Hippocampal Remapping During a Reward-Oriented Spatial Task

Cognitive Science Honors Thesis
By Austin Gallagher
Honors Committee: Lara Rangel, Douglas Nitz, and Pamela Riviere

Intro & Background

The act of navigating through a familiar environment often doesn't require an *exploratory mode* of immediate attention or thought on what each next step will be. To a degree, it is a passive act of moving from one known location to another known location. However, when changes within that familiar environment take place (e.g. new hours at which a store you're visiting is open, construction impeding a daily route, a change in class meeting location, etc.) this "passivity" is drawn back and an exploratory mode towards the present external moment is brought forward; even more so when in completely new and unknown places. One's knowledge or current spatial representation of how the world is becomes insufficient. During the experience and recognition of these unfamiliar/novel moments, an eventual process of *updating* ones spatial representations of the external world or *cognitive map* [1,2] occurs, providing a more accurate knowledge or memory of the current state of things.

The study of spatial navigation and spatial memory is often associated with the neurophysiological study of the hippocampal formation, of which spatial memory formation, consolidation, and memory recall [2,3,4,5,6], among others, have been experimentally approached using the rat animal model. While recording *in vivo* with electrophysiological methods in the rat, hippocampal pyramidal cells, known as *place cells*, are found to develop high firing rates for select locations in space called *place fields* [2,7]. In addition to this observed neuronal spatial relation, the spatial characteristics of place cells (place field location and place cell firing rate) can be affected through the manipulation of environmental settings and object cues, a phenomenon known as *global and rate remapping* [6,8,9,10]. In instances of object cue shifting, Dupret et al. studied global remapping (place field shifting) in the subregions of CA1 and CA3 of the rat hippocampus within a behavioral paradigm where rats were tasked with learning reward locations that changed daily within a familiar open field environment [6]. By the end of each session, place cells within CA1 often globally remapped their place fields towards the new reward locations of that day, suggesting the network of neurons adapted their past network representations to the new reward locations to account for the environmental cue change. In addition to this, CA1 place cells had a higher rate of remapping as compared to place cells in CA3, indicating how the hippocampal network is differentially processing spatial input within particular environmental constraints.

Project & Aims

For my project, I approached the experimental study of hippocampal remapping in relation to the notion of updating ones spatial representations by further exploring how the subregion of CA3, a region not commonly thought to remap, might still be playing a role of remapping under different environmental constraints. I analyzed *in vivo* rat hippocampal CA3 neural data that was recorded during a spatial reward association task that took place on a circular track. In this task, there was one designated reward location that shifted to a new random location every fifteen trials, totaling 4 reward locations (60 trials), with the last reward location a repeat of the first (figure 1).

The aim of my honors project was to analyze hippocampal CA3 neural data, on single unit (action potentials) and network levels (local field potential), from a rat that performed a shifting spatial reward task in order to classify single unit and network level factors that parallel environmental reward shifts and identify possible place cell remapping responses.

Results

In the analysis of three sessions of CA3 neural data from a single rat, I focused on one session in particular that presented data of consistent place field activity, spatial reward centered firing, and remapping from a single neuron that aligned temporally with a reward location shift (figure 1). In addition to these spatial neuronal field properties, I further observed a possible temporal relationship between the spike timing of two neurons, which took place when the animal was occupying reward locations. These two neurons had the property of spatial reward centered firing and one of the neurons maintained a consistent place field across the session. They had a noticeable tendency as compared to the other identified neurons to fire within a temporal proximity of 15-85 ms for 5 out of the 60 trials (example: figure 2).

Using the method of spectrogram analysis, which allows one to look at the power of a given frequency range for any given moment in time, I focused on the local field potential during the time points when the rat had a reward encounter. Taking the average spectrogram of the total 60 trials across the full session (figure 3, left) a noticeable division in frequency ranges is observed for before reward encounter and during; whereupon the approach there is a tendency for lower frequencies (0-15 Hz) and a tendency for higher frequencies (15-60 Hz) when the rat is occupying the reward location. Analyzing this data further, I took a spectrogram which averaged across the first three trials of

each reward location encounter (figure 3, middle) and another for the last three trials of each reward location encounter (figure 3, right). These show a distinct division in the oscillatory profile that occurs during particular phases (beginning vs ending of 15 trials) of a reward location experience. Where within the initial experience of a new reward location (first three trials) there is a high power in lower frequencies within the delta to theta range (0-15 Hz) and towards the end of a reward location experience (last three trials) there is a high power in higher frequencies within the beta to low gamma range (15-60 Hz).

