The contributions of entorhinal cortex and hippocampus to error driven learning

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Abstract

Computational models proposed that the medial temporal lobe (MTL) contributes importantly to error-driven learning, though little direct in-vivo evidence for this hypothesis exists. To test this, we recorded in the entorhinal cortex (EC) and hippocampus (HPC) as monkeys performed a task using an error-driven learning strategy, defined as better performance after error relative to correct trials. Error-detection signals were more prominent in the EC relative to the HPC. Early in learning hippocampal but not EC neurons signaled error-driven learning by increasing their population stimulus-selectivity following error relative to correct trials. This same pattern was not seen in another learning task where error-driven learning was not used. After learning, different populations of cells in both the EC and HPC signaled long-term memory with enhanced stimulus-selective responses. These results suggest prominent but differential contributions of EC and HPC to learning from errors and a particularly important role of the EC in error-detection.

Introduction

A large body of behavioral work supports the idea that feedback from errors is an important teaching signal to help supervise learning, adjust behavior and achieve learning goals[1-4]. Generally, errors are defined as the difference between the received and expected outcome after the execution of a particular behavior. Seminal work by Rabbitt and colleagues in the mid 1960's [5-8] first raised the importance of a system that detected errors to adjust performance. Evidence for neural signals that processed errors initially appeared in the early 1990s with the observation of negative electrical potential that occurred in the medial frontal region of the brain, approximately 50 to 100 ms after making an error, termed error-related negativity (ERN) [9,10]. Combining ERN measurement and functional magnetic resonance imaging (fMRI), a prominent error detection network has been described in humans[11,12]. Areas including anterior cingulate cortex (ACC), anterior insular (operculum), ventral lateral prefrontal cortex (PFC), dorsal lateral PFC and parietal lobe have been reported to contain signals sensitive to errors, with the ACC most consistently found to be involved in error detection. Using behavioral neurophysiology, various groups have also identified prominent error-detection signals in the ACC of non-human primates[11,13-21], consistent with human literature.

Recent work suggests that this error detection network may extend to structures within the medial temporal lobe (MTL). Parallel findings in humans, monkeys and rats suggest that structures of MTL not only participate in encoding both error and correct signals (termed outcome-selective cells) but that a subset of these outcome-selective cells also signal learning as well. Using an object-place associative learning task (OPT), Wirth et al. [22] reported that half of the neurons recorded in the monkey hippocampus differentiated between correct and error trials during the inter-trial interval period of the task. While about half of the outcome-selective hippocampal neurons responded preferentially to erroneous outcome (error-up cells) the other half responded preferentially to correct outcome (correct-up cells). Further analysis showed that while the correct-up cells also increased their stimulus-selective response after learning, the

error-up cells did not, suggesting that the correct-up but not the error-up cells also participate in the learning process. Another study reported prominent trial outcome signals in both the entorhinal cortex (EC) and hippocampus (HPC) in monkeys and humans performing the same associative learning task using local field potential (LFP) and blood-oxygen-level dependent (BOLD) fMRI approaches [23], respectively. In that study, however, the relationship between outcome-signals and learning was not examined. Similarly in rodents, Ahn and Lee [24] reported error-related activity in another medial temporal area, the perirhinal cortex, during the performance of an object-target association task. In contrast to the Wirth et al. [22] finding, this group showed that error-up outcome cells carried more information about the learned associations immediately after error trials than after correct trials.

Work by Lorincz and Buzsaki [25] and Ketz et al. [26] suggest a computational framework with which to understand these reports of error-detection and learning signals throughout the MTL. Their models outline an anatomically specific three-step process underlying error driven learning. The first step starts with error detection in the EC, which then induce synaptic modification in the HPC to correct for the errors as the second step. The resulting modified hippocampal synaptic output is the third step that is proposed to entrain long-term memory traces in the EC. The idea that a memory trace is first rapidly formed in HPC then transferred to EC for long term memory function is consistent with system consolidation theory [27–31]. The goal of the present study is to examine the role of the EC and hippocampus in error-driven learning and the early consolidation process based on the predictions of the models of Lorincz, Buszaki [25] and Ketz [26]. We examined the behavioral and neurophysiological responses in these areas as monkeys performed an associative learning task during which they used an error-driven learning strategy (i.e., they performed significantly better after an error trial relative to after a correct trial). During the task, we observed both error detection signals as well as associative learning signals in both the HPC and EC that are consistent with some, but not all of the predictions from Lorincz, Buszaki and Ketz [25][26]. By contrast, when we examined neural activity in HPC using a different associative learning task, during which animals solely employed a correct-based learning strategy (i.e., animals perform significantly better after a correct trial than after an error trial), we did not find the same signature prominent error-based learning signals in HPC as when the error driven learning strategy had been employed during the initial task.

Results

Error-driven learning strategy was used in the Location-Scene task

To test whether and how MTL was involved in error-driven learning, we recorded HPC and EC in three and two of the monkeys, respectively while they performed a conditional motor associative learning task (location-scene associative learning task, or LST; Fig. 1A). In this task, each day, monkeys learned to associate a visual cue to a particular rewarded target location through trial-and-error (Fig. 1B; Supp. Fig, 3). Across 373 sessions, the five monkeys saw 1556 new scenes, of which they learned 1015. They

learned 3.1 ± 0.11 location-scene associations per session and needed 10.57 ± 0.55 trials to learn a new association to criteria.

To determine if animals used an error-driven learning strategy to perform the LST, we asked whether the monkeys performed better on the trials immediately following errors compared to the trials immediately following correct responses (Fig. 1C), excluding all trials the animals aborted or did not make a target selection [32]. Because there were almost always fewer error trials than correct trials in one session (99% of cases, see Supp. Figure 3 for some examples), and most of the errors occurred during the early acquisition stage of learning, we used the same number of correct trials as error trials from the beginning of the session to calculate the mean behavioral performance immediately after either correct or error trials. We termed this period of learning the 'memory acquisition stage' (Fig. 5). We included 282 behavioral datasets from the five monkeys where they learned at least one location-scene association and made at least 20 error trials in one session. Across all sessions, the averaged performance immediately after error trials was 76% ± 0.7%, which was significantly better than the performance seen after correct trials (69% ±0.7%, p < 0.0001, paired t-test; Fig. 1C), suggesting that monkeys used an error-driven learning strategy to perform this task.

Error detection signals in EC and HPC

Since the animals used an error-driven learning strategy to perform LST, we asked if we could see evidence for an error detection signal in the neurophysiological responses of EC or hippocampal neurons in the same 5 monkeys used in the behavioral analysis. We previously showed that many hippocampal cells signaled trial outcome during the inter-trial interval of an object-place associative learning task [22] by either increasing their firing rate on correct trials relative to error trials (correct up cells) or by increasing their firing on error trials relative to correct trials (error up cells; Method 4C). To examine the correct up and error up signals in the HPC and EC during the performance of the LST, we analyzed 135 hippocampal neurons and 143 entorhinal neurons (Recording sites see Supp. Figure 1). Similar to our previous publication [22] we defined outcome selective cells based on their mean firing rate during the first and second 1000 ms of the inter-trial interval (ITI) separately. We determined whether the neurons responded significantly more to correct or error outcome during either of these periods by performing t-test. To correct for multiple comparisons the statistical significance threshold was set to p < 0.025 (see Methods 4C). In EC, we found 45% (67/143, Table 1) of recorded cells were outcome selective, i.e. the neurons responded significantly differently to correct versus error outcome during the ITI. Of these, 67% (45/67 cells) signaled errors by responding to error outcome at a significantly higher rate than correct outcome, while the remaining 33% (22/67 cells) signaled correct trials (responding to correct outcome at a significantly higher rate than error outcome). By contrast, in the HPC, only 21% (29/143, Table 1) of the hippocampal cells were outcome selective with 72% (21/29 cells) signaling errors and the remaining 28% (8/29 cells) signaling correct trials. In both EC and HPC, the proportion of error up cells was higher than correct-up cells (F-test, p < 0.05 for both EC and HPC).

