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Ankith Arun March 31, 2022

Preferential hippocampal reactivation of previous emotional events during offline consolidation

by

Ankith Arun

Dr. Joseph Manns
Adviser

Neuroscience and Behavioral Biology

Dr. Joseph Manns

Adviser

Dr. Gillian Hue

Committee Member

Dr. Patrick Cafferty

Committee Member

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Ankith Arun

Dr. Joseph Manns

Adviser

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a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

Preferential hippocampal reactivation of previous emotional events during offline consolidation

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Background: While it has been established that emotional memories are remembered better than non-emotional memories during encoding, it remains to be seen how neural events during consolidation can further increase this disparity in retention of emotional events. The current study aimed to investigate how offline reactivation (measured as ripple activity) during sleep and non-locomotion following encoding of emotional or neutral stimuli can impact subsequent performance during the retention phase.

Methods: 6 rats were trained in a hippocampus-dependent memory task that involved affective and non-affective stimuli. Following 80 trials during the learning stage, they immediately spent 30 minutes in an isolated sleep box for the consolidation period. Their retention of the task was tested the following day.

Results: There was an overall significantly higher hippocampal ripple rate for the affective condition as opposed to the nonaffective condition. This significant difference in ripple rate was not observed in the Basolateral complex of the amygdala (BLA).

Conclusion: We predicted that both the HIP and BLA played a notable role in the consolidation of memories post encoding. However, the preliminary date suggests that the HIP could be playing a differential role in consolidation compared to the BLA. It remains to be seen if ripple activity, and more generally offline reactivation, play a significant role in the consolidation of emotional memories as opposed to non-emotional memories. With an increased sample size and increased fine-tuning of various parameters, the current trends can be better validated.

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Table of Contents

Emotional memories tend to be more durable than non-emotional memories, and amygdala-hippocampal interactions are known to be key for the boost to emotional memories (McGaugh, 2004). Emotional arousal during an experience leads the basolateral complex of the amygdala (BLA) to modulate memory through its axonal projections into other regions, notably the hippocampus (HIP) (McGaugh, 2004). The widely accepted idea (McGaugh, 2004) is that amygdalar modulation of hippocampal activity at encoding influences a cascade of events related to synaptic plasticity in the HIP, a cascade that is often referred to as cellular consolidation (Mednick et al., 2011). Cellular consolidation unfolds over hours, up to a full day or more, and involves molecular and cellular processes that stabilize recently altered synapses (Mednick et al., 2011). An open question, the focus of the current project, is how a transient increase in emotional arousal at the moment of memory encoding can have a persistent yet specific effect on the slow cellular consolidation of that memory. This thesis looked at how, during sleep and quiet wakefulness (also known as periods of non-locomotion), offline reactivation of recently encoded memories could serve as one way to increase the consolidation of emotional memories compared to neutral memories.

Given our interests in understanding memory and emotion, we looked at activity in the ventral HIP along with activity in the BLA. The ventral HIP is widely known for its role in forming object-context associations (Barker & Warburton, 2020). Connectivity with the amygdala enables the emotional prioritization of those memories for objects with emotional salience. This is supported by findings that the amygdala receives direct hippocampal input from the ventral HIP (Maren and Fanselow, 1995).

Sleep has been well studied with respect to its role in memory and the consolidation of experiences (Rasch and Born, 2013). Of specific interest to us is offline reactivation of memories that occurs during sleep and periods of non-locomoting (Cutsuridis and Taxidis, 2013). A potential way to gain more insight into offline reactivation is through analysis of local field potentials (LFPS). LFPs reflect the activity of a large group of neurons at a specific time, which allows for examination of the information that modulates the activity of a brain region (Buzsáki et al., 2012). Spectral analyses of LFPs permits capturing oscillatory patterns that reflect rhythmic fluctuations in the voltage of a large group of neurons. An example is that theta-

modulated gamma oscillations in the HIP have been associated with good performance on the paradigm (Figure 1) the present study used (Ahlgrim & Manns, 2019; DiFazio et al., 2021; Tort et al., 2009).

LFP activity during offline reactivation is visible as sharp-wave ripples (Rasch and Born, 2013), due to the fast (150-200 Hz) oscillations that ride atop the large deflections in the LFPs. During these ripple events, hippocampal neuron firing rates increase and the replay of sequential firing of neuronal cell assemblies that encode recent spatial experiences occurs in a compressed form (Wilson and McNaughton, 1994; Buzsáki, 2015; Squire et al., 2015). This spontaneous reactivation of recently active neurons is thought to aid in the consolidation of the recent memory and consequently improves retention of the memory after the sleep consolidation period (van de Ven et al., 2016). Replaying memories through this method has been correlated to better retention in spatial memory tasks and overall improves memory consolidation (Fernández-Ruiz et al., 2019). Though not the only mechanism, reactivation of recently active neurons could serve as a means of bringing about a persistent yet specific effect on the slow cellular consolidation of a recent experience.

Emotional arousal during the encoding stage could bias reactivation of some cell assemblies over others. As a result, those emotional memories could have greater reactivation during the consolidation period and thus a stronger level of retention as opposed to neutral memories. This enhanced retention could further be strengthened since, as previously discussed, emotional memories correlate with increased synaptic plasticity via amygdalar modulation (McGaugh, 2004). Moreover, more recent studies have observed ripple events in the amygdala following emotional learning experiences (Girardeau et al., 2017). Thus, synaptic plasticity in the HIP could be strengthened by subsequent reactivation of recently altered synapses in either the amygdala or HIP through offline reactivation in the form of sharp-wave ripples. A growing gap could then be predicted in memory retention between emotional and non-emotional memory as time progresses due to the self-amplifying effects of reactivation.