Conclusions

From these results, CA3 shows instances of reward location activity shifts in spatial firing and remapping that temporally coincides with reward location changes, possibly suggesting that the CA3 network might be remapping place fields to account for the experienced changes in reward locations. Along with this phenomenon of remapping is the mechanisms by which remapping occurs, in which close proximal temporal firing (15-80 ms) among a network of neurons can increase or decrease the probability of how these interconnected neurons actively respond to one another, and in turn influencing the likelihood of their spatial firing properties. I've shown that this temporal proximity in firing occurs between two CA3 neurons while the animal is at reward locations. And while this particular observation doesn't suggest neuronal connectivity or correlation to remapping there is literature to suggest that further analysis and study of neural activity in the hippocampus during reward location encounters might be a significant timepoint for spatial encoding of relevant information [11].

In addition to spike timing of CA3 neurons during reward encounters, the local field potential expressed a rhythmic profile shift in neural coordination with respect to the learning phase (first three trials vs last three trials) of a reward location (figure 3), indicating a parallel between the experiential learning of a reward location and the CA3 network activity patterns changing along with this experience, from low frequency oscillations (delta to theta) to high frequency oscillations (beta to low gamma). However, in opposition to this shift in neural oscillations that parallel the phase of reward location experience, Berke et al. show findings from *in vivo* CA3 and CA1 mouse hippocampus in which beta (23-30 Hz) is more prominent during the initial phase of experiencing a new linear track environment and a decrease of beta seen for the increased experience in that environment [12]. The results of Berke et al.'s study provides a contrast between the results of this current study with respect to novel and familiar experience, suggesting further study into the experiential (novel vs familiar) aspect and environmental characteristics that might be influencing the subregion of CA3's instantiation of the beta rhythm as a heightened neural process during distinguished behavioral moments.
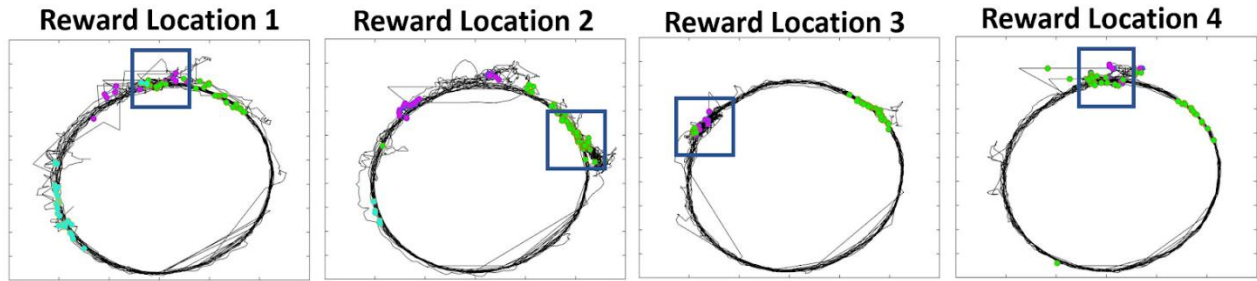
Future Directions

To extend the reach of this initial study with respect to the conclusions that can be drawn from CA3's potential to remap, would be to increase sessions, systematically vary the number of trails for each reward location, and record from a larger population of CA3 neurons, possibly extending into the subregions of CA3a, b, and c to observe how the phenomenon of remapping might be occurring differentially across the horizontal of CA3 as a whole. In addition to recording from the subregion of CA3, recording from other hippocampal subregions simultaneously, for example, upstream DG and downstream CA1 subregions could provide insights into the larger integrative picture of possible interregional interactions that influence remapping in the hippocampus. Along this same line of interregional interaction, it would be interesting to further study hippocampal CA3 remapping in the context of hippocampal sharp wave ripples, a neural event associated with the consolidation of memories, planning, and stabilization of spatial representations [5,11,13,14,15]. Also, under the possible condition that CA3 has a higher degree of remapping when the environment is a linear track paradigm as compared to an open field paradigm [6], then this too can be further studied, in which the constraints of these environmental paradigms be further experimented with in relation to how the CA3 network, and possible other hippocampal subregions, go about its network interactions on a single unit and oscillatory scale.

