Grid cells in an inhibitory network

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Grid cells have been proposed to reflect competitive interactions in inhibitory neural networks. Experimental results obtained using optogenetics to identify spikes emitted specifically by parvalbumin interneurons now constrain the mechanisms by which such networks could give rise to grid cells.

How do you know where you are? As far back as the early days of experimental psychology, Tolman suggested that animals and humans form internal representations of the spatial environment and use such representations to navigate from one place to another[1]. Modern neuroscience has provided evidence for such a neural representation of space[2,3]. The representation includes a variety of functionally specialized cell types, such as place cells, which fire when animals are at a certain location[2,4], and grid cells, which fire at multiple locations that, for each individual cell, define a hexagonal lattice[3,5]. Place cells are abundant in the hippocampus; grid cells, in the medial entorhinal cortex (MEC). The discovery of these cell types deep in the association cortices immediately raised questions about how such well-defined correlates of the external world come to be, so many synapses away from any specific sensory input. A common idea is that place cells are derived from grid cells[3,6,7] and that grid patterns arise intrinsically in the MEC during competitive interactions between interconnected cell populations via mechanisms referred to as attractor dynamics[6–8]. In agreement with the predominantly inhibitory nature of some types of MEC connectivity, inhibitory interconnections have been assigned a critical role in several theoretical models of grid cells[8–10]. In this issue of *Nature Neuroscience*, Buetfering *et al.*[11] explore the spatial firing properties of one major type of inhibitory interneuron, parvalbumin-expressing GABAergic cells (PV^+ cells), in the MEC. Their findings pave the way for a better understanding of the local circuitry in the entorhinal cortex and have important implications for the implementation of inhibitory attractor dynamics in the grid-cell system.

To investigate spatial properties and connectivity patterns of interneurons in the MEC, Buetfering *et al.*[11] used a combination of optogenetic and electrophysiological methods. The authors virally expressed channelrhodopsin-2 (ChR2) selectively in PV^+ interneurons in the MEC of PV-Cre mice and implanted tetrodes and an optic fiber in the same area. PV^+ interneurons could then be identified as cells that responded instantaneously to blue-wavelength light pulses delivered locally through the fiber. In this way, the authors were able, unequivocally, to determine the firing properties of PV^+ neurons. The analysis is the first of its kind to evaluate the spatial selectivity of PV^+ cells, their interaction with various functional cells types in MEC layer II and the influence of the activity of PV^+ cells on the spatial firing pattern of entorhinal excitatory cells.

The study reports several interesting observations. First, the authors show that the degree of spatial selectivity in PV^+ cells varies across a wide spectrum, with some cells showing practically no spatial bias and others firing preferentially and reliably at certain locations, although the firing fields were rarely as constrained as those of place cells and grid cells. Spatially selective PV^+ cells often showed multiple firing fields, but the firing patterns were almost always aperiodic. The aperiodic nature of firing fields in PV^+ cells may have implications for mechanisms of grid cell formation in the MEC. In attractor models of grid cells, cells are arranged on a two-dimensional lattice in which neighboring cells have similar grid phases (that is, they fire at similar locations). Each cell is connected preferentially to nearby cells on the lattice; cells with larger separations have progressively weaker connections. Such a connectivity pattern is necessary for the formation of spatially confined firing (referred to as a 'bump'). In the earliest models[6,7], connections were thought to be excitatory; however, paired recordings from entorhinal stellate cells, which include at least a major subset of the grid cells, showed that recurrent excitatory connections are almost absent in this network[8,12]. This led to the development of models in which grid cells with similar grid phase are linked instead via inhibitory interneurons. All of these more recent models showed that, in the presence of an external excitatory drive, inhibition is sufficient for grid patterns to evolve[7–9]. The description of firing patterns of PV^+ cells by Buetfering *et al.*[11] adds substance to discussions about the validity of these inhibitory attractor models.

The most straightforward observation by Buetfering *et al.*[11] is the lack of PV^+ cells with sharp and confined periodic firing fields. This is in contrast to what would be expected from the simplest implementations of the inhibitory attractor network models for grid cells (**Fig. 1a**). Here a grid cell recruits an inhibitory interneuron to exert inhibition on other grid cells. The inhibitory neuron itself expresses grid-like firing by inheriting it from the grid cell from which it receives input. Conversely, if the inhibition is mediated by direct connections from inhibitory cells to grid cells, the PV^+ cell should show an inverted hexagonal firing pattern compared with the grid cell (**Fig. 1b**). Buetfering *et al.*[11] found that, at least for the subset of PV^+ interneurons, these two possibilities do not hold. However, these circuitries are not the only ways by which interneurons might be activated in a grid-cell circuit. Inhibitory neurons may be tonically discharged by other sources of input, with only small changes in