To investigate how the consolidation period between encoding and the retention stage could create a disparity in the offline reactivation of emotional memories compared to neutral memories, we had rats perform an object-context association task that included a learning,

consolidation, and retention phase. Using sleep and non-locomoting as periods of consolidation, we observed ripple activity in both the BLA and HIP. We predicted that the time spent non-locomoting would vary across the conditions. We also predicted that previous Affective salience (used to induce activity in the BLA), during the learning as opposed to the control condition, which does not possess Affective salience, would elicit higher levels of ripple activity in both the HIP and amygdala. Within the overall Affective condition, we predicted that the number of ripples in the BLA and HIP would scale with the amount of affective salience in the previous condition. Lastly, we predicted to see coincident ripples in both the BLA and HIP for affective versus nonaffective conditions.

Method

All procedures involving rats were approved by the Institutional Animal Care and Use Committee at Emory University. I have received IACUC approval on protocol #201700501 in Dr. Manns' lab.

Subjects

Subjects used in this study were Long Evans female rats. We used only female rats because conspecific, same-sex urine has been known to elicit an affiliative social signal for females and an aggressive social signal for males (Kappel et al., 2017). Kappel and colleagues (2017) suggest this predicted difference is due in part to natural tendencies of many female rats living with one male rat. We also built off a previous study that used female rats (Song et al., 2021). Subjects were housed individually on a 12:12 light-dark cycle with testing conducted during the light period. Subjects had free access to water but restricted access to food to motivate them to eat food rewards; subjects never fell below 90% of their free-feeding weight.

Surgeries

Rats were anesthetized with 1-3% of isoflurane during stereotaxic surgery for probe implant surgeries involving placing an electrophysiological recording probe in the BLA

(coordinates relative to bregma in mm: -3.5AP, ±5.1ML, -8.55DV) and HIP (coordinates relative to bregma in mm: -5.0AP, ±2.8ML, -9.822DV). Buprenorphine was administered before (0.015 mg/kg) and after (0.02 mg/kg) surgery, along with the following day (0.02 mg/kg). A meloxicam pellet was provided before and after surgery and on the following two days.

Behavioral Procedures

Subjects were trained to associate a certain spatial context with an object that elicits Affective salience (i.e., scented with female urine, male urine, or fox urine) using a previously established hippocampal-dependent declarative memory task shown in Figure 1 (Komorowski et al., 2013). Following trials during the testing day, subjects spent 30 minutes in an empty, familiar sleep box separate from the testing apparatus. Periods of non-locomoting were counted as sleep when the completely stopped moving.

Data Analyses

Neural data was recorded through *in vivo* electrophysiological recordings. Accelerometer data obtained from electronics attached to the rats' heads were used to identify periods of non-locomotion. The data were analyzed in Matlab and SPSS. Matlab was used to identify the following for each subject: total time (m) motionless, BLA ripples during non-locomotion, BLA ripple rate (ripples/total time motionless), hippocampal ripples during non-locomotion, hippocampal ripple rate (ripples/total time motionless), and co-occurrence of ripples in the BLA and the HIP within 100 ms of each other. Means and standard errors of means (SEM) were calculated and plotted as shown in the Figures section. SPSS was used to conduct statistical analyses. A mixed effects GLM was used for analyses across the 4 conditions. This was used as opposed to a repeated measures ANOVA to account for missing data for one of the subjects. A Paired Samples t-test was used for analyses between the Nonaffective and Affective conditions.

Results

Note: The results in this section reflect preliminary findings with only half of the final target number of subjects.

During the learning stage, preliminary data suggests that subjects were able to correctly associate a particular scent with its context over 80 trials (Fig. 2 left). While there were some discrepancies among the conditions, rats learned all the conditions similarly well [$F(21,123.02) = 0.95$; $p = 0.532$]. Figure 2 (right) illustrates performance during the retention phase. For the first 40 trials, the object-context association contingencies are similar to the learning phase. During this set of trials, all the subjects performed similarly well [$F(9,60) = 1.950$, $p = 0.062$, $\eta_p^2 = 0.226$]. For trials 41-80, the odorants were removed. Following odorant removal, performance was differentially impaired across conditions [Block 5; $F(3,15) = 3.657$, $p = 0.037$, $\eta_p^2 = 0.422$]. The preliminary data in Figure 2 (right) suggest that the higher Affective salience created more durable object-context associations that is evidenced by the fox condition showing the least impairment from odorant removal while the Nonaffective control condition showed the largest dip in performance. The current study focused on data from the post-learning period, which did not involve testing rats on the task.

Surgeries involved implanting 32-channel probes into the BLA and HIP, with the probes possessing 32-channels spanning along the dorsal-ventral axis. This spanning of the channels increased the chances of successfully placing at least one channel in the region of interest. Probe placements were verified using post-mortem histology. Figure 3 shows an example of a probe placed in the BLA and HIP from one of the preliminary rats.

The transient nature of SWRs permits summing across given amounts of time. To do so, we filtered the signals from 150-250 Hz and summed the number of SWRs in the BLA and HIP while rats were immobile during the consolidation period. We used this information to produce BLA and HIP ripple rates (ripples per minute of non-locomotion) and BLA-HIP coincident ripple (i.e., 'co-ripple') rates (co-ripples per minute of non-locomotion). Figure 4 shows an example of a SWR recorded from a previous study.

