Charles University

Faculty of Science

Study programme: Biology

Branch of study: Biology

Veronika Lobellová

Coding of stable and moving objects in the brain
Kódovanie stabilných a pohyblivých objektov v mozgu

Bachelor´s thesis

Supervisor: Prof. RNDr. Aleš Stuchlík, Ph.D., DSc.

Prague, 2018

Poďakovanie

Rada by som poďakovala svojmu školitelovi Prof. RNDr. Alešovi Stuchlíkovi, Ph.D., DSc. za trpezlivosť, ochotu a cenné rady poskytnuté pri písani tejto práce a ďalej každému, kto mi pri písaní práce pomáhal a podporoval ma.

Prehlásenie

Prehlasujem, že som záverečnú prácu spracovala samostatne a že som uviedla všetky použité informačné zdroje a literatúru. Táto práca a ani jej podstatná časť nebola predložená k získaniu iného alebo rovnakého akademického titulu.

V Prahe 16.8.2018

Podpis

Abstract

Spatial navigation in an environment is essential for one's survival. Animals need to monitor location of self and location of other animate or inanimate objects. Navigation is a hippocampus dependent process supported by activity of place cells. Object location in space is thought to be coded as a point of interest on cognitive map formed by place cells. Place cells change their firing fields, process known as remapping, when a new object is introduced into the environment. However we do not yet know how location of moving objects such as predators or other animals is presented on the cognitive map. This work summarizes findings of chosen studies concerning the role of hippocampus and place cells in spatial coding of stable and moving objects.

Key words: spatial navigation, hippocampus, place cells, single cell recording, moving objects

Abstrakt

Priestorová navigácia je nevyhnutná pre prežitie vo svete. Zvieratá musia neustále aktualizovať svoju polohu a polohu iných živých či neživých organizmov. Navigácia je závislá na hipokampe a na hipokampálnych bunkách miesta. Predpokladá sa, že poloha objektu v priestore je v mozgu kódovaná ako bod na kognitívnej mape, ktorá je tvorená bunkami miesta. Bunky miesta zmenia svoje pole aktivity, proces známi ako premapovanie, keď je do prostredia umiestnený nový objekt. Stále však nie je známe, ako presne je na kognitívnej mape kódovaná poloha pohyblivých objektov ako napr. predátor alebo iné zviera. Táto práca zhŕňa výsledky vybraných štúdií zameraných na úlohu hipokampu a buniek miesta v priestorovom kódovaní stabilných a pohyblivých objektov.

Kľúčové slová: priestorová navigácia, hipokampus, bunky miesta, jednotkové nahrávanie, pohybujúce sa objekty

Table of contents

1 Introduction

One of the basic requirements for survival is knowledge of the environment surrounding us. Natural selection has favored organisms with an ability to navigate. Navigating to shelter, to or away from other animals and conspecifics to ensure mating, scavenging for food or fleeing from enemy requires one to keep constantly updated position of oneself in the environment. It is now accepted that hippocampus plays a crucial role in spatial memory and navigation. Pyramidal cells in hippocampus display interesting property – they only fire when a rat's head is in a certain part of the environment called firing field creating a spatial map of the environment. O'Keefe & Dostrovsky, 1971 named them "place cells" after their correlation with rat's spatial position.

Place cells are thought to also code position of other objects in space allowing for allocentric navigation. Animals need to keep an updated map of different objects' location on their cognitive map and although we know hippocampal place cells are crucial for this, it is still unclear how exactly other objects are coded in the brain.

This work aims to summarize methods commonly used in search for neural correlates of spatial navigation in rats, concentrating on behavioral tasks using small robots as stable or moving objects of interest. Short part is dedicated to outlining neuron discharge recordings as an important method for understanding neural basis of behavior. Last, findings in spatial coding of objects in the brain are reviewed with regards to different types of objects – animate vs. inanimate and stable vs. moving.