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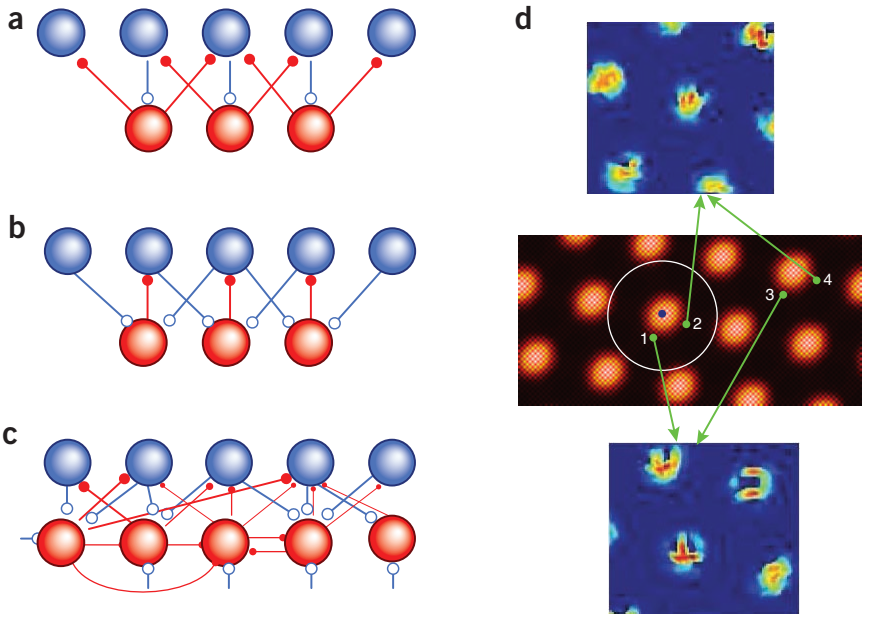

Figure 1 Alternative implementations of inhibitory connectivity in attractor models of grid cells. (**a**) Each grid cell (large blue circle) makes an excitatory connection to an inhibitory neuron (large red circle). Recruitment of the interneuron causes inhibition of other grid cells. Axons of grid cells and interneurons are shown in blue and red, respectively. Small circles indicate synapses. In this scenario, the inhibitory neuron inherits the spatial firing map of the grid cell that projects to it and it should show a grid-like firing pattern. This coupling pattern is ruled out by the results of Buetfering *et al.*[11]. (**b**) Each grid cell receives inhibitory input from an inhibitory neuron that receives input from a spectrum of grid cells. In this case, the inhibitory interneuron will fire out of spatial phase from the grid cell, thereby showing an inverted grid firing map. This pattern is also ruled out by the results of Buetfering *et al.*[11]. (**c**) The effective inhibition can be a consequence of network level processing by the inhibitory circuitry possibly involving lateral connections and time-coordinated spike patterns. The size of small circles indicates synaptic strength. (**d**) Inhibitory attractor network and rate maps for pairs of cells at different locations in an inhibitory attractor network. Top and bottom, color-coded firing rate maps expected in a square environment for grid cells in two different regions of the attractor network. Red indicates a high firing rate, blue a low firing rate. Middle, color-coded activity in the inhibitory attractor network, with neurons arranged according to grid phase (that is, location of grid nodes). Red and yellow indicate high activity. Each grid cell in the network receives input from neighboring cells in the neural lattice. This connectivity, combined with nonspatial external drive, generates a stable grid-like activity pattern on the network that, when translated across the network in accordance with the animal's movement in the environment, is reflected in the spatial firing pattern of neurons. The blue dot indicates the location of an example cell. Green dots indicate location of four other cells, two of which (1 and 2) have inhibitory connections to the blue cell and two of which (3 and 4) do not. The white circle indicates the radius of inhibition received by the blue cell. Arrows point to expected rate maps for the four example cells. The rate maps can be identical at distant locations of the network, so long as the phase of the grid is the same (cells 1 and 3 have a common grid phase; cells 2 and 4 also have a common phase, different from that of cells 1 and 3). This makes it difficult or impossible to detect statistical differences in the similarity of the rate maps of cells projecting to a grid cell (inside the white circle) and cells not projecting to it (outside the circle).

firing rate following inputs from particular grid cells. Or the effective inhibition may be a consequence of a network-wide processing in which inhibitory neurons receive input from many grid cells as well as from each other, such that, in the end, they inhibit the right cell at the right position (**Fig. 1c**). Given that many PV^+ cells carry substantial spatial information, this is certainly a possibility. Finally, a grid cell may modulate the activity of two or more inhibitory neurons to make them more synchronized. This may affect their inhibitory impact on their postsynaptic targets, without much influence on the firing rates of the interneurons. Most computational models of grid cells do not explicitly model how the inhibition is mediated; they focus only on effective inhibition[8,9]. To determine how the inhibition is actually implemented in the network requires more experimental data.