Figure 5 shows the results of the average time in minutes spent non-locomoting for each condition during the 30-minute consolidation period. The average time (m) of non-locomoting exhibited similar values across the four conditions (mean ± SEM: Control = 10.70 ± 1.36; Fox = 10.56 ± 1.22, Male = 11.24 ± 1.41; Female = 10.01 ± 1.53; [F(3, 6.779) = 0.266, p = 0.848]). This suggests that any differences in ripple activity cannot be due to differences in time spent non-locomoting, but rather are due to the affective properties related to the conditions. Note that one subject was unable to provide data for the Fox condition, leading to n=5 for that condition.

Despite the similar amount of time spent non-locomoting across conditions, the analysis nevertheless proceeded by first calculating the overall number of ripples. Then, the time of non-locomotion along with the number of ripples were used to find the ripple rate. Figure 6 shows the results of the average number of ripples during non-locomotion for each condition during the 30-minute consolidation period. The average number of ripples in the BLA showed similar values across conditions (Fig. 6 left; mean ± SEM: Control = 25.33 ± 10.72; Fox = 14.40 ± 4.05, Male = 29.67 ± 8.13; Female = 10.50 ± 5.13; [F(3,11.550) = 1.350, p = 0.306]). The average number of ripples in the HIP showed similar values across conditions (Fig. 6 right; mean ± SEM: Control = 34.83 ± 11.86; Fox = 46.60 ± 13.41, Male = 36.50 ± 10.46; Female = 10.50 ± 5.13; [F(3,4.477) = 4.421, p = 0.081]). These results suggest that the number of ripples recorded in each region was independent of affective properties related to the conditions. Note that one subject was unable to provide data for the Fox condition, leading to n=5 for that condition.

Figure 7 shows the results of the average ripple rate during non-locomoting for each condition in the BLA and HIP. As mentioned above, ripple rate was calculated by dividing the number of ripples in the respective region by the total time (m) spent non-locomoting. The ripple rate in the BLA showed similar values across conditions (Fig. 7 left; mean ± SEM: Control = 1.96 ± 0.68; Fox = 1.26 ± 0.19, Male = 2.81 ± 0.83; Female = 1.14 ± 0.57; [F(3,12.061) = 1.160, p = 0.365]). There was a statistical significance of ripple rate in HIP at an alpha of 0.05 (Fig. 7 middle; mean ± SEM: Control = 3.16 ± 0.99; Fox = 4.59 ± 1.19, Male = 3.39 ± 0.98; Female = 7.07 ± 1.49; [F(3,18.353) = 6.286, p = 0.004]), indicating that at least one of the conditions differed from the mean of the others. The ripple rate results suggest that ripple activity could be

differentially impacted in the HIP depending on the affective property related to the condition. The average co-ripples exhibited similar values across the four conditions (Fig. 7 right; mean ± SEM: Control = 0.27 ±0.12; Fox = 0.33 ± 0.08, Male = 0.60 ± 0.24; Female = 0.56 ± 0.41; [F(3, 5.416) = 0.691, p = 0.593]). The co-ripple results suggest that coincidence of ripples in the BLA and HIP was not clearly related to the affective properties related to the conditions. Note that one subject was unable to provide data for the Fox condition, leading to n=5 for that condition.

We next wanted to collapse data across affective (urine-based) conditions to compare affective conditions with the nonaffective (control) condition. Accordingly, Figure 8 investigated the results of the ripples during the consolidation phase, now comparing the average of the Affective conditions to the Nonaffective condition found in Figure 7. Analyzing the data in this way found that ripple rates in the BLA (Fig. 8 left) were similar across nonaffective and affective conditions (mean ± SEM: Nonaffective = 1.96 ± 0.68; Affective = 1.74 ± 0.31; $t(5)$ = 0.345, p = 0.372). Ripple rates in the HIP (Fig. 8 middle) were statistically significant across nonaffective and affective conditions at an alpha of 0.05 (mean ± SEM: Nonaffective = 3.16 ± 0.99; Affective = 5.11 ± 1.08; t(5) = -3.143, p = 0.013). The average co-ripple rate (Fig. 8 right) exhibited similar values across the two conditions (mean ± SEM: Nonaffective = 0.27 ± 0.12; Affective = 0.50 ± 0.22; $t(5)$ = -1.317, p = 0.245). The ripple rate results suggest that during periods of consolidation, the HIP plays a notable role in ripple activity depending on the affective properties related to the conditions, whereas the BLA may be less involved in offline consolidation. Further, the co-ripple results suggest that the Affective conditions increased the co-ripples in the consolidation phase of the task, though not to a level significantly different than consolidation during the Nonaffective condition.

Discussion

Data collection is still ongoing with the present study, and conclusions offered here should be viewed as preliminary. Nevertheless, the current data suggests some notable patterns.

We predicted that the affective properties related to the condition would lead to differences in the time spent non-locomoting. At the start of the study, we thought exposure to fox urine during learning could lead to subsequent avoidance and freezing behavior due to the presumable negative valence associated with the urine. Once we exposed the rats to the urine, we realized they did not exhibit such behaviors; they readily engaged and learned the fox condition without any hesitation. Since the fox urine did not elicit the avoidance behaviors but is still presumably high arousal, we predicted that arousal would lead to more activation of the autonomic nervous system and thus movement. Similarly, the conspecific male urine was presumably high arousal but positive valence (compared to fox urine). However, the time (m) of non-locomotion for both conditions was comparable to the low arousal, neutral valence control odorant (Fig. 5). One reason why arousal did not seem to impact non-locomotion during the consolidation period may be due to the arousing nature of the stimuli possibly wearing off by the end of the long learning phase (which could take multiple hours for any given rat on any given day). Thus, the affective salience of the conditions could have led to differences in movement early during the testing day but wore off by the time they entered the rest-box. As a result of habituation to the affective properties, exposure during the testing period may not have led to the high arousal we predicted and thus led to similar time of non-locomotion. Though the female urine was lower arousal and positive valence, any arousing property that it may have elicited in the rats could have worn off through habituation during training, similar to the Fox and Male conditions.