Table 1
recorded cell count and their categorization in EC and HPC

	Entorhinal cortex (EC)		Hippocampus (HPC)	
	Cell count	% total	Cell count	% total
Total	143		135	
Error up	45	31	21	16
Correct up	22	15	8	6
Outcome (correct + error up)	67	45	29	21

The averaged time courses of error and correct detecting cells in the EC and HPC are shown in Fig. 1(D-G). To quantify the strength of error-up and correct-up cells to differentiate correct and error outcome, we used receiver-operating characteristic (ROC) analysis to estimate the information carried by each population in both the EC and HPC. The averaged time courses and area under ROC curve (AU-ROC) of all error-up (sup. Figure 4A) and correct-up cells (sup. Figure 4B) in EC showed that the outcome selective signals in error-up cells sustained over the 2000 ms ITI, while the AU ROC-curves of the correct-up cells decreased after 1500 ms. In contrast, the separation in the hippocampal subtypes is relatively weak. The AU-ROC of error-up cells in HPC was significantly higher than zero (supp. Figure 4C $p < 0.05$), however, it was significantly smaller than in EC ($p < 0.001$). The AU-ROC of correct up cells in HPC was not significantly greater than zero (sup. Figure 4D, $p > 0.05$, ttest). The results indicate that outcome selective signals (including error detection signals) exist in both EC and HPC with a stronger overall representation in EC.

Error-driven learning signals in EC and HPC

Given the striking error-driven learning seen at the behavioral level, we next searched explicitly for error-driven learning signals in the neural activity of entorhinal and hippocampal cells. Given that behavior improves significantly more after error but not after correct trials during memory acquisition stage (as defined previously, details in Methods 4A & B, Fig. 1C, Fig. 5), we hypothesized that early in the learning process, cells in the EC or HPC might reflect this behavioral improvement with higher stimulus-selective visual responses during the scene or delay periods of the task immediately after error trials relative to correct trials. We analyzed a total of 114 entorhinal neurons from two monkeys and 168 hippocampal neurons from three monkeys recorded during the same 282 sessions used for the behavioral analysis (see Method 1 for rational for the cell counts used). We found that during memory acquisition stage, as defined for behavior when the same number of correct trials from the beginning of learning as error trials are taken into account, hippocampal neurons showed significantly higher visual selectivity following error trials relative to correct trials during the scene period ($p < 0.05$, Wilcoxon signed-rank test, Fig. 2A) but not in the delay period of the task ($p > 0.05$, Wilcoxon signed-rank test, Fig. 2B). In EC, the selectivity was not different following error trials relative to correct trials during either scene or delay periods ($p > 0.05$,

Wilcoxon signed-rank test, Fig. 2C & D). These results are consistent with predictions from computational models [25] that the error signals induce early plasticity only in HPC.

To test the specificity of this early hippocampal error-driven learning signal during the LST, we examined the behavior and neurophysiological responses in the HPC as two monkeys performed another associative learning task, the Object-Place Task (OPT; Fig. 3A & B; EC recordings were not done). This task has been described in detail before [22]. Briefly, monkeys learned to associate an object-place combination to one of two possible bar-release responses (early vs. late) to obtain rewards (Method 3B). The OPT was significantly more difficult than the LST task with animals learning significantly fewer object-place combinations per OPT session (1.99 ± 0.1) relative to the LST (3.1 ± 0.11, p < 0.001, t-test). Also consistent with this idea, animals took significantly more trials on average to learn each new associations in the OPT (16.08 ± 1.34 trials) than for the LST (10.57 ± 0.55 trials, $p < 10^{-10}$, t-test).

We analyzed 86 behavioral datasets from two monkeys in which they made at least 20 error trials within each session and learned at least one object-place association (same criteria as for LST). Using the same trial sorting strategy as we used for the LST, we calculated the mean performance of trials immediately after error trials and after the same number of correct trials from the beginning of the learning session during memory acquisition stage. The averaged performance immediately after correct trials across all sessions was 70%±1.7%, which was significantly better than that after error trials (61%±1%, p < 0.001, paired t-test, Fig. 3C). These findings suggested that unlike the LST, these animals used a correct-trial based strategy to learn the OPT. When we examined the selectivity of hippocampal cells after either correct or error trials, we found no increase in stimulus selectivity after neither of them (Wilcoxon-test, p > 0.05 for both object-location scene and delay period; Fig. 3D-E). This suggests that the hippocampal shift in selectivity seen in the LST was specific to a task where an error-driven, but not a correct-base learning strategy was used. Note EC cells were not recorded during the OPT task.

Long-term associative learning signals in EC and HPC

A third prediction of Lorincz and Buzsaki's [25] error-driven learning model indicates that the new learning signal generated by the HPC induced by entorhinal error inputs will train long-term memory traces in the EC. To test this hypothesis, we asked if there were long-term memory signals seen in either the EC or HPC after learning occurred towards the end of the sessions [22]. We previously reported that during the performance of the OPT (in which animals used a correct-trial based learning strategy), correct-up cells signaled long-term memory for the learned object-place combinations by increasing their stimulus selective visual response after learning relative to before learning, presumably signaling a more precise memory signal for the learned associations [22]. Based on these findings we examined correct-up, error-up and non-outcome selective cell populations in the EC and HPC during the LST for similar long-term memory signals. In HPC, neither the error-up, correct-up nor the non-outcome selective cells changed their selectivity index with learning (paired t-test, p > 0.05, Fig. 4C & D, Supp. Figure 2C & D). However, in the EC, we found that during both the scene and delay periods of the task, error-up cells increased their stimulus-selective response after learning relative to before learning (paired t-test, delay: p < 0.005, Fig. 4A & scene:

p < 0.05, Supp. Figure 2A). By contrast, neither the entorhinal correct-up cells (paired t-test, p > 0.05, Fig. 4A & Supp. Figure 2A) nor the entorhinal non-outcome selective cells changed their selectivity indexes (paired t-test, p > 0.05, Fig. 4B and Supp. Figure 2B).

We also previously reported that cells in the HPC signaled long-term memory for learned location-scene associations by changing their stimulus-selective activity correlated with learning the LST (changing cells, [33]). Here we show that the same pattern of changing cells was seen in 17% of the newly recorded hippocampal cells used for this study (23/135 cells; Method 4D, Supp. Figure 3A & B). This proportion is similar to the 18.5% of hippocampal changing cells previously reported in Wirth et al. [33] (p > 0.05 z-score test). By contrast, only 8% (11/143, Sup. Figure 3C & D) of entorhinal neurons were changing cells, which was significantly lower than in HPC (p < 0.05, z-score test). Taken together, these results suggest that at the later stage of the learning sessions when performance is significantly above chance levels, neurons in both the EC and HPC provide long-term representations of learned associative information though represented in different neural populations. The long-term memory signals were represented in changing cells in HPC but in the error-up cells in EC.