2 Stable and moving world – insights from behavioral tasks

Commonly used approach to testing animal's behavior around objects is allowing the rat to move freely on an arena and explore. Rats exhibit strong exploration behavior and thus examine space of the arena and any objects on it without any need of reward. This is mainly used for paradigms like the open field, in which the rat explores an arena, and object recognition tests which are used to test object memory. However this work will not deal with behavioral tests developed for object memory and will rather focus on tests that examine rat's spatial navigation around objects serving as landmarks or mimicking predators.

Important part of these behavioral studies is correlating rat's behavioral responses to stable or moving objects with activity in the brain. One of the most commonly used techniques in animal brain research – single cell recordings, will be discussed in the next chapter.

2.1 Stable objects and freely moving rat

To investigate involvement of rat's anterior claustrum, Jankowski & O'Mara, 2015 allowed food deprived rats to collect food pellets on a circular or squared arena in 16 - 20 min long sessions. After the rats were trained in this pellet chasing task, objects were introduced into the arena. Aiming to see the effects of object location and object identity, authors used different protocols such as object substitution, in which they substituted the object for another distinct object of different color, shape and material; object repositioning in which they distinctly changed positions of known objects; recordings with simultaneous presentation of new and known object in which new and already presented objects were positioned far apart in triangle manner on the arena; recording in different environments of different shape (above mentioned circular and square arena).

Combining different sets of environment and object properties, mainly object location and using old vs. new objects, which rats should prefer due to their explorative behavior and recording cell discharge allowed authors to assess function of recorded brain region in spatial mapping related to objects as points of interests.

Manns & Eichenbaum, 2009 used an object recognition memory task while recording hippocampal pyramidal cells. Task consisted of multiple trials in which rats explored a new object, objects from previous trials and their copies in new locations. Authors recorded time for each instance a rat's nose was close to the object for a minimum of 0.25 s. This way authors combined object recognition memory task with a spatial parameter.

Works by Choi & Kim, 2010 and Kim et al., 2018 aimed to test the role of amygdala in predator-induced fear expression. To mimic a predator they used a predator-like looking robot which moved closer to the rat and snapped its jaws when the rat approached a food pellet placed on the arena. Rats were first trained to collect food pellets on the arena, then trained to collect food pellet placed in gradually increasing distance from the nest every day. On the robot encounter day, three sequential sessions were employed: pre - robot, robot in which the robot emerged and moved towards the pellet in above described manner, and post - robot session.

Work by O'Keefe & Dostrovsky, 1971 also implicated design in which a rat was allowed to move freely on an arena for 15 - 30 min while recording cell firing via 8 microelectrodes. Unit activity was recorded in freely moving rats during spontaneous behavior and during elicited behavior as orienting, sniffing, etc. This allowed them to observe place cells as 8 units only responding when the rat was placed in a particular part of the platform facing a particular direction, suggesting that hippocampus provides spatial reference map.

Other work using this simple and effective design is by Fenton & Muller, 1998 showing excess firing variance in place cells.

2.2 Interaction of two rats on the arena

Recording cell activity during rat - rat interaction has also been used. Using this paradigm, we can observe neural correlates of processing moving animate objects, conspecifics and social interactions. According to Zynyuk et al., 2012, using live rat instead of robot increases spontaneous interaction between the subjects without need for a reward motivation. More advantages of this approach are more natural path executed by the subject rat when

compared to angular trajectory of the robot or a toy car controlled by the experimenter and closer approximation to species specific conditions for recording.

Zynyuk et al., 2012 used a design in which they trained food deprived rats to forage pellets on an arena. After, they recorded cell discharge in three sessions: standard sessions on odd numbered days and rat - rat sessions interposed between a pair of standard sessions. The second rat was equipped with LED allowing them to track positions of both rats and make assumptions based on distance of the two rats.

Telensky et al., 2009 demonstrated that rats can navigate with respect to moving goal – another rat by training the subject rat to avoid another rat on an arena. In this "enemy avoidance task" subject rat received a small electric shock when the distance between the two animals was smaller than 25 cm. Subject rat was again pre-trained to move on the arena in order to collect food pellets and was food deprived.