Figure 8 shows the results of ripple rate in the BLA and HIP between the Nonaffective and Affective (made up of Fox, Male, Female) condition. The current data refutes our initial hypothesis that BLA plays a prominent role in post learning consolidation. In particular, the data shows that post-encoding consolidation events are driven primarily by the HIP as opposed to the BLA. Across both the Nonaffective and Affective conditions, there was a higher ripple rate in the HIP (Fig. 8 middle) compared to the BLA (Fig. 8 left). This suggests that while the BLA has a role during initial encoding, the HIP is the primary region for offline reactivation and subsequent consolidation. Initially, affect appears to be in the BLA and object-context associations in the HIP (Langston & Wood, 2010). Then, during consolidation, the HIP appears

to be the site of reactivation for both, namely with affective properties being processed by the HIP. Although the BLA ripples are similar in quantity across the Affective conditions (Fig. 2 left), they may differ in quality (length, frequency, etc.), leading to a benefit of affective salience that we are not picking up with our measure. Additionally, we may not be seeing a significant number of ripples in the BLA, but rather modulation of BLA cells by the HIP SWRs (Girardeau et al., 2017). This would suggest that the BLA may play a role in post-learning consolidation through different or additional mechanism than ripples, one of which being the initial biasing of hippocampal neuronal cell assemblies. As such, the significant difference in ripple rate within the HIP across the Nonaffective and Affective conditions may arise from heightened BLA inputs during encoding for the Affective conditions.

Within the Affective conditions, we noticed opposite trends between the BLA and HIP ripple activity of Figure 7. When the BLA is producing ripples, ripple activity in the HIP seems to decrease and vice versa. For example, the Fox and Female condition have the lowest ripple activity of the four conditions in the BLA, but the highest in the HIP. This would support the idea of hippocampal ripples supporting both affective and object-context information once the BLA disengages following encoding.

Although we found only a few instances of coincidental ripples between the BLA and HIP, the occurrences of these co-ripples was numerically higher in the Affective condition relative to the Nonaffective condition (Fig. 8 right). It is important to note how few co-ripples occurred within the Affective conditions. While the low level of co-ripples may again suggest that post-encoding consolidation events are driven primarily by the HIP rather than the BLA or a coordination between the two regions, the overall low occurrence of BLA ripples likely drives the low co-ripple occurrences.

In general, we did not expect to find such few ripples recorded in the BLA and HIP during non-locomotion across the testing conditions (Fig. 7). One potential limitation could be the way we are identifying motionless periods. The accelerometer provides X,Y,Z coordinates of the probes throughout recordings, which we translated into motion or non-locomotion based on the change in these coordinates across time. This may not be the most accurate readout of non-locomotion because unintended moments, like rearing, might be flagged. To help increase

the accuracy of capturing motionless epochs during the 30-minute consolidation period, we plan to use a deep neural network, DeepLabCut (Mathis et al., 2018). Using this network, along with accelerometer data, will ensure we are collecting ripple data during non-locomotion. Accurately capturing ripples during non-locomotion and adding data from the 4-6 to-be-tested subjects will lead to more conclusive results. Future studies could also look at how ripple rate changes as time spent in the consolidation period increases.

Overall, our current data suggests that initial biasing of Affective memories during the encoding period leads to better retention as opposed to Nonaffective memories (Fig. 2 right). However, it remains to be seen if ripple activity during consolidation, specifically localized in the HIP, plays a role in this disparity. Alongside the aforementioned limitations, any notable impact of arousal may be gone at the onset of the consolidation period. Also, studies have shown that the BLA inactivation after an experience can impair learning (Zhu et al., 2011). This suggests that rather than just the HIP, the BLA is also playing an important role in consolidation. By adjusting how we identify locomotion and ripple activity during the consolidation period and increasing our sample size, we will be able to better understand the role that offline reactivation during non-locomoting plays in the consolidation of emotional and non-emotional memories.