Acknowledgments

Figures

Figure 1: Tracking data of the rat as it ran across the circular track, where each circle represents the 15 trials for that reward location superimposed on top of it. In addition, there are three identified neurons (purple, green, and light blue), where each circle represents an action potential from that neuron as the rat occupied that region of space. Consistent place field activity is indicated at the top right edge of the circle (green neuron), where across reward locations it is maintained. Spatial reward centered firing is indicated by the neurons (green and purple) shifting there firing with reward. And remapping from a single neuron (light blue) that aligned temporally with a reward location shift (reward location 1 to 2).
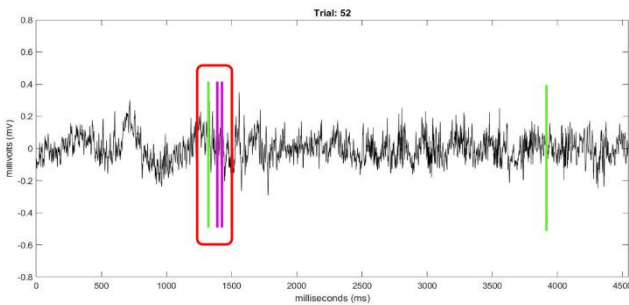
Figure 2: Trial 52 local field potential, in which 0 is the time point of when the rat reached the reward. Green and purple lines indicate spike time of two distinct neurons and the red box indicates the occurrence of temporal proximity (15-85 ms) between these two neurons, which are known to be important for synaptic plasticity changes.
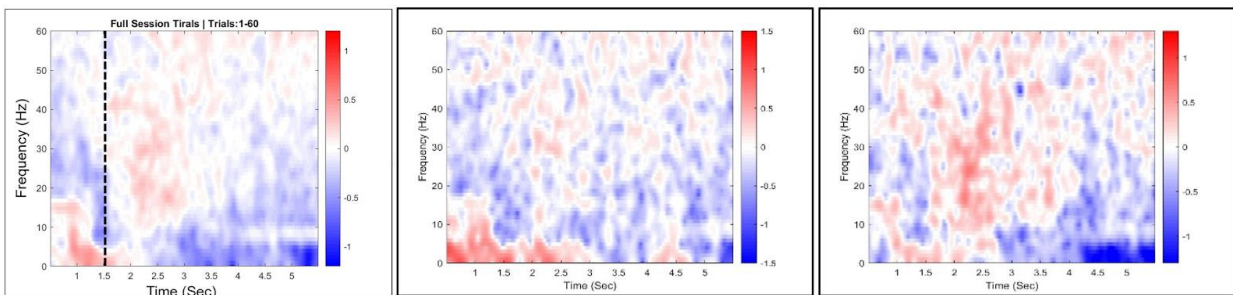
Figure 3: Spectrogram analysis of frequency ranges during reward encounters, where on each x-axis of each spectrogram the 1.5 second time point indicates when the rat reached the reward location. (Left) total of 60 trials of reward location encounters, (middle) first three trials of every reward location encounter, and (right) last three trials of every reward location encounter.

References

1. Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review, 55*(4), 189-208. http://dx.doi.org/10.1037/h0061626
2. OKeefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. New York: Oxford University Press.
3. Morris, R. G., Garrud, P., Rawlins, J. N., & Okeefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, 297(5868), 681-683. doi:10.1038/297681a0
4. Buzsáki, G. (1989). Two-stage model of memory trace formation: A role for "noisy" brain states. *Neuroscience*, 31(3), 551-570. doi:10.1016/0306-4522(89)90423-5
5. Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25(10), 1073-1188. doi:10.1002/hipo.22488
6. Dupret, D., O'Neill, J., Pleydell-Bouverie, B., & Csicsvari, J. (2010). The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nature Neuroscience*, *13*(8), 995–1002. doi:10.1038/nn.2599
7. Okeefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, 34(1), 171-175. doi:10.1016/0006-8993(71)90358-1
8. O'Keefe J., Conway D. H. (1978). Hippocampal place units in the freely moving rat: why they fire where they fire. Exp. Brain Res. 31, 573–590.
9. Muller R. U., Kubie J. L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. 7, 1951–1968.
10. Latuske, P., Kornienko, O., Kohler, L., & Allen, K. (2018). Hippocampal Remapping and Its Entorhinal Origin. *Frontiers in behavioral neuroscience*, *11*, 253. doi:10.3389/fnbeh.2017.00253
11. Foster, D.J. and Wilson, M.A. (2006) Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature 440, 680–683
12. Berke, J. D., Hetrick, V. , Breck, J. and Greene, R. W. (2008), Transient 23–30 Hz oscillations in mouse hippocampus during exploration of novel environments. Hippocampus, 18: 519-529. doi:10.1002/hipo.20435
13. Pfeiffer BE. (2017). The content of hippocampal "replay". *Hippocampus*. 2018;00:1–13. https://doi.org/10.1002/hipo.22824
14. Gupta, A. S., Meer, M. A., Touretzky, D. S., & Redish, A. D. (2010). Hippocampal Replay Is Not a Simple Function of Experience. *Neuron*, 65(5), 695-705. doi:10.1016/j.neuron.2010.01.034
15. Roux, L., Hu, B., Eichler, R., Stark, E., & Buzsáki, G. (2017). Sharp wave ripples during learning stabilize the hippocampal spatial map. *Nature Neuroscience*, 20(6), 845-853. doi:10.1038/nn.4543