signaling in HD striatum parallels studies that demonstrate a role for this receptor in other neuropsychiatric disorders (Fujii and Kunugi, 2009) and provides a novel, promising set of therapeutic targets for the treatment of HD.

**REFERENCES**

Altar, C.A., Cai, N., Bliven, T., Juhasz, M., Conner, J.M., Acheson, A.L., Lindsay, R.M., and Wiegand, S.J. (1997). Nature *389*, 856–860.

Fujii, T., and Kunugi, H. (2009). Curr. Mol. Pharmacol. *2*, 70–76.

Gauthier, L.R., Charrin, B.C., Borrell-Pagès, M., Dompierre, J.P., Rangone, H., Cordelières, F.P., De Mey, J., MacDonald, M.E., Lessmann, V., Humbert, S., and Saudou, F. (2004). Cell *118*, 127–138.

Gerfen, C.R., and Surmeier, D.J. (2011). Annu. Rev. Neurosci. *34*, 441–466.

Gray, M., Shirasaki, D.I., Cepeda, C., André, V.M., Wilburn, B., Lu, X.H., Tao, J., Yamazaki, I., Li, S.H., Sun, Y.E., et al. (2008). J. Neurosci. *28*, 6182–6195.

Menalled, L.B., Kudwa, A.E., Miller, S., Fitzpatrick, J., Watson-Johnson, J., Keating, N., Ruiz, M., Mushlin, R., Alosio, W., McConnell, K., et al. (2012). PLoS ONE *7*, e49838.

Milnerwood, A.J., Gladding, C.M., Pouladi, M.A., Kaufman, A.M., Hines, R.M., Boyd, J.D., Ko, R.W., Vasuta, O.C., Graham, R.K., Hayden, M.R., et al. (2010). Neuron *65*, 178–190.

Parsons, M.P., and Raymond, L.A. (2014). Neuron *82*, 279–293.

Plotkin, J.L., Day, M., Peterson, J.D., Xie, Z., Kress, G.J., Rafalovich, I., Kondapalli, J., Gertler, T.S., Flajolet, M., Greengard, P., et al. (2014). Neuron *83*, this issue, 178–188.

Pouladi, M.A., Morton, A.J., and Hayden, M.R. (2013). Nat. Rev. Neurosci. *14*, 708–721.

Raymond, L.A., André, V.M., Cepeda, C., Gladding, C.M., Milnerwood, A.J., and Levine, M.S. (2011). Neuroscience *198*, 252–273.

Simmons, D.A., Belichenko, N.P., Yang, T., Condon, C., Monbureau, M., Shamloo, M., Jing, D., Massa, S.M., and Longo, F.M. (2013). J. Neurosci. *33*, 18712–18727.

The Huntington's Disease Collaborative Research Group (1993). Cell *72*, 971–983.

Zuccato, C., Ciammola, A., Rigamonti, D., Leavitt, B.R., Goffredo, D., Conti, L., MacDonald, M.E., Friedlander, R.M., Silani, V., Hayden, M.R., et al. (2001). Science *293*, 493–498.

Zuccato, C., Marullo, M., Conforti, P., MacDonald, M.E., Tartari, M., and Cattaneo, E. (2008). Brain Pathol. *18*, 225–238.

# Learning by Example in the Hippocampus

Joseph O'Neill[1] and Jozsef Csicsvari[1,*]
[1]Institute of Science and Technology Austria, Am Campus 1, A-3400 Klosterneuburg, Austria
*Correspondence: jozsef.csicsvari@ist.ac.at
http://dx.doi.org/10.1016/j.neuron.2014.06.013

Learning can be facilitated by previous knowledge when it is organized into relational representations forming schemas. In this issue of *Neuron*, McKenzie et al. (2014) demonstrate that the hippocampus rapidly forms interrelated, hierarchical memory representations to support schema-based learning.