Figures

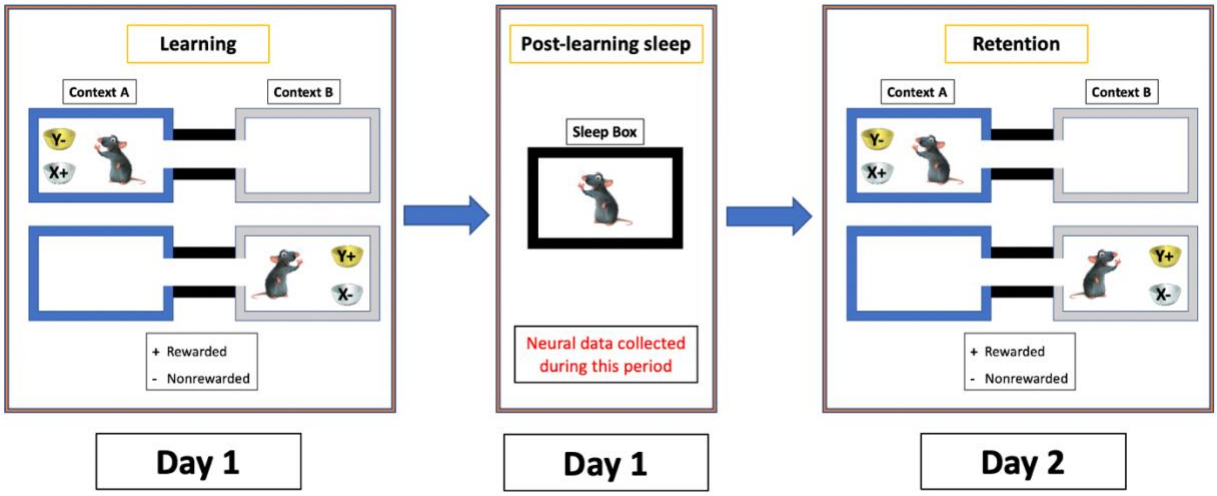

Figure 1: Stages of training involving object-context association and sleep box. During the learning stage on day 1, after 15s of context exploration, one Affective (yellow) and one Affective (clear) object are both placed in the box. The Affective object is rewarded in one context while the Nonaffective object is rewarded in the other. Control test condition will use two Nonaffective (clear) objects. Immediately following learning, subjects spend 30 minutes in an empty sleep box. On day 2, the object-context associations are tested again to look at memory retention.

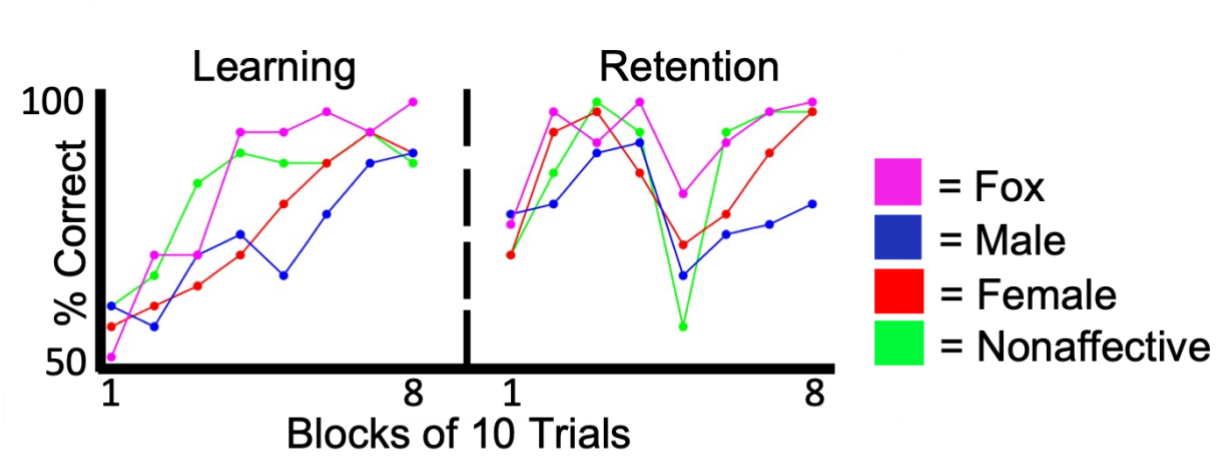

Figure 2. Preliminary data of behavioral performance on the learning phase of the object-context association task averaged across 5 rats that performed each odorant condition (left). Preliminary data of behavioral performance on the retention phase of the object-context association task averaged across 5 rats that performed each condition (right). Odorants of the objects were removed at trial 41 to determine the impact of object-context associations and the corresponding neural activity.