2.3 Use of small moving robot

To examine rat's interaction with objects on the arena, lot of studies use a small programmable robot, controllable toy car or a more recent biomimetic rat robots. This approach allows the experimenter to easily manipulate with the moving object's trajectory, speed and task motivation and is ecologically relevant (Choi & Kim, 2010; Kim et al., 2015).

Ho et al., 2008 and Markus et al., 1995 used a design in which the rat was rewarded for keeping a close distance to a motorized car moving on the arena. In Ho et al., 2008 study, rewarding brain stimulation was delivered if the rat stayed in proximity of the robot after staying further away for 10 s.

Rats had to avoid randomly moving small robot (fig. 1A) on a circular arena in study by Telensky et al., 2011 and Svoboda et al., 2017. This task was derived from enemy avoidance task using a live rat as the enemy (Telensky et al., 2009) and requires rat to forage on the arena while navigating around the moving, slowly moving or stable robot. If the distance between the rat and the robot decreases to 25 cm the rat receives a mild electric shock (fig. 1B).

2.4 Biomimetic rat robot

Using live rat instead of a robot has its advantages, as mentioned earlier. However live animals are unpredictable and can affect the experiment in undesirable way. Shi et al., 2015 thus developed a biomimetic robotic called WR-5 rat that mimics a live rat. This robot consists of four links – head covered in plastic shell to mimic rat's head, two links for waist
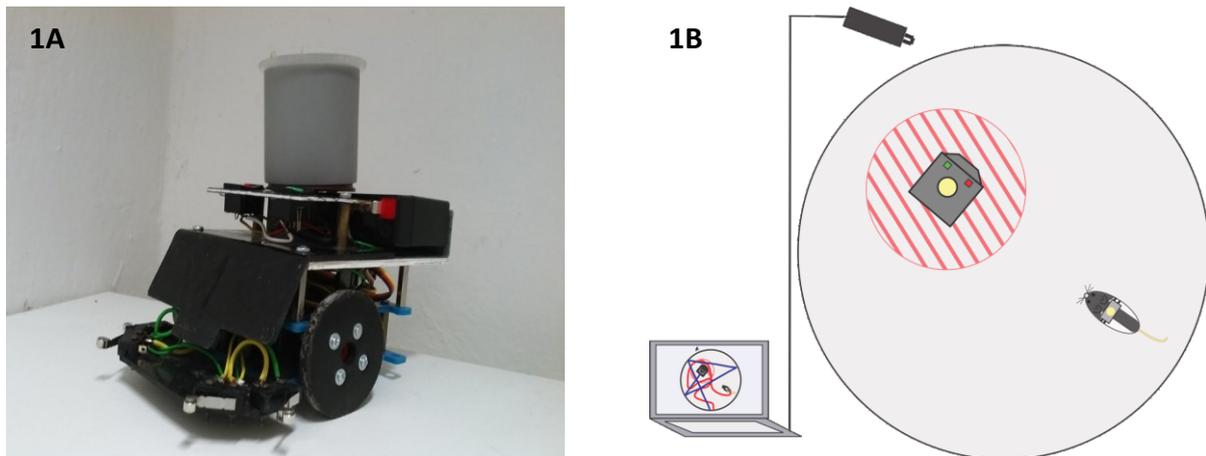

Figure1: Enemy avoidance task. **A** Picture of the programmable robot. **B** Scheme of the apparatus with the forbidden zone around robot highlighted in red. If rat entered this zone, it recieved a mild electric shock. From Svoboba et al., 2017

and a link used as a hip. WR - 5 is controlled remotely by wireless communication with a computer that processes the robot's angular movement and rat's movement with an overhead camera in real time. WR - 5 can mimic spontaneous actions like rearing, mounting, rotating, body grooming and can also adjust its head and body position to follow a target rat in real time. Following the test rat induced fear. Authors also tested this robot with multiple rats on the arena showing the ability of the robot to continuously follow one rat while other two rats were present, suggesting its use for studying sociality in rats.