Discussion

Here we showed that EC and HPC play prominent but distinct roles in error-driven learning. First, we showed that in a task based on error-driven learning strategy, error-detection signals (error-up cells) were observed in both the EC as well as the HPC. However, we found significantly more error-detection cells and an overall stronger (i.e., more differential) error−detection signals in the EC relative to the HPC. Second, we report early error-driven learning-related increases in stimulus-selective responses in the population of hippocampal cells but not the EC. This hippocampal shift in selectivity was specific to a task where animals used an error-driven learning strategy and was not seen in another associative learning task in which they used a correct-based learning strategy. Third, we show evidence for different types of long-term memory signals in the EC (enhanced selectivity in the error-up cells) and HPC (changing cells) after learning. We discuss each of these findings with respect to the time course of behavioral learning (Fig. 5A) and predictions from the computational models of error-driven learning in the MTL[25,34].

Error Detection in EC-HPC and its Relation with other Brain Areas

Perhaps the most surprising finding reported here is the prominent error-detection signals in EC (45/143 cells, 30% of recorded neurons in EC, Table 1), with a smaller proportion of EC neurons signaling correct outcome (correct-up cells, 22/143 cells, 15%). These prominent EC error-up signals support the first prediction of error-driven computational learning models and suggests that the EC is part of the error detection network identified in the human and non-human primate brains[11,14,35] with the best studied error-related activity described in ACC[14,36]. In monkeys, the early studies showing error-detection signals

did not use learning tasks but still identified error-detection signals in ACC. Using a saccade-countermanding task, a substantial proportion of neurons recorded in ACC showed selective and sustained activity after the animals made an erroneous saccade[18]. During a voluntary movement selection task, a subset of rostral cingulate motor area cells (part of ACC) fired spikes persistently over several hundred milliseconds for decreased reward relative to previous trials[37]. Recently Kawai and colleagues recorded from the ACC and lateral habenula in monkeys performing a reversal learning task, reporting that about half of the neurons in ACC encoded trial outcomes, and nearly 80% of lateral habenula neurons preferred negative relative to positive outcome[38]. In this study the animals needed to use the trial outcome history in order to know which saccade target was associated with higher reward probability in the current trial. Similarly, in our study the monkeys needed to estimate which saccade target was associated with a specific visual stimulus by learning the reward contingency through a trial-and-error procedure. The error-detection neurons in lateral habenula in Kawai's study shows increased responses with no reward trials and the same neurons decreased their responses with reward trials. In contrast, and similar to the EC pattern of activity in the present study, ACC neurons tended to fire preferentially to either positive or negative outcomes and did not decrease their firing rate during opposite outcome periods. The bidirectional interconnections between the ACC and EC[39−42] and the prominent and similar error outcome signals in the two brain regions suggest that these areas may be functionally related to each other, i.e. they either work together to monitor the error outcome information or one may provide the error signals to the other. Further studies involving simultaneous recording the ACC and EC will be required to determine the directionality and functional interconnectivity between these regions.

There is also detectable but decidedly smaller error signal in HPC relative to the EC (Sup. Figure 4, Fig. 5B vs. Figure 5C). Similar to the present study, Wirth et. al. also reported error detection signals in HPC while the monkeys performed the object-place associative learning task (OPT, Fig. 3, [22]). Previous studies also reported hippocampal error signals in humans and rodents. For example, intracranial human EEG recording studies reported hippocampal error signals in multiple tasks[43]. Deadwyler et al. [44] applied population analysis to hippocampal CA1 and CA3 recordings while rats performed a two-lever operant version of a spatial delayed-nonmatching-to-sample task. They found that errors contributed to a significant portion of the variance of the population neural activity in both hippocampal CA-fields. In addition to the previous studies, the present study shows not only the error signals in HPC but also provides a direct comparison to EC, and suggests that EC might play the more prominent role than HPC in error-detection during error-driven learning.

Beyond the EC and HPC, other studies suggest the involvement of neuromodulatory systems in error detection. For example, serotonin has long been suggested to play the major role in responding to unwanted outcome and provoke inhibitory responses[45]. Previous studies have shown that serotonergic neurons in dorsal ralphe nucleus (DRN) signal either the positive or negative reward value[46,47]. The serotonergic cells in these studies resemble the EC-HPC outcome selective neurons in that they encode reward value with a stable response amplitude. This contrasts from the well-studied, reward-predicting dopaminergic (DA) neurons of the ventral tegmental are (VTA) that respond maximally to unpredicted

reward with a gradually diminishing response as the reward contingency becomes more predictable or learned[48,49]. Other studies have shown that acute depletion of serotonin impairs reversal learning, which is mainly based on negative feedback information[50]. In addition, DRN sends extensive projections to both EC and HPC[51], and evidence showed that the serotonergic inputs to the MTL highly influence learning performances. All 18 types of serotonin receptors are expressed in HPC, and pharmacological manipulation of different types of receptors highly influences the learning behavior in different manner[52,53]. These findings suggest that the error-related or reward value related information originating from the DRN may influence the error signals observed in the EC and HPC.

Assessing the effect of different learning strategies on neural activity

One key realization we made during the course of our analysis is that the monkeys used in our studies were not using the same learning strategy across the two different associative learning tasks we have used in the lab[22,33,54,55]. First, we found clear evidence that in the LST animals used an error-driven learning strategy defined as better behavioral performance after error trials relative to after correct trials. This led us to ask which learning strategy animals were using during an object-place associative learning task (OPT) in which we also had extensive hippocampal recordings. To our surprise, in this latter task, animals used a correct-driven learning strategy (i.e., better performance after correct relative to after error trials). We report that for the error-driven learning task (LST), we saw a clear population selectivity shift during the early stage of learning in HPC (Fig. 2A and Fig, 5D), that was not seen during OPT where animals used a correct-driven learning strategy (Fig. 3D and Fig. 5F). Differential neural signals associated with distinct behavioral strategies was also reported in a study in IT showing striking shifts in recognition-related signals with a subtle shift in task demand which required a different behavioral strategy[56]. Taken together our results suggest that the hippocampus plays differential roles in error-driven relative to correct- based learning. Future studies comparing the neural signals in the EC across both types of learning strategies will be of interest.

Timing of new associative learning in HPC and EC

One of the questions we were most interested in was comparing and contrasting the time course of error driven learning related signals between the HPC relative to the EC (Fig. 5). Consistent with predictions by Lorinz and Buzsaki [25] that the earliest selectivity shift would take place in HPC, we found enhanced stimulus selectivity following error relative to correct trials in the hippocampus before behavioral learning criterion was reached (Fig. 2A & Fig. 5D), but no such early learning signals in the EC (Fig. 2C and Fig. 5F). A finding by Li et. al.[57] also supported early learning signals in the rodent hippocampus, though parallel recordings in the EC were not done. In that study, Li et. al. monitored activity in the mouse hippocampus as they performed an odor-based associative learning task. Using a combination of optogenetic and electrophysiology, they showed that hippocampal pyramidal neurons acquired olfactory selectivity before the animals reached learning criteria and that selectivity continued to increase as animals continued to learn.

