Rate Remapping: When the Code Goes beyond Space

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DOI 10.1016/j.neuron.2010.12.011

Rate remapping is a conjunctive code that potentially enables hippocampal place cells to jointly represent spatial and nonspatial information. In this issue of *Neuron*, Rennó-Costa et al. introduce a theoretical model wherein the convergence of the medial and lateral entorhinal excitatory inputs, combined with local inhibition, explains hippocampal rate remapping.

Deciphering the neural code has triggered many investigations and debates over the past decades. Both firing rate and temporally governed spike patterns of individual neurons or neuronal ensembles have been shown to provide means to encode information in brain circuits. In hippocampal principal cells, the distribution of firing rate across an environment is skewed such that each cell, referred to as a "place cell," tends to fire in a specific location (spatial firing field or "place field"), leading to the classical view that hippocampal place maps represent space in the form of a rate code. Hippocampal place maps, however, are flexible: changing environments and task demands lead to "remapping" phenomena in which the neural code is altered to mirror the animal's experience. It has recently been shown that when there are certain sensory changes in the environment, place cells maintain their location-specific activity, but exhibit modulation of the firing rate within that location (Leutgeb et al., 2005; Muller, 1996). This "rate remapping" may reflect the simultaneous encoding of spatial and nonspatial information. In this issue of *Neuron*, Rennó-Costa et al. provide a theoretical model to quantitatively account for hippocampal rate remapping by fluctuations in the nonspatial input to cells of the dentate gyrus (DG) (Rennó-Costa et al., 2010). In addition to presenting this model and its implications in this preview, we also explain why rate remapping represents a unique neural code and discuss how this code must ultimately be linked to temporal coding and network oscillations.

In their influential book, O'Keefe and Nadel (1978) proposed that "the hippocampus is the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated." Indeed, hippocampal neural activity has also been associated with a variety of nonspatial stimuli, including the sensory features of the environment, task-contingent demands, and the representation of temporal delay (Eichenbaum, 2004; O'Keefe and Nadel, 1978; Pastalkova et al., 2008). This highlights the possibility that place cell firing can be related to perceptual, behavioral, or cognitive events, in conjunction (or not) with the location where these events have been experienced. Thus, hippocampal place cells could serve as building blocks to generate multimodal representations necessary to guide behavior within a spatial framework.

The hippocampus represents different environments by means of distinct combinations of firing patterns: the assemblies of place cells that encode overlapping locations in one environment will not be the same when the animal is moved to another. Thus, from one environment to another, the hippocampal spatial map undergoes complete reorganization, a process referred to as global (or complete) remapping (Leutgeb et al., 2005; Muller, 1996). In rate remapping, however, place cells in the CA3 and DG regions of the hippocampus (and to some extent the CA1 region) display substantial changes in their firing rate without changing their place field location. This form of remapping has been reported when animals explore distinct recording enclosures in an otherwise constant environment (Leutgeb et al., 2005, 2007). In such cases, the combinations of cells that encode similar places remains the same, leaving the spatial maps intact. However, out of the cells that encode the same location, only a selected subgroup may exhibit strong firing with the given nonspatial environmental features. Thus, the firing rate of cells inside their place field can encode additional information to reflect nonspatial changes to the sensory environment. In this way, rate remapping could occur when distinct sensory experiences have to be discriminated in the same environment.

In this issue, Rennó-Costa et al. provide a computational model to explain the circuit mechanism of rate remapping in the DG (Rennó-Costa et al., 2010): they suggest that hippocampal rate remapping may derive from the convergence of spatial signals from the medial entorhinal cortex (MEC) and nonspatial signals from the lateral entorhinal cortex (LEC). Many MEC neurons exhibit spatially related firing, including grid cells characterized by multiple spatial fields arranged over the entire environment in a hexagonal grid (Hafting et al., 2005). By contrast, most neurons in the superficial layers of the LEC display only a weak spatial selectivity, which may indicate the influence of a nonspatial sensory drive (Hargreaves et al., 2005). Given that conditions that yield rate remapping in the hippocampus do not cause significant alterations to MEC grid cell firing patterns (neither realignment of the grid fields, nor statistically significant rate changes between the grid fields; Fyhn et al., 2007), it is assumed that LEC inputs are responsible for rate remapping (Leutgeb et al., 2007). Indeed, this assumption is supported by the finding that the model can best account for rate remapping in the DG by the combination of stable MEC and changing LEC inputs.