Earlier version of this robot, WR-4, is able to generate different types of behavior – friendly, stressful and neutral. Results show that rats exposed to robot mimicking stressful behavior decrease their activity and preference for the robot, whereas rats exposed to friendly robot exhibit friendly behavior (Shi et al., 2013).

3   Correlating behavior and neural activity

Many techniques are being used to record brain activity such as functional magnetic imaging, electroencephalography and magnetoencephalography. However, they do not allow for smaller scale resolution and only provide information about whole brain areas or their parts. Thus single unit recordings are of interest in many studies aiming to describe correlation of neurons with external events like behavioral tests described in previous chapter.

Single unit or cell recording is a method used to measure electro-physiological response of a single neuron. It has been used as a technique in neuroscience for more than 80 years, when Renshaw et al., 1940 used it to record pyramidal cells in the hippocampus using glass microelectrodes. John Eccles used single cell recording in his Nobel Prize awarded work in which he studied synaptic mechanism in motoneurons. In single cell recording, fine-tipped microelectrode is inserted in rat's brain to measure current flowing through the cell, which creates a changing voltage potential in and outside the cell. Fine tips are important to lessen the damage caused to the cell and increase the impedance. As of now, it is the only direct measure of neuronal activity capable of recording the cell activity anywhere in the brain, not being limited to the surface. Another huge advantage is high temporal resolution allowing us to record signals 1000 times per second. Biggest limitation of this technique is its invasiveness; brain tissue gets damaged when introducing the microelectrode in the brain.

Depending on where the electrode is positioned, unit activity can be recorded in intracellular or extracellular space. Intracellular unit recording provides more information on single cell discharge and can give information about resting membrane voltage, postsynaptic potentials and action potentials. However cells with large bodies are required for intracellular recording since recording from small neurons is difficult and should be supported with extracellular single unit records (Boulton, 1990). Extracellular recordings are much easier to obtain, especially in awake and moving animal. They do not damage the cell and can easily measure local field potential, which is dominated by summated synaptic potential.

Recently, multichannel recording has been used in many studies. Compared to single unit recording, it allows us to record multiple neurons close to each other, ranging from 400 to

50 μm away. Observing firing patterns of multiple cells in proximity can provide more information about function of small networks of neurons during various behavioral tasks. Multichannel recording allows examining neuronal connections and can show more complex pattern of neural activity.

Besides wide use in research, this method is also used in epileptic patients to help determine the position of epileptic foci.

4 Cells coding aspects of space – an overview

Focus of spatial navigation research lies in hippocampus. O'Keefe & Dostrovsky, 1971 recorded activity of hippocampal pyramidal cells in freely moving rat and identified place cells. A place cell only fires selectively when rat's head is in a certain area called a firing field of that particular place cell. This makes them directly related to a property of the outside world: animal's location. Different place cell become active at different places and the combinations of activity in many place cells creates and internal neural map representing a particular environment. Together place cells create a cognitive representation of a specific location in space known as cognitive map (O'Keefe and Nadel, 1978). Place cells have the ability to rapidly change their firing field – known as re-mapping when the animal enters a new environment or when the task is changed and are highly sensitive to changes in landmarks and context (Redish et al., 2000).

Another important type of cell that plays a role in spatial navigation is a grid cell found in entorhinal cortex. Grid cells collectively create a hexagonal pattern organizing environment into regular pattern of electric impulses from the neuron. Grid cells are of small and large range with their scale increasing from dorsal to ventral axis. In comparison to place cells, grid cells are much more rigid and universal in all environments, the same map is used repeatedly. Grid cells are also involved in measuring movement distance and thus provide a metric component to the spatial map in the hippocampus (Hafting et al., 2005).