Two additional learning-related signals were seen in the present study, one in the HPC and the second in the EC. In HPC, nearly 20% of the recorded neurons increased or decreased their firing rates in parallel with learning (the changing cells, Fig. 1B & 5E supp. Figure 3A & B) as we have reported before [33]. By contrast, in EC, the error-up cells increased their stimulus selectivity after learning relative to before learning (Fig. 4A & 5F, sup. Figure 2A). Igarashi et. al.[58] also reported cells in both dorsal CA1 and lateral EC (LEC) acquired odor-selectivity as rats learned to associate an odor-cue to a specific location over 3 days of training, though in that study they reported the LEC selectivity shifts occurred slightly earlier than HPC. Task and species differences between the present study and the Igarashi's study may underlie the difference in timing of the associated learning signals reported by the two studies.

Figure 5 summarizes the time course of both the error detection signals and the various learning-related signals we observed during the LST. These findings suggest strong interplay between the EC and HPC during error-driven learning. Future studies doing simultaneous recordings in both MTL areas during associative learning will be essential to further specify the nature of these interactions.

Conclusion

Many computational models have hypothesized that the MTL is critical for error-driven learning[59-61], however, few behavioral physiology studies have been done to directly characterize predictions from these models. Here we identify an associative learning task in which animals used a clear error-driven learning strategy to characterize, compare and contrast the neural signals in the EC and HPC. While it is not surprising that EC and HPC are involved in associative learning, this study highlights the prominent error detection signals and the strong error related learning signals in the EC. Similarities of the EC error-detection signals to those described in the ACC[14,36] suggests a more prominent functional link between the EC and the classical error-detection network centering at the ACC than previously appreciated. But this is not the first time that the EC and ACC have been functionally linked. Many previous studies have studied the relationship between these two structures in long-term consolidation[62-64]. The findings we report here suggest that connections between the EC and ACC[39-42] are not only involved in the consolidation of long-term memories, but those connections may also be involved in the earliest stages of new long-term associative learning through their strong error detection signals. Following the time course of the interactions between these two areas from the very first trial of learning through long-term consolidation will be of great interest in future studies.

Methods

1. *Subjects*

All procedures and treatments were done in accordance with NIH guidelines and were approved by the NYU animal welfare committee. Six male and one female macaque monkeys were used in this study. The datasets acquired from the entorhinal cortex (EC) and hippocampus (HPC) of monkey A (rhesus, 11.5kg)

and B (bonnet, 7.8kg) were previously described in Hargreaves et al [23]. The data acquired in the HPC of monkey A (the same monkey as EC recording but in different sessions) and C (rhesus, 13kg) were from the same dataset as described in Wirth et. al. [33]. The dataset from Wirth et. al.[33] was only used for calculating the stimulus selectivity shift but not for calculating the outcome selective signals because the neural activity during inter trial intervals (ITI) were not recorded. The data acquired in the HPC of monkey M (rhesus, 14.2kg) and Er (bonnet, 6.3kg) performing the Object Place Task was the same dataset as in Wirth et al [22]. The hippocampal neurons recorded in monkey El (female rhesus, 6.0kg) and the behavior measurement during the location-scene task in monkey N (rhesus, 14kg) have not been previously published.

2. Recording and surgery

Most of the recording and surgical methods have been described previously [22,23,33]. Shortly, the animals were implanted with a headpost prior to their behavior training. After they were familiar with the tasks, a recording chamber was placed stereotaxically during the surgery after identifying the recording sites in each of the animals' brain using magnetic resonance imaging (acquired prior to the implantation surgery). The same images were used to identify the recording sites. The electrodes used include single tungsten electrodes (Epoxylite insulation, FHC, USA), glass-coated tungsten electrodes (Alpha-Omega, Israel), or tetrodes (platinum-tungsten, quartz insulated, Thomas Recording, Germany). The electrodes were inserted into the brain through a stainless guide-tube (23G) positioned in a grid-recording system (Crist Instrument, USA). The data were recorded with the Plexon Multichannel Acquisition Processpr Data Acquisition System, and the newly recorded data were offline-clustered with the Plexon Offline sorter software (Plexon Inc, Dallas, TX USA). The behavior was monitored and recorded with the Presentation (Neurobehavioralsystems, Peking, China) using customized software.

The recording sites of newly recorded hippocampal neurons in monkey A, B and El were plotted in Supp. Fig. 1A. The recording sites in HPC of monkey A and C performing LST (where activity during the inter-trial intervals were not recorded) are shown in Wirth et., al. [33]. The recording sites in HPC of monkey M and E performing OPT were shown in Wirth et. al. [22]. The recording sites of EC neurons were plotted in Supp. Fig. 1B.

3. Behaviorial Tasks

A. Location Scene Task (LST, Fig1A)

The LST has been used extensively in previous studies from our laboratory [23,33,54,55]. Briefly, each trial starts with a baseline period where animals were required to visually fixate on a central fixation spot (300~750ms; fig 1A). Then four targets superimposed on a novel, natural, colorful scene were presented (500~750ms). A delay period followed, during which the scene was removed, but the targets remained (700~1000ms). Subsequently, the fixation spot disappeared, cueing the animals to make a saccade to one of the four targets (200ms). Following the target selection the animals were rewarded with a few

drops of juice if the selected target was the correct one following a specific scene (1000ms) and ending with an ITI (1000ms). Fixation was required from the beginning of the baseline period until they were cued to make an eye-movement, and only one of the targets was rewarded for each visual scene. Each day 2-4 novel scenes were presented and animals learned to associate each new scene with a specific rewarded target location through trial and error. Randomly intermixed in with the new scenes were 2-4 highly familiar "reference" scenes presented to control for the eye-movement or reward-associated neural activity.

B. Object Place Task (OPT, Fig. 3A & B)

This task has been described in detail before [22]. Here, monkeys learned to associate an object-place combination to one of two possible bar-release responses (early vs. late) to obtain rewards. The animals initiated each trial by holding a bar and fixating a central fixation spot (Fig 3A). After a 500ms baseline period one of the two novel objects was shown for 500ms at one of the two locations (that changed daily) on the screen (4 combinations total). After a 700ms delay the animals could release a bar either during the 500ms presentation of an orange cue stimulus ("early" release) or continue holding until a green cue stimulus was presented (for 500ms) immediately afterwards to make a "late" release. If the response was correct, an auditory feedback tone was played, and after a random delay (30~518ms) 2-4 drops of juice were delivered as rewards. The animals were required to fixate from the beginning of the baseline period until the early or late bar release. The associations between the object-place combinations to the bar-release responses were counterbalanced as illustrated in Figure 3B.

4. *Data Analysis*

All data-analysis was done with custom written Matlab programs (Mathwork, Natick, MA). The outcome related criteria and selectivity index analysis were the same as previous publication [22] with several modifications to accommodate the present dataset. The same as the previous study, the baseline period was defined as the 300ms before the scene onset and the scene period was the 500ms duration from the onset of the scene. Slightly different from the previous study, the delay period was defined from scene offset to 600ms afterwards (instead of entire 700ms period). The outcome period started at the end of the subject's 30ms fixation of the chosen target (after making a saccade from the central fixation spot) and continued for the following 2000 ms. We used only 600ms instead of the full 700 ms delay period in the calculation of the scene selectivity index because another study [65] using a similar behavioral paradigm reported eye-movement direction related changes of cortical spiking activity during the 100 ms right before the eye movement so we did not include this time period in our analysis.

