

Abstract representations of space in the mouse dentate gyrus

Felix Taschbach (f.taschbach@student.maastrichtuniversity.nl)

Maastricht University, Minderbroedersberg 4-6

Maastricht 6211 LK (Netherlands)

Fabio Stefanini (fs2545@cumc.columbia.edu)

Marcus K. Benna (mkb2162@columbia.edu)

Stefano Fusi (sf2237@columbia.edu)

Zuckerman Mind Brain and Behavior Institute, Columbia University, 3227 Broadway,
New York, NY 10027 (USA)

Abstract

The hippocampus is known to encode variables that are relevant for navigation, like the position of the animal. However, it is unclear whether its neural representation is the result of an abstraction process or it reflects the encoding of complex sensory experiences that determine unequivocally a particular location. To answer this question, we analyzed calcium imaging data from the dentate gyrus and CA1 of mice freely exploring an arena. Both the position and the direction of motion of the animal could be decoded with high accuracy. We then analyzed the geometry of the neural representations to determine whether these variables are represented in an abstract format. The analysis revealed that the direction of movement is abstract when the animal is at the center of the arena, but not in the vicinity of a wall. These results reveal qualitatively different geometries of the neural representations in these different locations which have been traditionally considered to have different behavioral valence for the animal. Our study represents a fundamental step towards the description of an abstract map of space in the hippocampus.

Keywords: Calcium Imaging; CA1; Dentate Gyrus; Hippocampus; Spatial Representations; Decoding; Abstraction

Since the proposal of a cognitive map (O'Keefe & Dostrovsky, 1971), the hippocampus has been studied as the main center for spatial representations. The main focus of the vast majority of these studies has been on 'place cells', i.e., cells that show a strong response when the animal is in a particular location in an environment. Initially these responses have been interpreted as an abstract representation of space, since they aren't obviously tight to any specific sensory stimulus or motor response. However, these responses could be due to the common features of sensory experiences generated at every passage through a particular location. In a recent model, these correlations have been exploited to generate a spatial map of an environment using exclusively sensory stimuli and motor responses (Benna & Fusi, 2019). This raises the question of whether spatial maps are a result of combinations of sensory stimuli or if the hippocampus maintains an abstract representation of space, i.e., a representation that allows to generalize information from one sensory experience to another without re-learning the metrics of the environment.

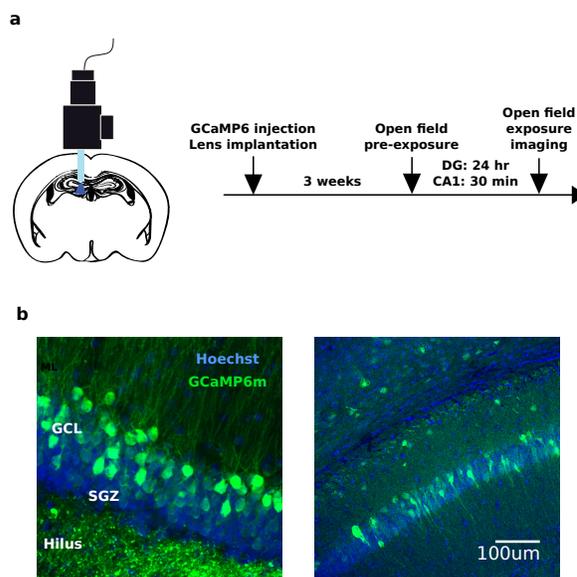


Figure 1: Experimental protocol. A virus encoding the calcium indicator GCaMP6m was injected into the dorsal DG in the DG mice, while a virus encoding GCaMP6f was used for the CA1 mice. A GRIN lens was then implanted and a baseplate was fixed to the skull of the mice at the desired imaging plane. GCaMP expression was examined three weeks after the surgery using a miniaturized microscope (Inscopix, Palo Alto, CA). b) DG recording site. GCL, granule cell layer; SGZ, subgranular zone. c) CA1 recording site. The figure has been adapted with permission from Stefanini et al. (2019).