Head direction cells are found in multiple brain regions (Taube et al., 2009; Yoder & Taube, 2009) and are not affected by hippocampus inactivation (Golob & Taube, 1999). These cells increase their firing rates when animal's head points in a specific direction, are mostly orientation specific and do not depend on location. Head direction cells fire at steady rate when the animal's head is facing the cell's preferred firing direction.

Boundary cells are found in hippocampus and respond to presence of an environmental boundary at a certain distance and direction from the animal. O'Keefe & Burgess, 1996 created a computational model describing boundary cells based on properties of place cells. Hypothetical boundary cells responded to environmental boundaries at particular distances and allocentric directions from the rat.

Together, place cells, grid cells, head direction cells and border cells create a complex network. 10% of cell population in medial entorhinal cortex consists of boundary cells, intermingled with grid cells and direction cells (Bjerknes et al., 2014). This network constitutes a comprehensive positioning system in the brain. However it still remains unclear how spatial information of not self, such as landmarks, moving objects, stable objects and conspecifics is represented in the hippocampus.

5   Neural coding of objects in space

Main focus of research in object location coding is aimed at hippocampus, entorhinal cortex and anterior cingulate cortex (ACC), in particular at activity of place cells in hippocampus. The idea is that place cells creating a cognitive map of environment code important objects or landmarks in the environment. Place cells in hippocampus are thought to primarily code the spatial location of objects and hippocampus also plays a role in object memory (Cohen et al., 2013). In general, objects with different properties are processed differently. Animals react differently to conspecifics, an inanimate object or a threat. Rats might process object location differently based on the task too. If the task requires the rat to navigating according to the object's position, rat has to make conscious effort to keep track of the object and pay attention to it. It is thus likely that place cells react differently depending on type of the object.

5.1 Place cells signal other rat's location in reward-based task

First category of often discussed objects is conspecifics. Is place cell firing affected by presence of different rat in the environment? Zynyuk et al., 2012 tested this by observing two freely moving rats confined to a small arena and recording place cell activity in the hippocampus. Changes in hippocampal mapping system were very weak after introducing the second rat despite initial tendency of rats to stay close together. However firing fields became less organized and weaker in the presence of the second rat, depending on distance of the two animals. Only one pyramidal cell firing manifested strong dependency on distance from the second rat. Another study done by von Heimendahl et al., 2012 showed no effect of another rat's presence on immediate early gene c-Fos expression in dorsal hippocampus. Social interaction only had effect on specific expression in amygdala. However, neuronal response was more modulated by inanimate objects.

Recent study by Danjo et al., 2018 tested neuronal representations of rat's position and other rat's position in CA1 region of the hippocampus. Unlike in previously mentioned studies, the test rat was required to make decisions based on other rat's trajectory. According to type of the task, the subject rat was rewarded for choosing the same or

opposite direction as the other rat in T-maze. In this type of task, authors described four different types of cells: own place fields, joint place fields, other's place fields, and common place fields indicating that hippocampus encodes some attributes of spatial location of other animals.

Easily noticeable difference between these studies is the behavioral task. Two studies that didn't find strong effect of another rat's presence didn't require the subject rat to continuously pay attention to the other rat's position or were in no way motivated to navigate in the environment according to the other rat. It was shown in other studies using inanimate object that firing field of many place cells only remapped when following the object was rewarded (Markus et al., 1995) or that the control spatial cues exert over place firing may depend on cognitive requirements, including reward association (Ježek et al., 2010).

5.2 Location of nonmoving objects is represented by place cell firing

How are place cells altered in presence of inanimate non-moving objects? Most studies agree that introducing a new object in the environment causes remapping of firing fields. Manns & Eichenbaum, 2009 recorded hippocampal pyramidal cells in a variation of object recognition task, which consisted of presenting new and familiar objects in different locations to a rat in multiple trials. Hippocampal representation of encounters with the same object in the same location was more similar to each other than with different objects in the same location whereas presentations of the same object in different locations were not similar. In addition, repetition of an object in the same location corresponded to increased information about object identity and moving the object to a different location corresponded to decreased information about the object's position. Their results thus suggest that objects were in fact represented as points of interest on the hippocampal cognitive map. Neural information structure of object encounters represented object location as the primary dimension of information and by coding object identity only secondarily.