A. Estimating learning performance

We defined whether learning took place and the trial at which learning occurred using a dynamic logistic regression algorithm as described in Wirth et. al.[22,33] Learning sessions were defined as those in which animals made at least seven consecutive correct responses for at least one location-scene association. To estimate the learning curve we parameterized the performance of each trial into a binary sequence ("1"

for correct responses and "0" for incorrect responses). We then constructed the learning curve with this binary performance sequence together with 95% confidence bounds using a Bayesian state-space model [66]. The behavior learning trial was defined as the first trial that the lower 95% bound of the estimated learning curve crossed the random choice threshold and stayed above the threshold for the next three trials. The random choice threshold was defined according to how many targets were given in each session. For example, for 4-target LST the threshold was 0.25 and for 3-target LST the threshold was 0.33.

The animals performed at least 200 trials each day even when they reached learning criteria early in the session. For those sessions when the animals learned at least one location-scene association, 75% of error trials happened before the animals finished 57% of the trials in average. During the second half of the sessions the animals made significantly fewer mistakes than the first half ($p < 10^{-6}$).

B. Estimating learning strategy

We determined if animals used either an error-driven or a correct-driven learning strategy by asking whether they performed better immediately after error trials (post error trials) compared to immediately after correct trials (post correct trials). In a learning session containing a total of n trials (n was typically approximately 200.), there were p error trials and q correct trials (n=p+q). If the vector $P_{(1,p)}$ denoted all the error trials in this learning session and the vector $Q_{(1,q)}$ denoted all the correct trials, p was usually much smaller than q (99% of the cases, as described in Method 4A) . After parameterized the performance of each trial into binary series ("0" indicated error and "1" indicated correct trials) we compared the performance of $(P_{(1,p)} +1)^{th}$ trials (post error trials) and $(Q_{(1,p)} +1)^{th}$ trials (post correct trials) using a two-tail t-test. We discarded the last error trial if $P_{(p)}==n$. If the performance of post error trials was significantly higher than post correct trials, we defined this as an error-driven strategy to learn. If the performance of post correct trials was significantly higher than post error trials, this was defined as a correct-driven strategy.

For these calculations, we used only the performance of the first p (i.e., the total number of error trials) post correct trials and discarded the $(Q(p+1,q) +1)^{th}$ post correct trials to compare with that of the same number of post error trials ($(P_{(1,p)} +1)^{th}$ trials). As we mention in Method session 4A, this is because the animals performed at least 200 trials for each session, even though they have usually reached learning criteria (as defined in Method 4A) after about 100 trials. For about the second half of each session the animals were usually performing at ceiling with very few if any error trials. Thus, our calculations for defining either an error-driven or a correct-driven learning strategy was based exclusively on this early stage of learning using the same number of correct and error trials.

C. Outcome selective signals

The outcome selective signals (correct-up and error-up cells) were defined based on a previous publication [22] with two slight modifications (see below). As in the previous study, we analyzed spiking

activity from the end of the 30ms fixation of the target (after making a saccade from the central fixation spot) and for the following 2000ms of the inter trial interval (ITI). We calculated the mean firing rate during the first and second 1000ms of the ITI interval separately, normalized by subtracting the mean firing rate during the baseline period, and compared whether the neurons responded significantly more to correct or error outcome during either of these periods by performing t-test. To correct for multiple comparisons the statistical significance threshold was set to p<0.025. In our previous study [22] we separately reported neurons that increased their firing rates during either half of the ITIs compared to baseline after correct trials as correct-up cells and those that decreased their firing rates after error trials as error-down cells. However here, correct-up cells were defined as those cells whose normalized mean firing rate in either of the two halves of the ITIs after correct trials was significantly higher than after error trials. This differed from our previous study because there were no error-down cells in either EC or HPC while animals performed LST[22]. Also, slightly different from our previous work [22] was that error-up cells in this study were defined as the normalized mean firing rate during either half of the ITI after error trial had to be higher than correct trials, regardless where the difference came from. All error-up neurons in HPC increased their firing rates during either half of the ITIs compared to baseline after error trials. Of 43 error-up cells in EC, 37 neurons increased their firing rates after error responses compared to baseline, and six neurons decreased their firing rates after correct responses.

In our previous study we found that neither correct-up nor error-up cells changed the magnitude of their neural responses over the course of learning OPT [22]. Here, we also examined whether the amplitude of the neural responses of the outcome selective cells changed over the course of learning the LST. As in the previous study we used one-way ANOVA with time period (early, middle and late period of the session) as the main factor to examine the amplitude of the correct-up and error-up signals over time. We analyzed the first 1000ms and the second 1000ms after the saccade separately and found no difference in the amplitude of the correct-up and error-up signals over the course of learning.

D. Defining Changing Cells

In a previous publication using the same LST, we defined a population of changing cells in the HPC that signaled new associative learning by changing their stimulus-selective response correlated with learning [33]. We following the same criterion described in Wirth et. al. [33] to identify changing cells in the HPC and EC in this study. Briefly, for those neurons recorded during successful learning sessions (see Method 4A), we extracted the raw firing rates of the cells during the scene and delay period then correlated the trial-by-trial mean firing rates with the estimated learning curves in the same session. Those cells significantly correlated with the learning curves were defined as changing cells, and the significance level was set to p<0.025 to correct for multiple comparison (scene+delay). Consistent with the previous study, we found two categories of changing cells both in the HPC (Supp. Fig. 3A-B) and EC (Supp. Fig 3C-D). Sustained changing cells increased their firing rate correlated with the animal's behavioral learning curve while baseline sustained changing cells typically decreased their firing rate anti-correlated with behavioral learning.

E. Selectivity index

The selectivity index (*SI*) was calculated as in Wirth et al.[22]. We extracted the normalized mean firing rates of scene and delay periods by subtracting the mean baseline firing rate for each individual neuron. The following equation was subsequently used to calculate the selectivity index:

$$SI = \left(n - \sum_{i=1}^{n}\left(\frac{\lambda_i}{\lambda_{max}}\right)\right)/(n-1),$$

where *n* was the total number of location-scene combinations, was the mean firing rate of the neuron to the *i*th combination and was the maximum firing rate of all the combinations. The *SI* was calculated for each individual neurons before and after the monkeys learned the first scene-location association to the criteria. The performance of learning was estimated by the Baysian State-Space Model as used in our previous studies [22,33,54] (Method 4A). After the differential *SI* (defined as *SI after − SI before learning)* was obtained for each individual neuron, a simple t-test was applied to population differential *SI* for each group of neurons to estimate whether the neurons changed their *SI* depending on learning.

F. Area under receiver operating characteristic (ROC) curve

To quantify how well the outcome selective neurons can differentiate correct from error outcomes we calculated the time courses of area under receiver operating characteristic curve (area under ROC) of the mean firing rates during the inter-trial intervals. As the outcome selective signals, we analyzed spiking activity from the end of the 30ms fixation of the target (after making a saccade from the central fixation spot) and for the following 2000ms of the inter trial interval (ITI). For each outcome selective neuron we calculated the ROC curve using the mean firing rates of all correct and error trials every 300ms, with a sliding step of 50ms. The area under ROC curve is then calculated for each neuron over the 2000ms inter-trial-interval time. The averaged time courses of the area under ROC curve are then plotted separately for all the correct-up and error-up cells in EC or HPC to show the strength of differentiating correct from error outcomes.

