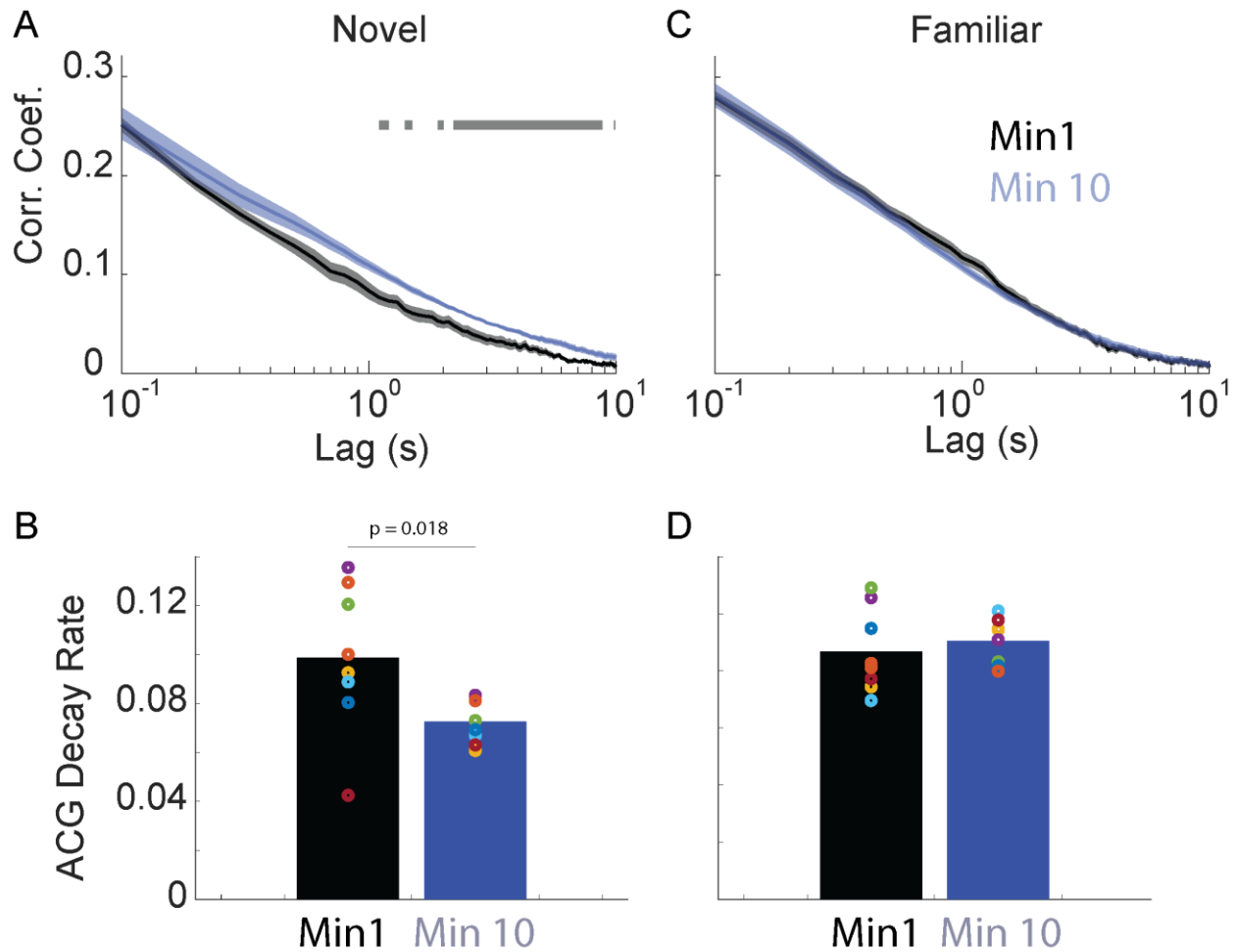
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1183 **Figure S5.** Time from context transfer explains $\text{Signal}_{\text{NE}}$ in the home cage. A) Change in
1184 CVMSE due to removal of various potential behavioral variables. Only removal of the terms
1185 related to time from home cage track transfer from the arena significantly decreased model
1186 performance, ($t(7) = 2.62, p = 0.03$) B) Same as Panel A with transitions to the home cage from
1187 the linear track ($t(5) = 4.44, p = 0.007$)