Kim et al., 2015 recorded cells in CA1 region of the hippocampus before, during and after encounter with predatory robot situated remotely from the nest. Robot induced remapping of firing fields in its proximity, while cells remained stable in the nesting area. These effects were prevented by amygdala lesions which, considering importance of amygdala in fear signaling, suggests that amygdalar fear signaling influences the stability of place cells in hippocampus.

5.3 Hippocampal inactivation impairs avoidance of moving object

Environment we live in is very dynamic, animals need to monitor spatial properties of many moving objects like predators and conspecifics and organize their own spatial behavior accordingly. However, neural correlates of navigation around a moving object have received little attention and are still not understood. Based on the cognitive map theory, navigation to visible goals, in contrast to navigation to unmarked places defines by their relationship to distant landmarks, does not depend on hippocampal function (O'Keefe & Nadel, 1978; Telensky et al., 2011). Nevertheless, cognitive map theory lacks details about navigation relative to moving objects. Since this is a relatively unexplored topic, studies are aimed more on whole brain structures than single cell recordings.

For its importance in spatial navigation, Telensky et al., 2011 tested the role of hippocampus in enemy avoidance task. Rats were trained to avoid moving and stable robot on the arena. After sufficient training, hippocampus was bilaterally inactivated by tetrodotoxin (TTX) injection and animals were tested in their ability to avoid the robot. Surprisingly, TTX application impaired only avoidance of the moving robot while avoidance of the stable robot remained unaffected. Authors suggest that the decisive factor of hippocampus involvement is the need for continuous updating and not just the visibility of the target as is suggested in the cognitive map theory. This would explain impairment of avoidance seen only in the moving object paradigm.

Similar design was used in study by Svoboda et al., 2017 in which they tested role of ACC in avoidance of moving and stable object. This structure is a good candidate because in the brain it is located to combine emotional, visceral and highly processed cognitive input,

participates in conflict monitoring and ACC neurons respond to objects in the environment. As in previously mentioned studies, ACC was inactivated by TTX injection after sufficient training in the enemy avoidance task. TTX had no effect on slowly moving or stationary robot but impaired performance in moving robot version of this task, suggesting that the robot speed itself is the crucial factor determining recruitment of the ACC during robot avoidance behavior.

Studies concerning single cell recordings in hippocampus show remapping of firing fields only when rats acquired rewards based on their distance from a moving car (Markus et al., 1995). However cell firing did not signal location of the car itself (Markus et al., 1995; Ho et al., 2008).

6 Discussion

This work summarized recent findings in neural correlates of object location in rat's brain and behavioral tests used in this field.

Based on studies presented here, one of the important parameters affecting results of place cell firing in hippocampus appears to be the use of motivation. Place cells appear to correlate with changes in task, e.g. introducing objects, with higher intensity (Markus et al., 1995) when interaction with an object is rewarded or when the rat has to make decisions based on an object (navigation in enemy avoidance task).

It is not yet clear how the location of moving animate objects is coded in cell firing patterns. We have some evidence of cells coding other rat's position when acquiring the other rat's position was rewarded (Danjo et al., 2018), other studies using no reward motivation did not see any effect of conspecifics on place cells (von Heimendahl et al., 2012; Zynyuk et al., 2012).

According to cognitive map theory, location of objects in the environment should be coded in place cells firing. This was confirmed by Kim et al., 2015 and Manns & Eichenbaum, 2009. Avoiding visible targets shouldn't be dependent on hippocampus, however in study by Telensky et al., 2011, hippocampal inactivation impaired avoidance of moving enemy. Since avoiding of nonmoving enemy was affected by the inactivation, it appears that spatial navigation to visible targets is hippocampus dependant. Other studies confirmed remapping of hippocampal place cells in the presence of moving object (Markus et al., 1995; Ho et al., 2008), but didn't find any evidence of place cells coding the position of the moving object itself. It is possible that hippocampus is required in the avoidance of moving enemy for continues update and that the location of a moving object itself is coded in different manner than location of stable objects. Candidate for involvement in speed processing is also ACC, since inactivation of ACC impaired moving enemy avoidance (Svoboda et al., 2017).