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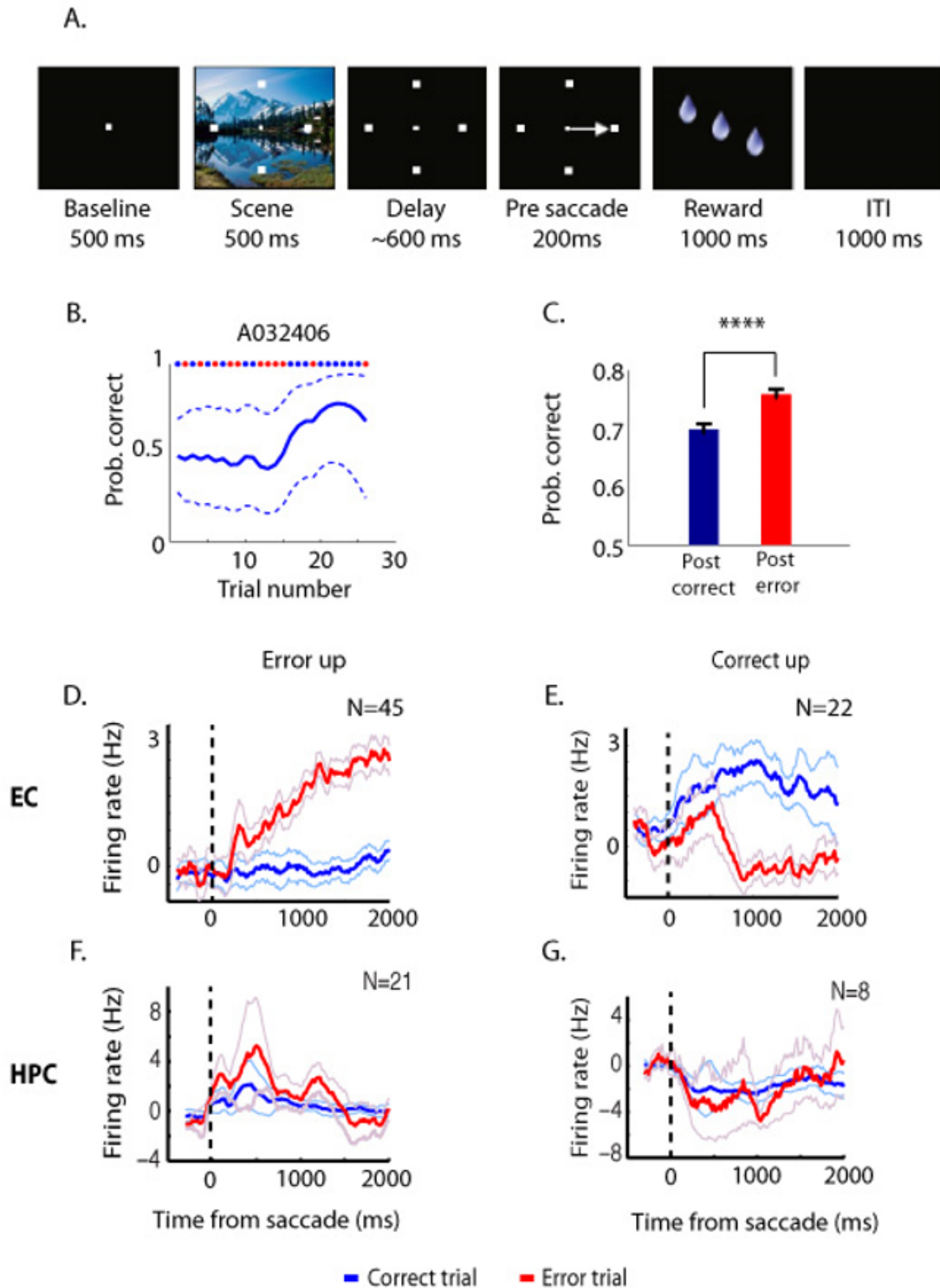
Figures

Figure 1

Location Scene Task (LST), performance and outcome selective signals. A) Schematic illustration of the LST (Method 3A). B) Estimated performance of one example session. The red dots on the top of the graph indicate error trials and the blue dots indicate correct trials. C) Averaged performance immediately

after error trials is significantly better than after correct trials during LST (averaging across 282 sessions, 5 monkeys). D,E) Averaged and normalized population time courses of EC error-up and correct-up cells. F,G) Averaged and normalized population time courses of hippocampal error-up and correct up cells. The lighter colored lines indicate the s.e.m. **** : p<0.0001
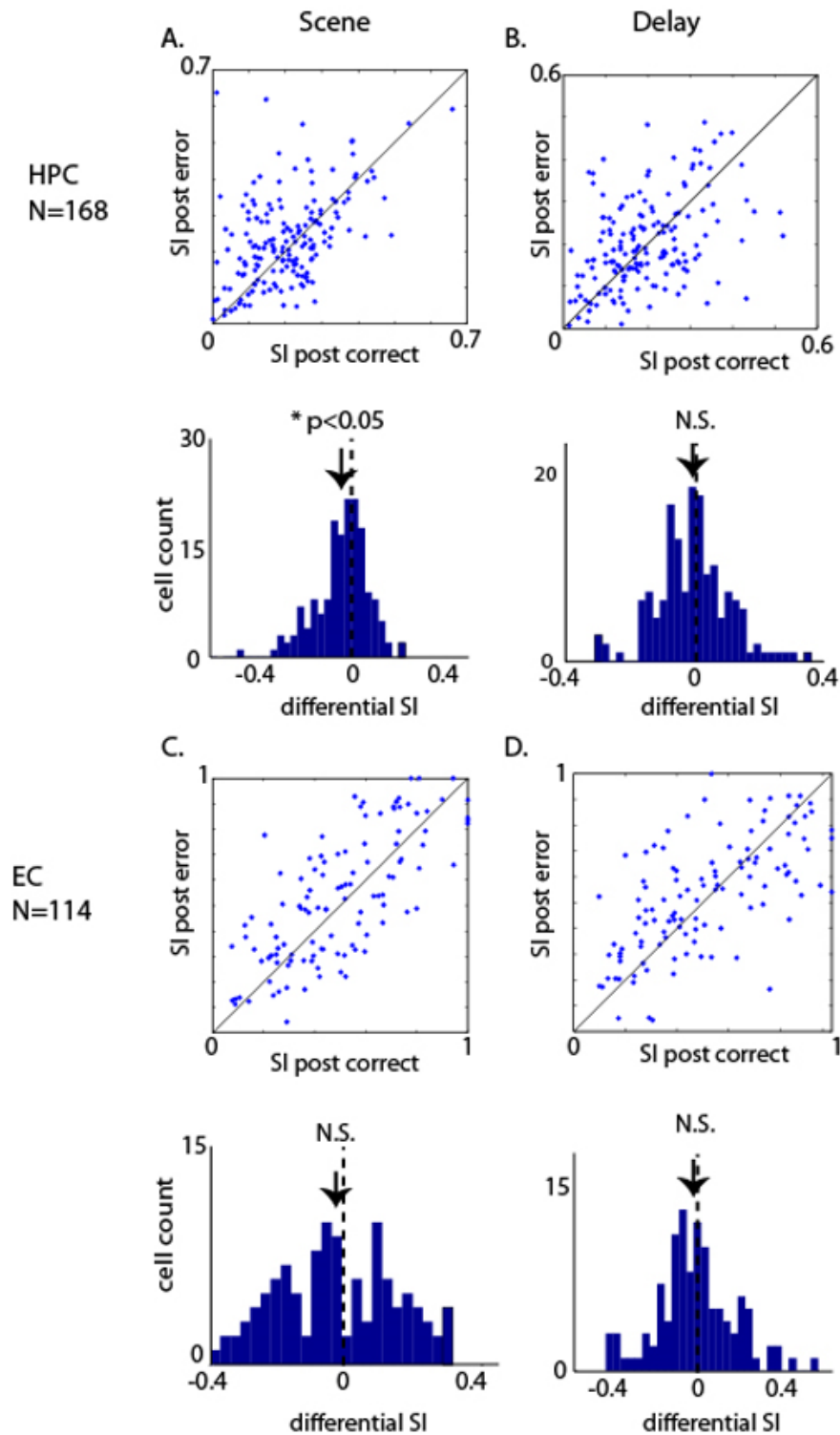