To test this hypothesis, we took advantage of a dataset of calcium imaging recordings from mouse hippocampus in freely moving animals using a mini-endoscope (Inscopix, Palo Alto, CA). These recordings included neural activity from the dentate gyrus (DG) and CA1 regions of the hippocampus (Fig. 1). The DG is the first stage of processing of the hippocampal formation. It has been shown to encode space with high spatial and temporal precision (Stefanini et al., 2019; van Dijk & Fenton, 2018) and it has been implicated in pattern separation (Leutgeb, Leutgeb, Moser, & Moser, 2007; Bakker, Kirwan, Miller, & Stark, 2008; Danielson et al., 2017). While the CA1 is the most studied region in the hippocampus, relatively little

is known about how the DG granule cells represents spatial information. It has recently been shown that both these regions encode both the position of the animal and the movement direction in a distributed manner (Stefanini et al., 2019). We leveraged the ability to decode these two variables to study whether these two variables were represented in an abstract format.

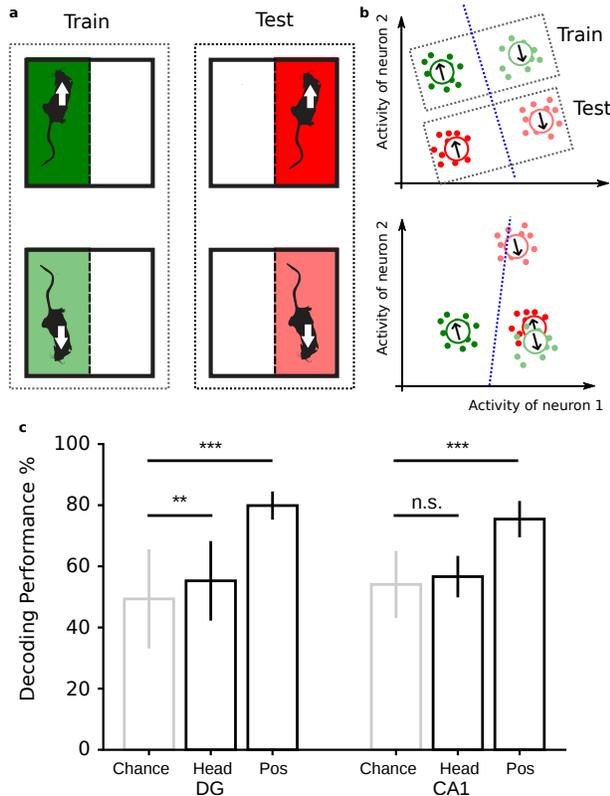


Figure 2: The Cross-Condition Generalization Performance (CCGP) (Bernardi et al., 2018). a) A mouse moving upwards (left) or downwards (right) through one of two locations highlighted in red and green. The decoder is trained on movement direction in one location (red, top) and tested on the other location (green, bottom). The CCGP is the performance of the tested conditions. b) One possible geometry of the neural representation in the case in which both movement direction and position are represented in abstract format. The performance of a direction decoder trained on one location and tested on the other location would be high. c) An example of unstructured geometry whereby decoding movement direction in A does not generalize well to location B.

One way to measure if a variable is represented in an abstract format is to introduce the Cross-Condition Generalization Performance (CCGP) (Bernardi et al., 2018). This quantity measures how the neural representation of one variable, for example the animal's instantaneous position, is stable across different conditions, for instance across movement directions. Hence, our strategy was to train a decoder to decode

the animal position on the time bins when it was moving in one direction and test it on the time bins corresponding to it moving in the opposite direction (see figure 2). Vice versa, we could train the decoder to distinguish two different movement directions in different locations in an environment, as described in the example cartoon of Fig. 2.

To estimate CCGP we divided the arena in two halves and focused on two opposite directions of motion (North-South, East-West). We then trained a linear decoder to discriminate whether the mouse was in one half of the arena or the other using time bins corresponding to movement in one direction and tested it on the rest of the time bins. We followed similar procedures adopted in Stefanini et al. (2019) and used a support-vector machine (SVM) with a linear kernel and excluded time bins corresponding to immobility. To control for the possibility that a higher than chance decoding performance was not due to abstraction but rather to a random displacement of the neural representations across different movement directions, we compared the decoding performance to a distribution of random models generated by shuffling the original representations of position while keeping the structure of the data within each condition (see - Bernardi et al. (2018)). In both DG and CA1 areas of the hippocampus we found a higher than chance CCGP for position but not for head direction (Fig. 2c). This is a strong indication that some form of abstraction exists in the way the hippocampus represents the position of the animal.