The Leutgeb et al. (2007) study reported that DG cells had multiple place fields and

that in response to a change in sensory inputs, individual place fields exhibited unrelated rate changes. To simulate DG cell responses, Rennó-Costa et al. first modeled well-tuned spatial firing fields of MEC grid cells and low spatial selectivity fields for LEC neurons. Modeled grid fields were not influenced by changes in sensory inputs, in accordance with the Fyhn et al. (2007) study, while distinct LEC rate maps were generated for different sensory conditions. The firing responses (and the spatial distributions) of DG cells were then simulated by summing the excitatory inputs from a randomly selected number of MEC and LEC rate maps, together with a gamma frequency-based feedback inhibition system. Under such parameters, the spatial firing of the modeled DG cells was originated from the MEC, while rate remapping effect was determined by LEC representations of the sensory environment. Although illustrated for DG cells, similar mechanisms might underlie CA3 and CA1 rate remapping as well. Future multiunit recordings and perhaps inactivation of the LEC can experimentally test the most important prediction of the model, namely that the LEC drives rate remapping. In addition, further refinement of the model could incorporate oscillatory activity and particularly theta phase precession. As we discuss below, such oscillation-driven temporal factors may be essential for rate remapping as a reliable coding scheme in the hippocampus.

One might consider that rate remapping supplements a rate-coding scheme in which different nonspatial features are encoded at the population level by distinct rate distributions among place cells representing the same location. However, rate code alone may not be able to accurately encode nonspatial features due to its coarseness: the fact that the firing rate is not homogenous inside the place field but increases toward its center causes ambiguities in the code. Let us assume that high peak-firing in the place field represents nonspatial feature A, whereas reduced peak-firing in the same location reflects feature B. When that cell fires at the reduced rate, we might assume that it is signaling feature B. However, the same low rate can also occur in the presence of feature A,

provided that the animal is only in the periphery of its place field (where rate is lower than at the peak by default). Theta phase precession enables a form of temporal code that can disambiguate this. The timing of a cell's spike relative to the theta rhythm holds information about the relative location of the animal within its place field: as the animal passes through the field, spike timing gradually shifts to earlier theta phases (O'Keefe and Recce, 1993). In one-dimensional mazes, where this phenomenon was first observed, theta phase is directly related to the animal's location. In this condition, theta phase precession has been suggested to provide a temporal code for place, allowing firing rate to encode additional nonspatial features (Huxter et al., 2003). Theta phase precession is also present in 2D environments, where theta phase can identify whether cells fire at the center or the periphery of their place fields (Huxter et al., 2008). To return to our example, the theta spike timing can code whether the animal is at the center or at the periphery of the place field, and can therefore discriminate which nonspatial feature was present. Thus, a theta-based temporal code may be required to reliably decode the rate remapping code for nonspatial information.

Rennó-Costa et al. highlight important roles for feedback inhibition and gamma oscillatory control in rate remapping. Gamma oscillations are thought to reflect rhythmic inhibition and have been suggested to occur during memory acquisition or recall periods (Colgin et al., 2009). Therefore, the encoding of nonspatial mnemonic features by the rate modulation of place cells might be expected to take place preferentially during gamma oscillations. Moreover, gamma epochs often occur superimposed on theta oscillations, and at the same theta phase at which many place cells tend to fire at their highest rate (Senior et al., 2008). As a result, place cells that fire together during theta-modulated gamma oscillations may encode together nonspatial features of the environment. Under this scenario, which is also suggested by the model, only one cell assembly that encodes nonspatial features can escape from gamma-related feedback inhibition at a time. Moreover, gamma oscillations

may play a role in removing coding ambiguities caused by low rate firing at the place field periphery. In CA1, gamma modulated cells can be separated into two populations, only one of which participates in theta phase precession; the other fires exclusively when the animal is in the center of their field (Senior et al., 2008). Thus gamma mechanisms attenuate the firing of these latter cells at the place field periphery, freeing them to encode features through rate remapping.

In summary, hippocampal neurons may encode a combination of spatial and nonspatial information by integration of LEC and MEC inputs. Moreover, it is possible that neuronal oscillations and in particular theta and gamma oscillations are essential to the coordination of this dual coding scheme. Future work is needed to test the validity of these ideas.

REFERENCES

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.

Eichenbaum, H. (2004). Neuron *44*, 109–120.

Fyhn, M., Hafting, T., Treves, A., Moser, M.B., and Moser, E.I. (2007). Nature *446*, 190–194.

Hafting, T., Fyhn, M., Molden, S., Moser, M.B., and Moser, E.I. (2005). Nature *436*, 801–806.

Hargreaves, E.L., Rao, G., Lee, I., and Knierim, J.J. (2005). Science *308*, 1792–1794.

Huxter, J., Burgess, N., and O'Keefe, J. (2003). Nature *425*, 828–832.

Huxter, J.R., Senior, T.J., Allen, K., and Csicsvari, J. (2008). Nat. Neurosci. *11*, 587–594.

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

Leutgeb, J.K., Leutgeb, S., Moser, M.B., and Moser, E.I. (2007). Science *315*, 961–966.

Muller, R. (1996). Neuron *17*, 813–822.

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

O'Keefe, J., and Recce, M.L. (1993). Hippocampus *3*, 317–330.

Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, G. (2008). Science *321*, 1322–1327.

Rennó-Costa, C., Lisman, J.E., and Verschure, P. (2010). Neuron *68*, this issue, 1051–1058.

Senior, T.J., Huxter, J.R., Allen, K., O'Neill, J., and Csicsvari, J. (2008). J. Neurosci. *28*, 2274–2286.