Figure 2

Illustration of selectivity index (SI) immediately after error trials versus after correct trials. (A, B) The SI during scene and delay period in HPC. (C, D) The SI during scene and delay period in EC. The distribution of differential selectivity index (after correct − after error) is also plotted below each scatter plot. During scene period in HPC the SI after error trials is significantly higher than after correct trials (p<0.05 signed-rank test).
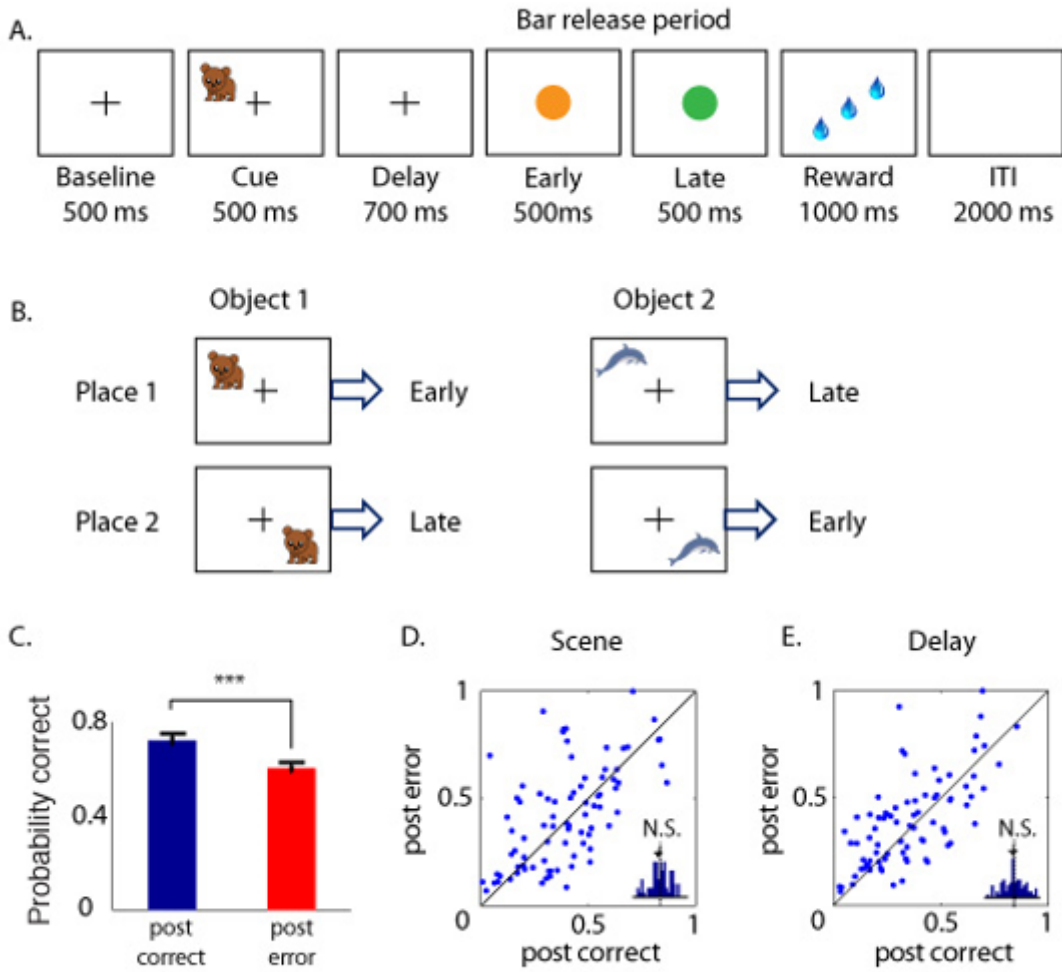