One of the timely questions of hippocampal research is to understand how learning influences hippocampal neuronal representations. New information may be incorporated into already existing representations or entirely new representations could be formed to prevent interference with previously formed memories. Schema-based learning would require the formation of interrelated memory representation into which new information could be rapidly assimilated (Tse et al., 2011). In this issue of *Neuron*, McKenzie et al. (2014) show that hippocampal cognitive maps can form such representations: different representations can be hierarchically organized, incorporating both spatial and task-related mnemonic information.

Using two different environments linked by a tunnel (Figure 1A), McKenzie et al. (2014) probed how hippocampal firing patterns reflect learned associations between objects, the presence of a reward, and environment (or context). Rats had to learn that in the first environment, one of two objects (flower pots, scented with different odors and containing different digging media) was rewarded, even when the position of the objects was swapped around. In the second environment, the rules were reversed, so that the other object was rewarded. Once learned, animals were able to associate the presence of a reward with new objects over far fewer trials, consistent with a schema-based learning. How does the hippocampal network encode different features of this task? And how is new information incorporated into previously formed representations?

To answer these questions, McKenzie et al. (2014) recorded from CA3 and CA1 pyramidal cells as rats performed this task, with two sets of objects (AB or CD), in randomly interleaved trials, focusing on the firing patterns around the point at which the animal sampled the object (Figure 1A). The majority of recorded cells showed differential firing responses, depending on the location or identity of the object sampled. In addition to position, many cells also encoded information about the object, including the object's identity, the set (AB or CD) to which it belonged, and whether the object was baited or not (valence). In this way, hippocampal population activity, or "cell assemblies" of such neurones, can collectively represent the spatial and nonspatial features of the task.

If cell-assembly coding of memory traces reflect distinct and separate representations, one might expect the
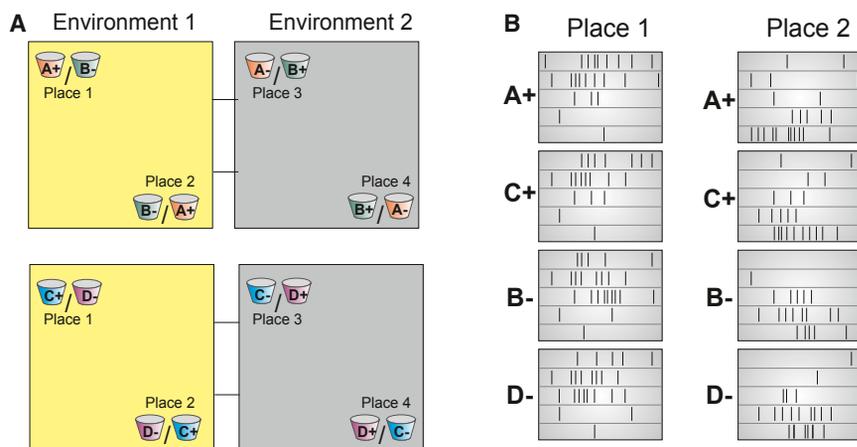
CrossMark

**Figure 1. Cell Assembly Patterns during the Object Association Task**
(A) Illustration of the object association paradigm. In environment 1, reward could be found inside object A and C with object B and D unbaited. Objects are presented in opposite corners (Place 1 and Place 2), but their positions were randomly swapped across trials. In environment 2, the reward value of the objects was switched.
(B) Illustration of the cell assembly firing during the exploration of objects. Only activity in environment 1 is shown. The parallel firing of five cells is illustrated in a raster plot marking the firing time of cells during an object exploration. Note that the assembly patterns are different in the two places, while firing of objects with similar reward value (AC and BD) is more similar than the ones with different reward values.

formation of divergent assembly firing patterns during the sampling of different object/place combinations. Alternatively, if information about objects and place are incorporated into existing representations, reflecting a relational coding structure, assembly patterns might overlap and diverge according to a hierarchical structure. Consistent with this second hypothesis, they found that cell assemblies expressed increasing separation when representations of objects and places were compared (Figure 1B). Assemblies representing objects in different environments were the most divergent. Surprisingly, objects associated with the same reward value had more similar place-associated population code than objects with different reward value. Overall, firing patterns showed increasing similarity with environment, position, valance, and item.