To further verify that the effect was not due to the vicinity of the walls, we looked at the influence of the walls of the arena on the representation of space and head direction. In order to maximize the effect, we focused on two opposite walls and separated the data into direction of motion parallel or perpendicular to these walls and we removed time bins in which the mouse was close to either of the other two walls (Fig. 3a). We then looked at pairs of regions elongated along the direction of the walls, at various distances and equally centered in the arena. We used data within these regions to estimate CCGP for movement direction across regions and CCGP for position (in which area the animal was) across different movement directions. For perpendicular directions of motion, we found a significantly higher than chance CCGP at all distances from the wall in two mice. For parallel directions of motion instead the same was true only when the regions were close to the center of the arena but not when the animal was close to the walls. In two mice this effect was even stronger and resulted in a weakly lower than chance CCGP performance (Fig. 3b-c).

A lower than chance performance could be due to an inversion of representations from one side of the arena to the other. In terms of neural representations, this would mean that the representations of upward motion in one region would be on the same side of the hyperplane of the representations for downward motion in the other region of the arena. To verify this hypothesis we focused on the time bins in which the mouse was close to the walls of the arena, re-labeled the data for direction of motion in "wall on left" and "wall on right", corre-

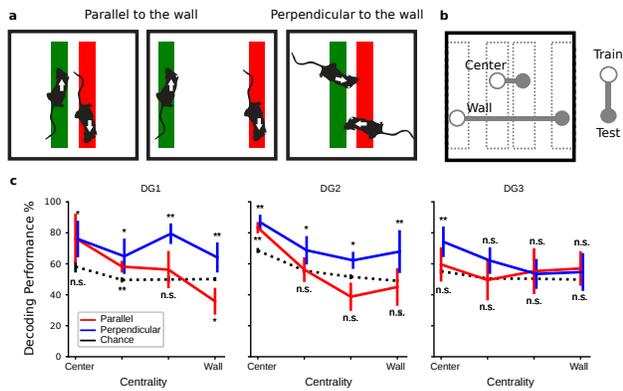


Figure 3: Ego-centric system in the periphery of the arena and allocentric system in the center. a) Schematic of how the arena was separated into different regions of interest with a width of 5 cm, from the closest ones to the center (Center) to the ones closest to the walls (Wall). Linear decoders were trained on distinguishing movement direction (either moving North vs. South, or West vs. East) in one region and were then tested on a region at the same distance to the center of the arena. b) The dotted lines highlight regions at different distances from the center as used in c. c) Decoding performance of movement direction in the different regions of interest. Black dotted lines correspond to a chance level computed by shuffling the movement direction labels in a way that preserves autocorrelation of the original data (mean \pm st.dev.). Red lines: CCGP for movement direction parallel to the chosen two opposite walls. Blue lines: CCGP for perpendicular movement directions. (Two-sided Mann-Whitney U test for significance, *** $p < 0.001$, ** $p < 0.01$).

sponding to position of the closest wall with respect to the animal, and computed CCGP on this new dataset (Fig. 4a). We then trained a linear decoder on pairs of adjacent corners and tested it on the other two (Fig. 4b). In line with our prediction, CCGP was higher than chance for the two animals for which we formulated the prediction (Fig. 4c). We repeated the analysis on CA1 and we did not find similar levels of abstraction (Fig. 4d).

Our results suggest that spatial representations in DG show some degree of abstraction that allow a decoder to generalize information across different conditions. This is true in regions of the arena that are further away from the walls, where presumably an absolute map of the environment is required to successfully navigate. Our data also show that in regions of the arena close to the wall spatial representations don't generalize across walls. We interpret these results as an evidence that the hippocampus, at least at the level of the DG, represents spatial information in both an ego-centric way, i.e., in relation to the local experience of the animal, and in an allocentric way, i.e., on the basis of an abstract representation of space. The ability of the hippocampus to rapidly switch among spatial maps has been observed in other studies (Jezek et al.,