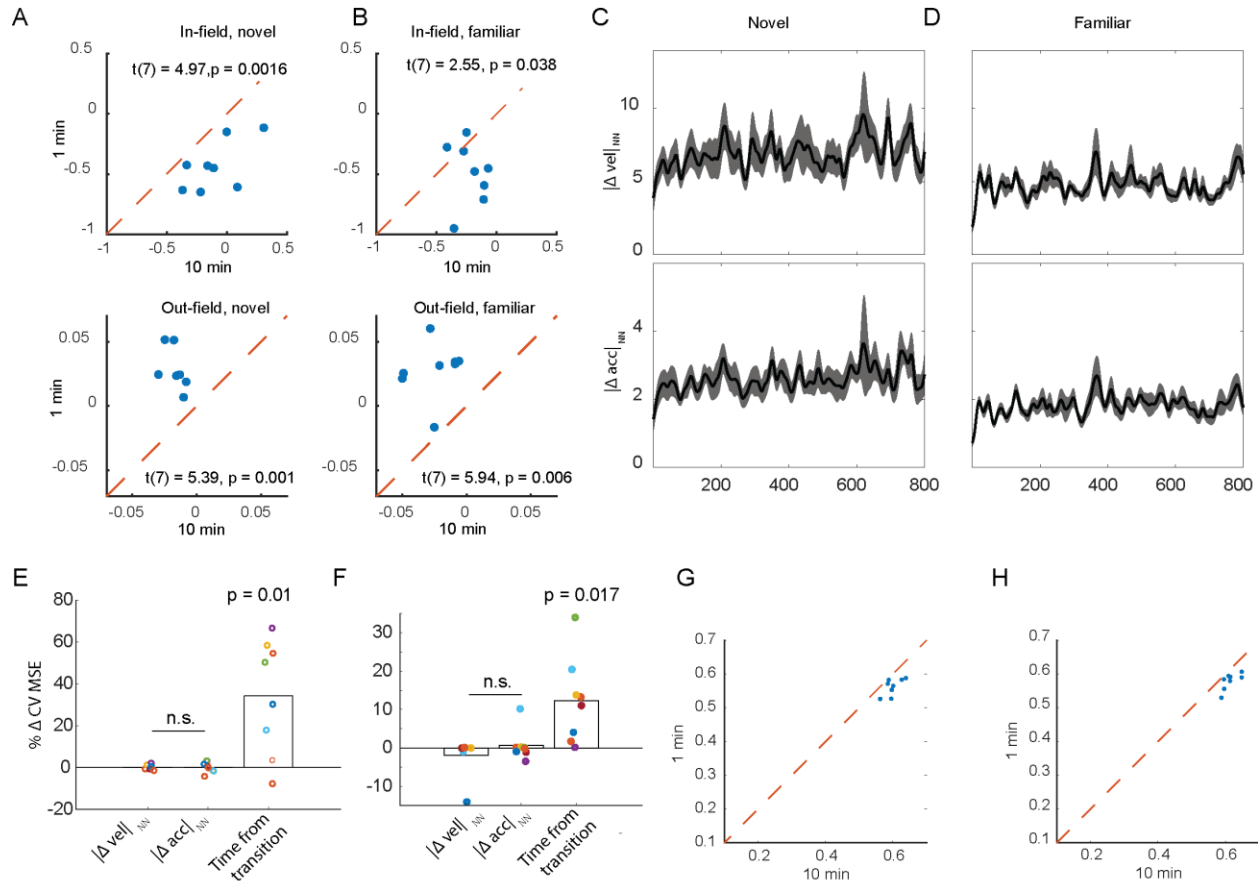
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1190 **Figure S6** CA1 activity decorrelates faster in the first minute after transfer to a novel, but not
1191 familiar, environment. A) Population vector correction plotted as a function of lag (note log
1192 scale) during Minute 1 (black) or Minute 10 (blue) after transfer to a novel environment. Bar =
1193 $p < 0.01$. B) The decay rate of the autocorrelation was significantly steeper in the first minute of
1194 exposure ($t(7) = 3.07, p = 0.018$). C) Same as Panel A with data recorded in a familiar
1195 environment. D) No difference in ACG decay rates during the minute 1 vs minute 10 of exposure
1196 to a familiar environment ($t(7) = 0.50, p = 0.63$).

1197



1198 **Figure S7.** Variations in velocity and acceleration do not explain time-dependent changes in
 1199 nearest-neighbor (NN) representational similarity. A) Deviations in z-scored firing rates from the
 1200 mean place field activity in a novel environment. *Top*, firing rates within a place field increased
 1201 over time. *Bottom*, out-of-field firing decreased over time. B) Same as Panel A with data
 1202 recorded in familiar environments. C) At each moment after transitioning to a novel
 1203 environment, we identified another 100-ms time bin with the most similar neural representational
 1204 and calculated the absolute difference in velocity ($|\Delta vel|_{NN}$) and acceleration ($|\Delta acc|_{NN}$) recorded
 1205 at these times. As compared to Figure 7C, neither $|\Delta vel|_{NN}$ nor $|\Delta acc|_{NN}$ co-varies with time as did
 1206 the measure of representational uniqueness. D) Same as Panel C recorded after a transition to a
 1207 familiar environment. E) Only removing time from transition decreased ability to predict NN
 1208 representational similarity, $t(7) = 3.52, p = 0.01$. F) Same as panel E, recorded in a familiar

1209 environment, $t(7) = 3.12$, $p = 0.017$. G) In a novel environment, the patterns recorded in the first
1210 minute were less correlated to others captured in the same recording session than those observed
1211 10 minutes into the recording ($t(7) = 5.23$, $p = 0.001$). H) Same as Panel G recorded in a familiar
1212 environment ($t(7) = 5.60$, $p = 0.0008$).