To what degree can these findings be explained by what we know about the place-related firing of hippocampal cells? It is expected that cell assemblies representing different environments are more separated than assemblies representing different places in the same environment. This may be partially due to a larger number of cells firing at both reward locations within a given environment than across all four. Moreover, firing rates diverge be-

tween environments, particularly in the CA3, giving rise to subsets that are active solely in one of the two environments. It is not clear, however, whether the increased assembly separation across environments observed in the McKenzie et al. (2014) study could be explained by these factors or whether task parameters such as the reversal of object salience across environments strengthened this separation.

The finding that object-related population code was more similar than place-related code could be explained by previously observed partial remapping of place fields or firing rate. Previous work showed that changes in environmental features such as the color of the enclosure or its smell can lead to partial remapping in which only some of the place cells form new place fields (Anderson and Jeffery, 2003). Other studies reported that place cells may change their firing rate inside their place fields due to partial environmental cue changes or due to task parameter changes (Allen et al., 2012; Leutgeb et al., 2005). Presenting different objects in the environment could be considered as a change in the environment, which in turn could trigger partial or rate remapping, leading to object-associated changes in the firing of place cells. Moreover, it has been shown that presentations of objects in a familiar environment

can alter place cell activity (Lenck-Santini et al., 2005; O'Keefe and Nadel, 1978). To infer to what degree object-related changes in this task were triggered by environmental feature changes or by task-related factors, one could examine the activity of place cells outside the locations of object. This would answer whether object-related firing changes were solely restricted to the object locations or whether place cells altered their firing patterns throughout the environment. Yet, the fact that objects with opposing reward value led to more distinct assemblies than those with similar value suggests that the cell assembly separation cannot be explained solely by changes in the environment per se. Previous work showed that some place cells form new place fields at goal locations including those where reward can be found (Dupret et al., 2010; Hollup et al., 2001). However, reward locations marked by guide posts do not lead to the remapping of place cells in a highly familiar environment. Therefore, goal-related remapping cannot fully explain the object valence coding observed here; hippocampal cells clearly signaled object-reward associations and differentiated objects with different reward value.

This study was able to provide additional evidence for task-associated object coding in the hippocampus by examining the temporal expression of cell assemblies during object exploration. They show that cell assemblies encoded location in the beginning of the object-sampling periods, while object identity was encoded later, and object valence expressed last. Considering that object valence was expressed last, one may expect that the temporal expression of assemblies may reflect planning and decision processes, which ultimately require the recall of object-reward associations. It is possible that changes in network oscillations during object exploration may have signaled the shifts in cell assembly expression from places to object features. While place-related activity is strongly linked to theta-band (5–10 Hz) oscillations, faster, gamma-band (40–100 Hz) or ripple (150–200 Hz) oscillations may have been prominent during the object-related coding stages. Indeed, gamma oscillations are implicated in memory encoding and recall stages (Colgin et al.,

2009). Moreover, ripple oscillations have been linked to planning processes and memory recall (Carr et al., 2011; Csicsvari and Dupret, 2014; Pfeiffer and Foster, 2013). However, cell assemblies reflecting different hippocampal maps can flicker across theta oscillatory cycles during learning (Dupret et al., 2013) and transiently expressed cell assemblies during theta oscillations may have mnemonic roles (Gupta et al., 2012). Monitoring neuronal oscillations could provide further insight into circuit events that enable the expression of hierarchically organized cognitive maps in the hippocampus.

Note that the location of the object was not relevant for choosing the object with the reward; however, recognizing the environment was important. Therefore, the cell assembly code may not separate places better than the reward value of objects. Indeed, they showed that the population code of assemblies was not always separated best by place: assembly patterns of the same object at different locations were as different as assembly patterns of different valence objects at the same location. This suggests that hippocampal assemblies, while underpinned by spatial coding, may adjust their code metric to the decision conditions by incorporating factors that are needed to solve a behavioral task.