Figure 3

Object-Place Task (OPT), performance and selectivity index (SI). (A) Schematic illustration of the OPT. (B) Illustration of the object-place response contingencies used each day. (C) The averaged performance immediately after correct trials (70±1.7%) is significantly better than after error trials (61±1%) for the OPT (***: p<0.001, t-test). The SI immediately after error trials is not significantly different from after correct trials during either the scene (D) or delay (E) period of the task.
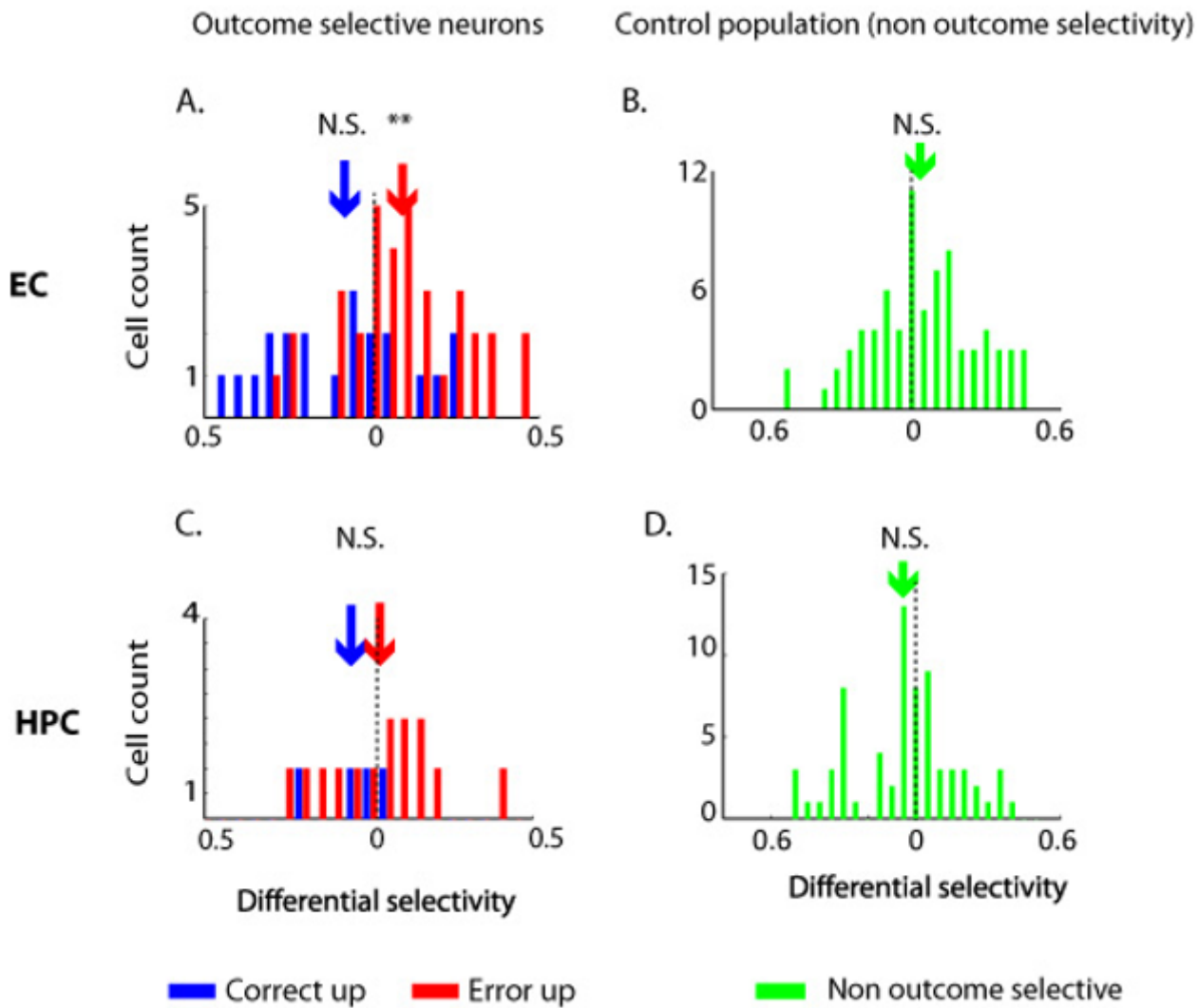
Figure 4

Error-up cells in EC increased their selectivity index (SI) while hippocampal cells did not. Distribution of differential selectivity indexes before and after learning for the correct-up (blue) and error-up cells (red) (A) and non-outcome selective cells (B) in EC during the delay period were plotted. The same information for cells in the HPC were shown in C and D. Arrows indicate the averaged differential selectivity of each population. (**) indicates the significant differences (p<0.005). The vertical dashed lines indicate no differential selectivity.
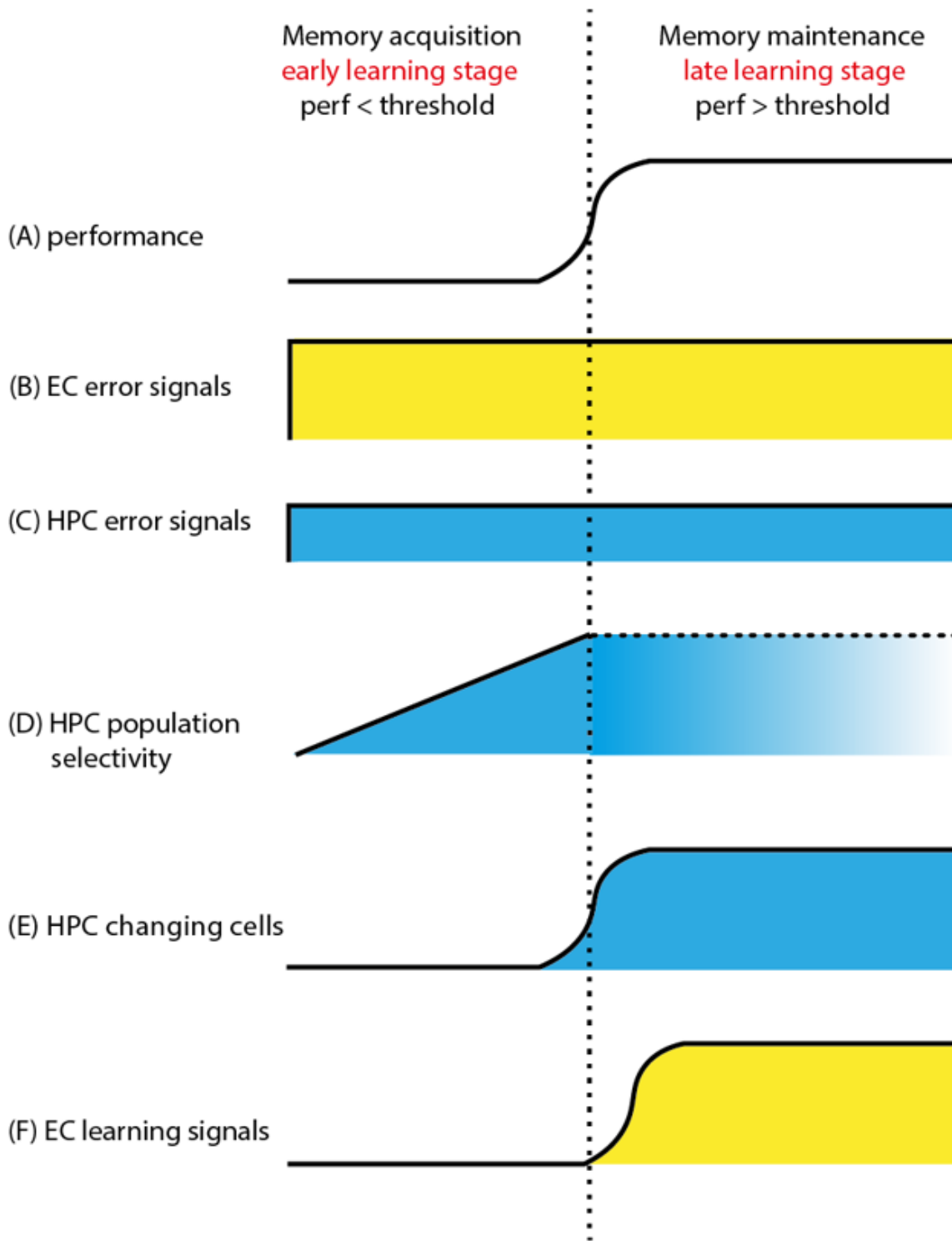
Figure 5

Schematic diagram and time course of error detection and learning signals in the HPC and EC Based on the performances of the animals (A), learning could be divided into early and late stages: During early stage of learning (left panel), also termed memory acquisition stage in the present study, the performance has not reached the learning criteria and the animals still made a lot of errors behaviorally. Error signals in EC (B) and HPC (C) are prominent and do not change their strength, stronger in EC and less in HPC. The

population selectivity in HPC increased after error trials readily in this early stage (D left) and cannot be determined during later stage of learning because there are not enough error trials (usually fewer than 10 errors). Late in learning (right panel), also termed memory maintenance stage, the performance surpass the threshold and the error signals in both EC and HPC maintained high (B,C). The learning signals in HPC develop into a sparser representation as changing cells (E) while in EC learning signals also emerged in the error-up cells, which are at the same time the error detection cells (F).

Supplementary Files

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