 SPATIAL PROCESSING

Connecting up the grid

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The periodic firing of grid cells is determined by an animal's movement. Indeed, each grid cell generates a hexagonal, grid-like firing pattern that, when combined with other grid cell firing patterns, maps the local environment, allowing self-localization. How such patterns are generated has been unclear. Now, two new studies provide insight into how grid cells are connected locally in the medial entorhinal cortex (MEC) and how they are influenced by inputs from the hippocampus.

Neighbouring MEC layer II grid cells generate firing patterns that exhibit similar spacing and orientation, suggesting that adjacent grid cells may influence each other through local microcircuits. To explore this connectivity, Couey *et al.* conducted simultaneous whole-cell recordings in clusters of three or more MEC layer II neurons in rat brain slices. In total, they assessed the connectivity between over 600 pairs of stellate cells, which are the candidate grid cells in this region.

Stimulation of one stellate cell per cluster carried a 4% chance of eliciting a response in a paired cell, and these responses were all inhibitory. By contrast, activation of three stellate cells per four-neuron cluster led to a 64% chance of a response in the unstimulated cell. Again, however, the observed responses were all inhibitory. In both cases, the connectivity pattern was bimodal, with cells having either strong connections or no connections. These findings indicate that stellate cells

of MEC layer II are connected by interneurons that are activated by the synchronous activity of the stellate cells. Indeed, further recordings revealed that the stellate cells showed high connectivity with local fast-spiking interneurons.

On the basis of these findings, the authors constructed a theoretical network in which adjacent stellate cells were connected to each other via inhibitory connections with unstructured all-or-none connectivity. This model was able to generate stable grid-like firing patterns resembling the experimental data when each stellate cell also received a constant, uniform excitatory input. These findings shed light on the underlying grid cell local microcircuitry in MEC layer II, but where might the excitatory inputs originate?

Hippocampus place cells fire when an animal is in a specific location. They receive input from the MEC, suggesting that place cell firing is determined by grid cell outputs. Grid cells, however, may also depend on place cell outputs, and it is this poorly understood interaction that Bonnevie *et al.* focused on in their study.

The authors assessed the influence of hippocampal backprojections on grid cells by recording cells in the rat MEC–parasubiculum before and after muscimol-induced hippocampal inactivation. The recorded cells included grid cells and head-direction cells, which fire when an animal is pointing in a specific direction.

As the hippocampal firing rate decreased, grid patterns became disrupted. These were restored, however, alongside CA1 firing rates 6 hours after muscimol infusion, suggesting that hippocampal backprojections are necessary for grid formation. Interestingly, as the grids broke down, most grid cells showed directional tuning, resembling the firing patterns of the head-direction cells.

The authors subsequently explored the effect of external excitatory drive in the aforementioned computational model of the MEC circuitry. They assumed that the hippocampal backprojections provided the external excitatory inputs to the grid cells. The effects of adjusting the strength of hippocampal input on grid cells as a virtual rat navigated a virtual environment were then assessed. Replicating the experimental data, a decrease in hippocampal input strength was associated with disruption of grid formation and an increase in head-direction tuning in grid cells.

Together, these studies reveal that grid formation in the MEC is dependent on both a local inhibitory network, comprising recurrent connections between stellate cells and fast-spiking interneurons, and excitatory backprojections originating in the hippocampus.

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ORIGINAL RESEARCH PAPERS Couey, J. J. *et al.* Recurrent inhibitory circuitry as a mechanism for grid formation. *Nature Neurosci.* 20 Jan 2013 (doi:10.1038/nrn.3310) | Bonnevie, T. *et al.* Grid cells require excitatory drive from the hippocampus. *Nature Neurosci.* 20 Jan 2013 (doi:10.1038/nrn.3311)