 It would be interesting to see if T-maze task done by Danjo et al., 2018 is hippocampus dependant and also to observe place cells discharge in hippocampus and grid cells firing in entorhinal cortex in the enemy avoidance task. Based on Shi et al., 2013 and Kim et al., 2015, it appears that amygdala is important in tasks where the object mimics a predator and

evokes fear in the rat. Studies concerning on the effects of amygdala fear signaling might shed some light on how the location of a predator is coded in the brain.

Building on this work we have designed a study aiming to compare expression of immediate early genes in the hippocampus in the enemy avoidance task, using stable, slowly moving and moving variations of the task.

References

Bjerknes, T. L., Moser, E. I., & Moser, M. B. (2014). Representation of geometric borders in the developing rat. *Neuron*, *82*(1), 71–78. https://doi.org/10.1016/j.neuron.2014.02.014

Boulton, A. A. (1990). Neurophysiological techniques: applications to neural systems. Clifton, New Jersey: Humana Press. ISBN 978-1-59259-620-1

Choi, J.-S., & Kim, J. J. (2010). Amygdala regulates risk of predation in rats foraging in a dynamic fear environment. *Proceedings of the National Academy of Sciences*, *107*(50), 21773–21777. https://doi.org/10.1073/pnas.1010079108

Danjo, T., Toyoizumi, T., & Fujisawa, S. (2018). Spatial representations of self and other in the hippocampus. *Science*, *359*(6372), 213–218. https://doi.org/10.1126/science.aao3898

Fenton, A. A., & Muller, R. U. (1998). Place cell discharge is extremely variable during individual passes of the rat through the firing field. *Proceedings of the National Academy of Sciences*, *95*(6), 3182–3187. https://doi.org/10.1073/pnas.95.6.3182

Golob, E. J., & Taube, J. S. (1999). Head direction cells in rats with hippocampal or overlying neocortical lesions: evidence for impaired angular path integration. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *19*(16), 7198–7211.

Hafting, T., Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, *436*(7052), 801–806. https://doi.org/10.1038/nature03721

Ho, S. A., Hori, E., Kobayashi, T., Umeno, K., Tran, A. H., Ono, T., & Nishijo, H. (2008). Hippocampal place cell activity during chasing of a moving object associated with reward in rats. *Neuroscience*, *157*(1), 254–270. https://doi.org/10.1016/j.neuroscience.2008.09.004

Jankowski, M. M., & O'Mara, S. M. (2015). Dynamics of place, boundary and object encoding in rat anterior claustrum. *Frontiers in Behavioral Neuroscience*, *9*(October), 1–19. https://doi.org/10.3389/fnbeh.2015.00250

Ježek, K., Lee, B. B., Kelemen, E., McCarthy, K. M., McEwen, B. S., & Fenton, A. A. (2010). Stress-induced Out-of-context activation of memory. *PLoS Biology*, *8*(12). https://doi.org/10.1371/journal.pbio.1000570

Kim, E. J., Kong, M. S., Park, S. G., Mizumori, S. J. Y., Cho, J., & Kim, J. J. (2018). Dynamic coding of predatory information between the prelimbic cortex and lateral amygdala in foraging rats. *Science Advances*, *4*(4), 1–9. https://doi.org/10.1126/sciadv.aar7328

Kim, E. J., Park, M., Kong, M. S., Park, S. G., Cho, J., & Kim, J. J. (2015). Alterations of hippocampal place cells in foraging rats facing a predatory threat. *Current Biology*, *25*(10), 1362–1367. https://doi.org/10.1016/j.cub.2015.03.048