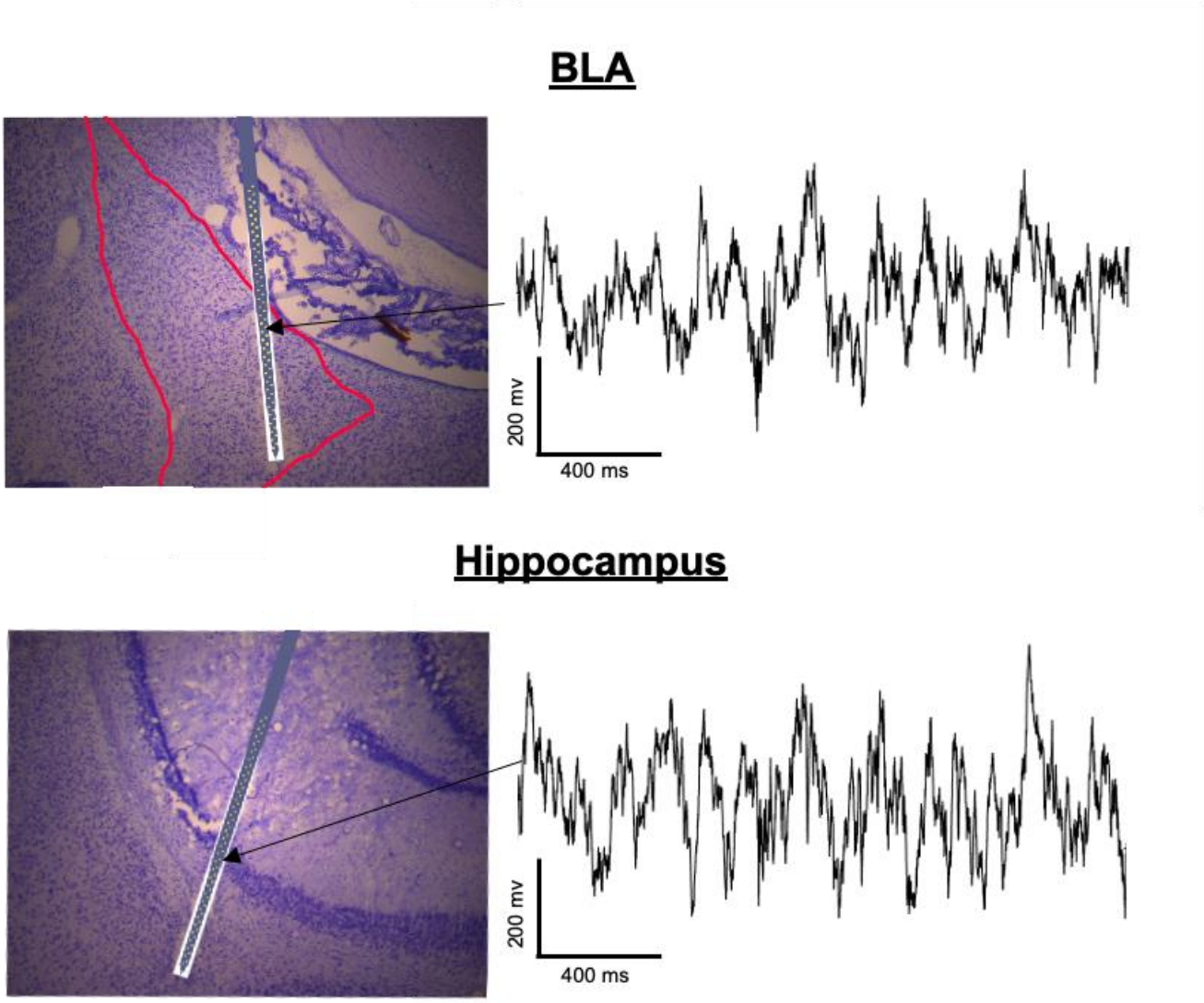

Figure 3: Example histology (left) taken from one of the preliminary rats along with LFPs (right). The top left image highlights the BLA (red outline), while the bottom left image highlights the HIP. Probe placement is shown in both images. Black arrows point to the channels producing the 2 s LFR traces.

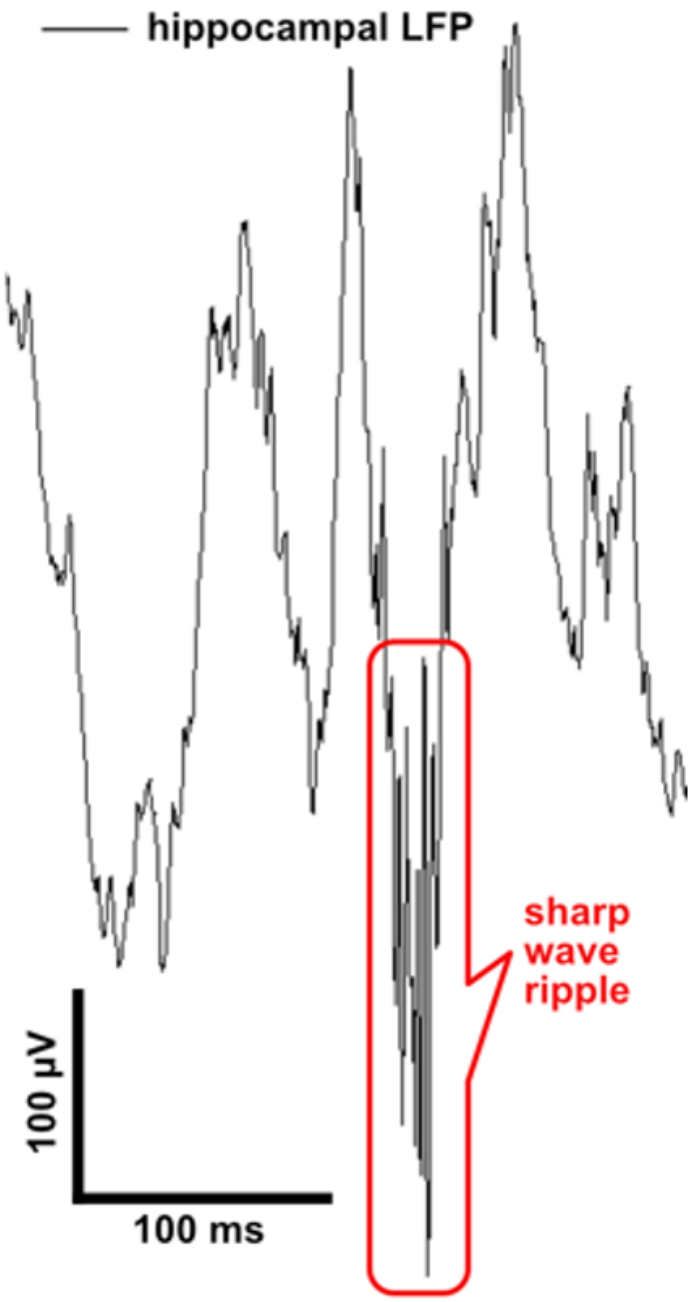

Figure 4: LFP recording from (dorsal CA1) of hippocampus that contains sharp wave ripple activity. Recording taken from previously collected data in laboratory.