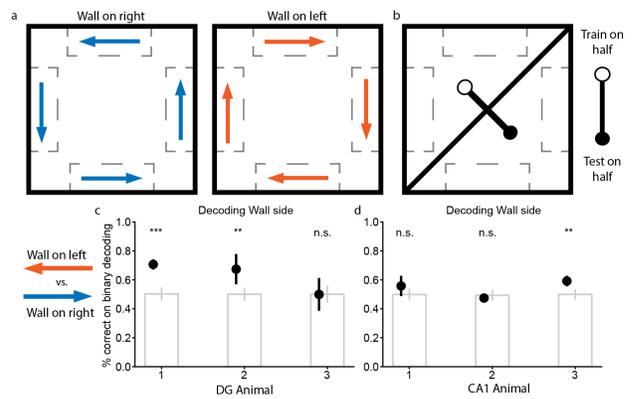


Figure 4: Wall side generalizes across different walls in DG but not in CA1. a,b) Regions of the arena considered in the analysis of wall side generalization, extending 5 cm into the arena. We relabelled time bins in which the mouse was moving parallel to a wall depending on which side the wall was on with respect to the mouse movement direction. b) Schematic showing a CCGP analysis on wall side. The data while the mouse was in either of two highlighted regions on one side of the diagonal was used as train set while the remaining two regions defined the test set. This was repeated for each combination of two walls. c,d) Decoding wall side performance in DG and CA1. The gray bars were obtained by reversing the wall side labels, rolling them over by a random amount and then training the linear decoders as described above (mean across different choices of training and test set \pm st. dev.). (Two-sided Mann-Whitney U test, *** $p < 0.001$, ** $p < 0.01$).

2011; van Dijk & Fenton, 2018; Kelemen & Fenton, 2010). However, in our work we observe a different phenomenon in which spatial representations with qualitatively different intrinsic geometries are in place in different regions of the environment. In particular, our results on the generalization of movement direction across different walls suggests a strong influence of sensory input in the vicinity of a wall. This seems to be in line with the hypothesis of an anxiogenic value attributed to the central part of an open field, the exploration of which is typically associated with a more audacious and fearless emotional state of the animal (Jimenez et al., 2018).

To our knowledge, since the seminal studies of O'Keefe in the Seventies, our study is the first of its kind in that it attempts to identify an abstract representation of a map of the environment, i.e., a "cognitive map". This map may be useful not only to represent just the animal's instantaneous position. Indeed, it may be related to the value associated to different locations in an environment, a quality strictly related to memory and apparent in both our data and in previous studies that considered the instantaneous representation of space in relation to a shock-related location (Kelemen & Fenton, 2010). This map may therefore have different properties across different behavioral contexts and the ability to decode position from neural activities may be insufficient to explain these fundamental dif-

ferences. By studying the geometry of spatial representations it is possible to access properties of hippocampal processing that are important for episodic memory formation.

Acknowledgments

SF, MKB and FS were supported by NSF's NeuroNex program award DBI-1707398, the Gatsby Charitable Foundation, the Simons Foundation, the Schwartz foundation, the Kavli foundation.

References

- Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal ca3 and dentate gyrus. *Science*, *319*(5870), 1640–1642.
- Benna, M. K., & Fusi, S. (2019). Are place cells just memory cells? memory compression leads to spatial tuning and history dependence. *bioRxiv*, 624239.
- Bernardi, S., Benna, M. K., Rigotti, M., Munuera, J., Fusi, S., & Salzman, D. (2018). The geometry of abstraction in hippocampus and prefrontal cortex. *bioRxiv*, 408633.
- Danielson, N. B., Turi, G. F., Ladow, M., Chavlis, S., Petrantonakis, P. C., Poirazi, P., & Losonczy, A. (2017). In vivo imaging of dentate gyrus mossy cells in behaving mice. *Neuron*, *93*(3), 552–559.
- Jezek, K., Henriksen, E. J., Treves, A., Moser, E. I., & Moser, M.-B. (2011). Theta-paced flickering between place-cell maps in the hippocampus. *Nature*, *478*(7368), 246.
- Jimenez, J. C., Su, K., Goldberg, A. R., Luna, V. M., Biane, J. S., Ordek, G., ... others (2018). Anxiety cells in a hippocampal-hypothalamic circuit. *Neuron*, *97*(3), 670–683.
- Kelemen, E., & Fenton, A. A. (2010). Dynamic grouping of hippocampal neural activity during cognitive control of two spatial frames. *PLoS biology*, *8*(6), e1000403.
- Leutgeb, J. K., Leutgeb, S., Moser, M.-B., & Moser, E. I. (2007). Pattern separation in the dentate gyrus and ca3 of the hippocampus. *science*, *315*(5814), 961–966.
- O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map: preliminary evidence from unit activity in the freely-moving rat. *Brain research*.
- Stefanini, F., Kheirbek, M. A., Kushnir, L., Jimenez, J. C., Jennings, J. H., Stuber, G. D., ... Fusi, S. (2019). A distributed neural code in the dentate gyrus and ca1. *bioRxiv*. doi: 10.1101/292953
- van Dijk, M. T., & Fenton, A. A. (2018). On how the dentate gyrus contributes to memory discrimination. *Neuron*, *98*(4), 832–845.