Manns, J. R., & Eichenbaum, H. (2009). A cognitive map for object memory in the hippocampus A cognitive map for object memory in the hippocampus, (404), 616–624. https://doi.org/10.1101/lm.1484509

Markus, E. J., Qin, Y. L., Leonard, B., Skaggs, W. E., McNaughton, B. L., & Barnes, C. A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *The Journal of Neuroscience*, *15*(11), 7079–7094. https://doi.org/10.1523/JNEUROSCI.15-11-07079.1995

O' Keefe, J., & Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature*. https://doi.org/10.1038/381425a0

O'Keefe, 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. https://doi.org/10.1016/0006-8993(71)90358-1

O'Keefe, J., & Nadel, L. (1978). The hippocampus as a cognitive map. Oxford: Oxford University Press. ISBN 0-19-857206-9

Redish, a D., Rosenzweig, E. S., Bohanick, J. D., McNaughton, B. L., & Barnes, C. a. (2000). Dynamics of hippocampal ensemble activity realignment: time versus space. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(24), 9298–9309. https://doi.org/20/24/9298 [pii]

Renshaw, B., Forbes, A., Morrison, B. R. (1939). Activity of Isocortex and Hippocampus: Electrical Studies with Micro-Electrodes. Journal of Neurophysiology. 3(1): 74-105.

hi, Q., Ishii, H., Kinoshita, S., Takanishi, A., Okabayashi, S., Iida, N., … Shibata, S. (2013). Modulation of rat behaviour by using a rat-like robot. *Bioinspiration and Biomimetics*, *8*(4). https://doi.org/10.1088/1748-3182/8/4/046002

Shi, Q., Ishii, H., Sugahara, Y., Takanishi, A., Huang, Q., & Fukuda, T. (2015). Design and Control of a Biomimetic Robotic Rat for Interaction with Laboratory Rats. *IEEE/ASME Transactions on Mechatronics*, *20*(4), 1832–1842. https://doi.org/10.1109/TMECH.2014.2356595

Svoboda, J., Lobellová, V., Popelíková, A., Ahuja, N., Kelemen, E., & Stuchlík, A. (2017). Transient inactivation of the anterior cingulate cortex in rats disrupts avoidance of a dynamic object. *Neurobiology of Learning and Memory*, *139*, 144–148. https://doi.org/10.1016/j.nlm.2017.01.003

Taube, J. S., Muller, R. U., & Ranck, J. B. (1990). Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *10*(2), 420–435. https://doi.org/10.1212/01.wnl.0000299117.48935.2e

Telensky, P., Svoboda, J., Blahna, K., Bures, J., Kubik, S., & Stuchlik, A. (2011). Functional inactivation of the rat hippocampus disrupts avoidance of a moving object. *Proceedings of the National Academy of Sciences*, *108*(13), 5414–5418. https://doi.org/10.1073/pnas.1102525108

Telensky, P., Svoboda, J., Pastalkova, E., Blahna, K., Bures, J., & Stuchlik, A. (2009). Enemy avoidance task: A novel behavioral paradigm for assessing spatial avoidance of a moving subject. *Journal of Neuroscience Methods*, *180*(1), 29–33. https://doi.org/10.1016/j.jneumeth.2009.02.010

von Heimendahl, M., Rao, R. P., & Brecht, M. (2012). Weak and Nondiscriminative Responses to Conspecifics in the Rat Hippocampus. *Journal of Neuroscience*, *32*(6), 2129–2141. https://doi.org/10.1523/JNEUROSCI.3812-11.2012

Yoder, R. M., & Taube, J. S. (2009). NIH Public Access, *29*(4), 1061–1076. https://doi.org/10.1523/JNEUROSCI.1679-08.2009.Head

Zynyuk, L., Huxter, J., Muller, R. U., & Fox, S. E. (2012). The presence of a second rat has only subtle effects on the location-specific firing of hippocampal place cells. *Hippocampus*, *22*(6), 1405–1416. https://doi.org/10.1002/hipo.20977