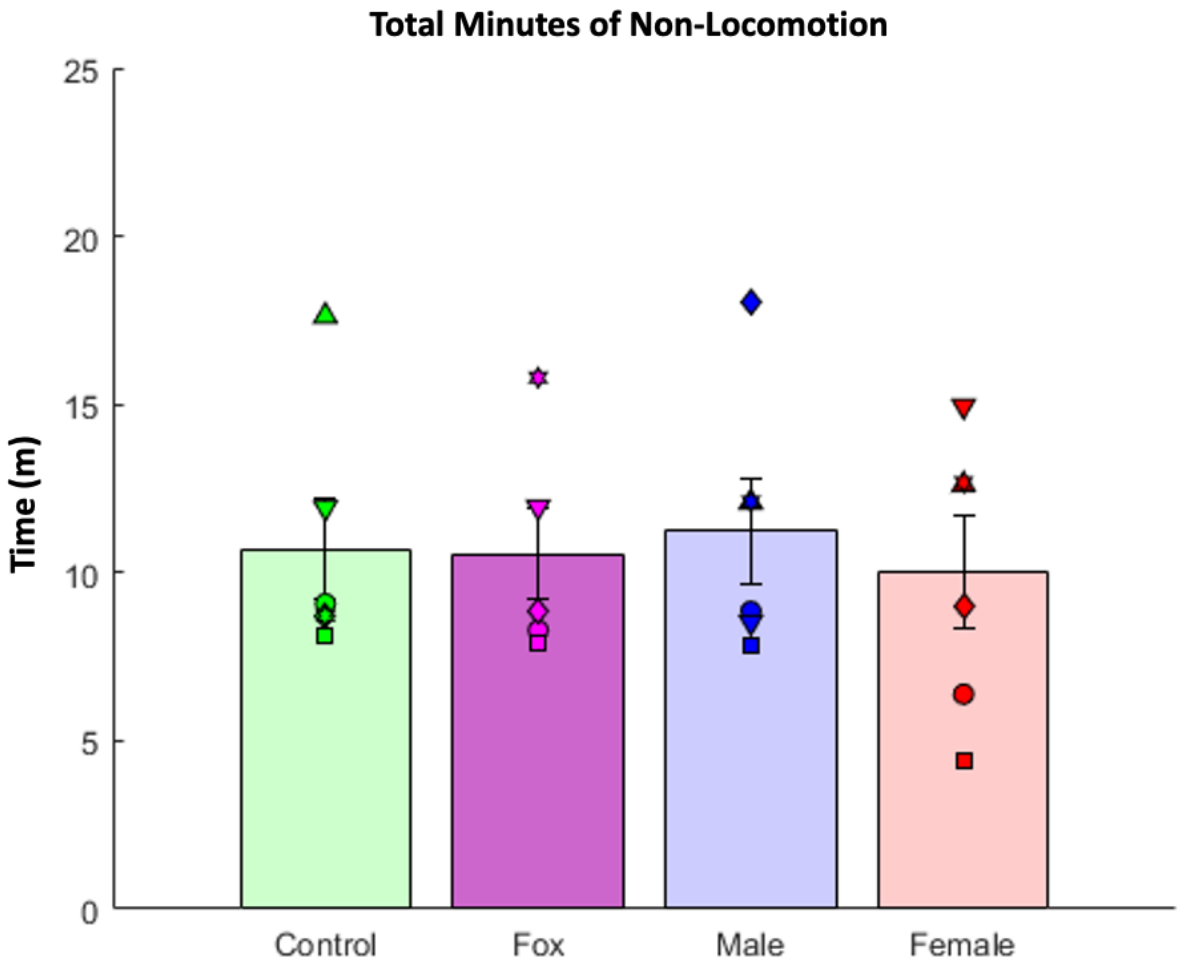

Figure 5. Amount of time (m) spent non-locomoting during the 30 m consolidation period. The bars show the time non-locomoting averaged across subjects for each condition, with each marker shape reflecting an individual subject. Control, Male, Female: n=6; Fox: n=5.

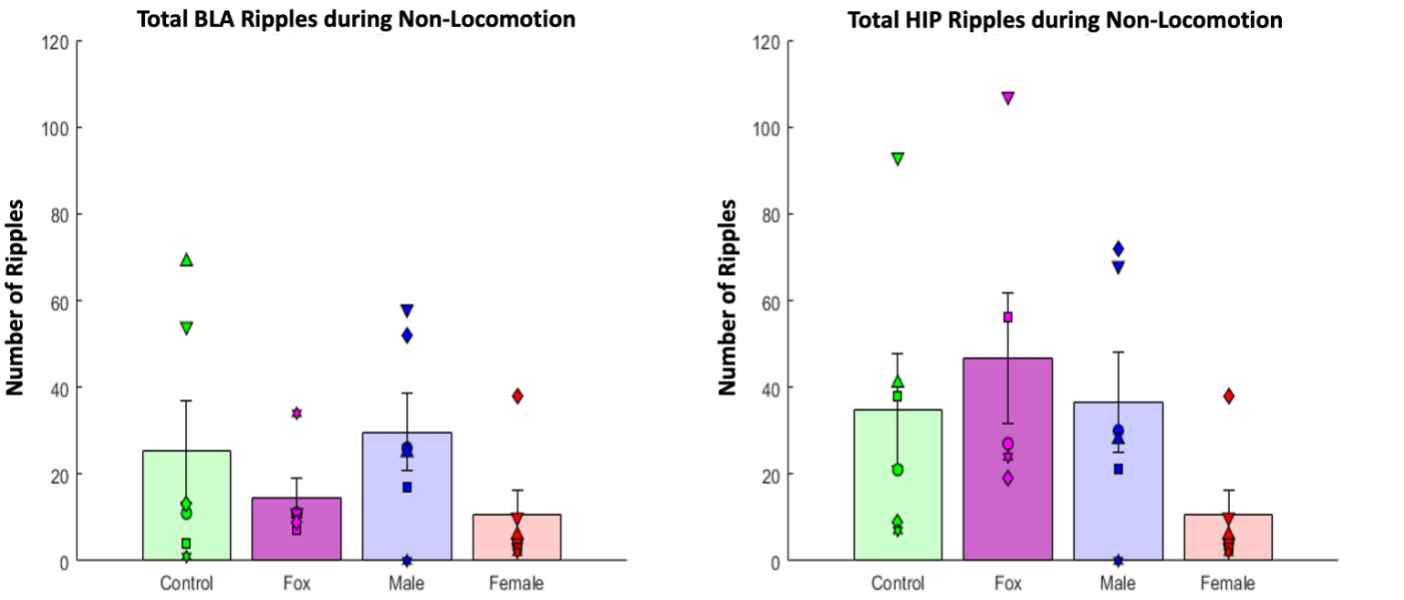

Figure 6. Total number of ripples in the BLA (left) and HIP (right) during non-locomotion within the 30-minute consolidation period. The bars show the total number of ripples averaged across subjects for each condition, with each marker shape reflecting an individual subject. Control, Male, Female: n=6; Fox: n=5.