How do the hierarchic hippocampal representations facilitate schema-based learning? In schema-based learning, animals often acquire the generalized rules of a task while learning it. Later this can help them to rapidly learn a similar task (Tse et al., 2011). In this work, the animals were first taught to differentiate the reward value of object by choosing between two objects (XY), and, in later days, trained to select first from a new set of objects (AB), and after 3 days of training, from an additional set (CD). Indeed, animals performed better on the first day when a new set was introduced (both AB and CD), than during the first session when the original set (XY) was encountered. This suggests that the animals indeed used a schema-based learning in this task. Importantly, this work was able to monitor hippocampal neuronal activity during learning of the two new sets of objects.

McKenzie et al. (2014) were able to monitor the activity of a limited number of cells over consecutive days and examine how they developed firing in relation to the new object set CD, as compared to the previously learned set AB. They showed that population code of new objects were more similar to the previously learned object with the same valence than the one with different valence. Such a relationship remained in later days as well when both objects sets were presented. Therefore, the work suggests that, in schema-based learning, new hippocampal representations are generated so that they remain similar to representations of other tasks of the same schema. This enables the use of similar representations for different tasks that use the same schema, while also encoding individual differences in task variants.

Investigating how hippocampal representations are updated during learning can provide deep insight into the formation of memory representations in the brain. They can highlight mechanisms that underlie the reorganization of existing memory representations to incorporate new knowledge. This work was able to demonstrate that schema-based learning paradigms are efficient tools to study such questions and reveal some of the rules governing how the hippocampal cognitive map builds up interrelated representations for efficient learning.

**REFERENCES**

Allen, K., Rawlins, J.N.P., Bannerman, D.M., and Csicsvari, J. (2012). J. Neurosci. *32*, 14752–14766.

Anderson, M.I., and Jeffery, K.J. (2003). J. Neurosci. *23*, 8827–8835.

Carr, M.F., Jadhav, S.P., and Frank, L.M. (2011). Nat. Neurosci. *14*, 147–153.

Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.B., and Moser, E.I. (2009). Nature *462*, 353–357.

Csicsvari, J., and Dupret, D. (2014). Philos. Trans. R. Soc. Lond. B Biol. Sci. *369*, 20120528.

Dupret, D., O'Neill, J., Pleydell-Bouverie, B., and Csicsvari, J. (2010). Nat. Neurosci. *13*, 995–1002.

Dupret, D., O'Neill, J., and Csicsvari, J. (2013). Neuron *78*, 166–180.

Gupta, A.S., van der Meer, M.A.A., Touretzky, D.S., and Redish, A.D. (2012). Nat. Neurosci. *15*, 1032–1039.

Hollup, S.A., Molden, S., Donnett, J.G., Moser, M.B., and Moser, E.I. (2001). J. Neurosci. *21*, 1635–1644.

Lenck-Santini, P.-P., Rivard, B., Muller, R.U., and Poucet, B. (2005). Hippocampus *15*, 356–369.

Leutgeb, S., Leutgeb, J.K., Barnes, C.A., Moser, E.I., McNaughton, B.L., and Moser, M.B. (2005). Science *309*, 619–623.

McKenzie, S., Frank, A.J., Kinsky, N.R., Porter, B., Rivière, P.D., and Eichenbaum, H. (2014). Neuron *83*, this issue, 202–215.

O'Keefe, J., and Nadel, L. (1978). Hippocampus as a Cognitive Map. (Oxford: Clarindon).

Pfeiffer, B.E., and Foster, D.J. (2013). Nature *497*, 74–79.

Tse, D., Takeuchi, T., Kakeyama, M., Kajii, Y., Okuno, H., Tohyama, C., Bito, H., and Morris, R.G.M. (2011). Science *333*, 891–895.