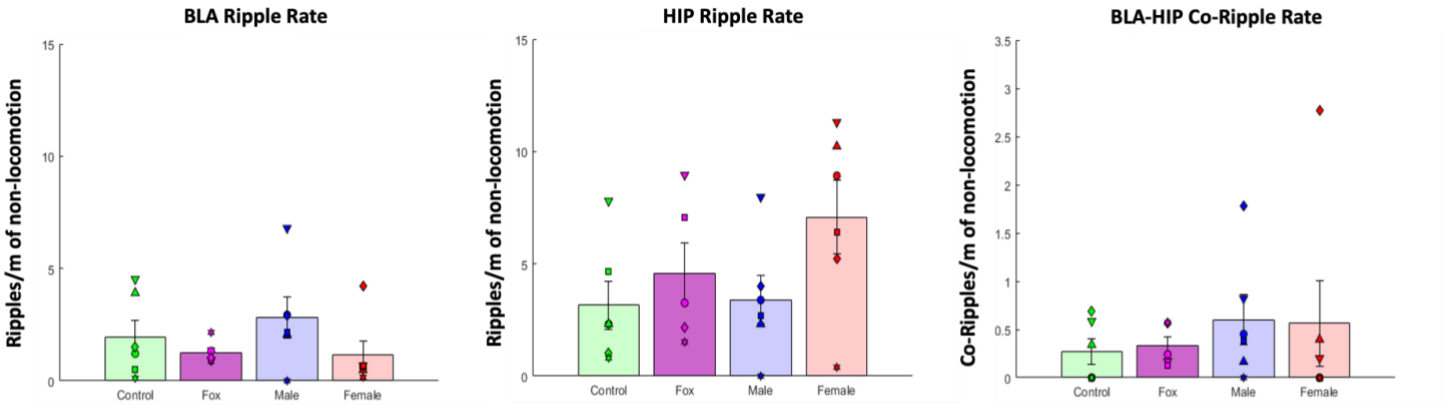

Figure 7. Ripple rate in the BLA (left) and HIP (middle) during non-locomotion within the 30 m consolidation period, along with occurrence of ripples in the BLA and HIP within 100 ms of each other (right). The bars show the ripple rate averaged across subjects for each condition, with each marker shape reflecting an individual subject. Control, Male, Female: n=6; Fox: n=5. Ripple rate = ripples / m of non-locomotion. Co-ripple rate = ripples in BLA and HIP within 100 ms / m of non-locomotion.

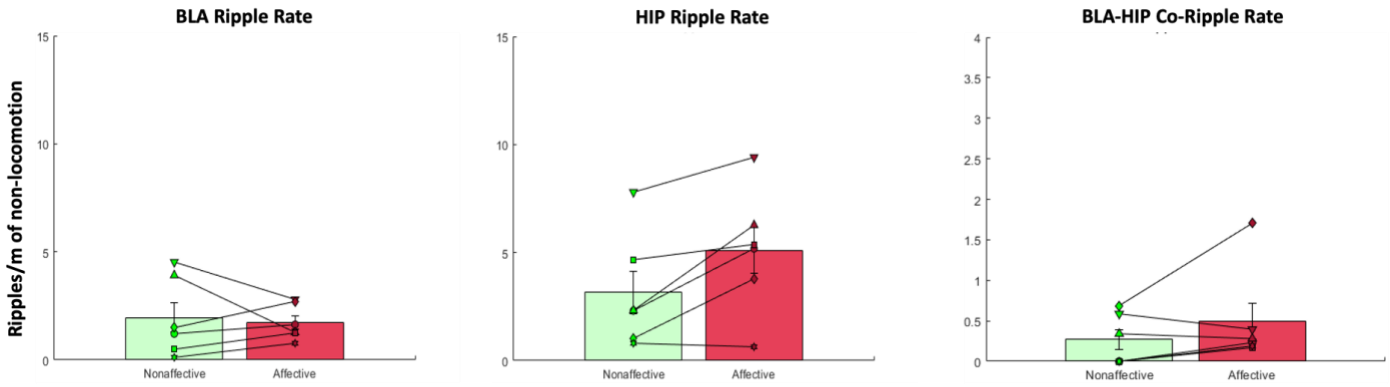

Figure 8. Ripple rate in the BLA (left) and HIP (middle) during non-locomotion within the 30 m consolidation period, along with occurrence of ripples in the BLA and HIP within 100 ms of each other (right). The bars show the ripple rate averaged across subjects within the Nonaffective (Control) and across the Affective (Fox, Male, Female) conditions. Marker shapes reflect individual subjects', with lines connecting individuals between condition types. Control, Male, Female: n=6; Fox: n=5. Ripple rate = ripples / m of non-locomotion. Co-ripple rate = ripples in BLA and HIP within 100 ms / m of non-locomotion.

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