The second theoretically interesting part of the study by Buetfering *et al.*[11] is the evaluation of the functional properties of neurons that project synaptically to the PV^+ neurons. The authors cross-correlated spike patterns from pairs of simultaneously recorded PV^+ cells and principal cells, taking a peak at short latency in the cross-correlogram to indicate the presence of a strong excitatory synapse between the two cells. They found that grid cells formed the main group of cells with short-latency peak correlations with PV^+ cells. They also found that individual PV^+ cells cross-correlated with grid cells that varied substantially in grid phase: that is, the actual firing locations of these grid cells covered all possible locations. Taken at face value, the heterogeneity of grid-cell inputs is in disagreement with the preferential coupling of interneurons to grid cells with similar grid phases required by the inhibitory attractor models.

However, as acknowledged by the authors, cross-correlograms cannot be taken as direct evidence of synaptic connections. Using the presence or absence of a short-latency peak in cross-correlograms to infer a connection or lack thereof may be a good first-order approximation, but it is likely to contain an unknown quantity of false positives or negatives. For example, short-latency peaks would also show up in cross-correlograms if cell pairs were activated by a common input and one of the cells was activated at slightly longer latency than the other because of intrinsic synaptic properties or differences in local circuit modulation. In simulated high-conductance states of cortical networks in which the connections are known, the peaks of the average cross-correlation between connected and unconnected pairs of neurons do differ, but the variation in cross-correlation functions within each group can be large, making it difficult to conclusively relate cross-correlograms to connectivity[13]. In the study by Buetfering *et al.*[11], only 1–3% of the cell pairs had cross-correlograms with short-latency peaks. It remains to be determined how many of these peaks reflected actual synaptic connections and what proportion of those connected cells were from grid cells with similar grid phases.

Finally, if we assume for a moment that individual PV^+ cells do receive inputs from grid cells with a broad spectrum of grid phases, the cross-correlation findings are still not necessarily incompatible with inhibitory attractor network models. Buetfering *et al.*[11] calculated the spatial correlation (map similarity) of pairs of grid cells whose cross-correlations with a given PV^+ cell showed a peak at short latencies (putatively connected cells) and pairs of cells that showed no peak (putatively unconnected cells). The distributions of map similarity in the two groups of cell pairs were found to be statistically indistinguishable, suggesting at first glance that grid inputs to PV^+ cells are not more similar than any combination of grid cells in the rest of the population. However, this interpretation is only valid if the attractor

network has a single bump of activity. If the attractor network has multiple bumps, the distribution of map similarities between grid cells that project to a third cell and those that do not may indeed be very similar (**Fig. 1d**). Each neuron receives input from a region that is comparable in radius to the distance between the bumps of activity. Within this circular area, cell pairs have a given distribution of phase similarities. The important point is that it is possible to find an equal number of cell pairs outside the circle (not projecting to the third cell) with the same spatial rate maps as the 'inside' pair. These 'outside' cell pairs are located in a different part of the network, but because firing patterns across the network are periodic, the outside pair may nonetheless fire at locations identical to those of the inside pair. Consequently, the rate-map similarities will be very similar for projecting and non-projecting cells, as seen in the data.

Understanding the circuitry involved in the generation of spatially selective cells in the medial entorhinal cortex is an important problem. The study from Buetfering *et al.*[11] is the first to characterize unequivocally the firing properties of one subclass of entorhinal interneurons, although this population is itself likely to be heterogeneous morphologically, anatomically and functionally[14]. Their approach is enormously useful as a way to unwind the functional circuitry of the MEC, with its multiplicity of cell types. The power of such experimental tools may be further enhanced by new methods of statistical inference of network connectivity that go beyond analyzing pairwise correlations[15].

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Astrocytes go awry in Huntington's disease

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It is widely believed that Huntington's disease is driven exclusively by neuronal dysfunction. Work now challenges this view, showing that mutant huntingtin in astrocytes leads to dysregulation of extracellular K^+.

Huntington's disease is a rare neurodegenerative disorder with a variety of symptoms, most notably uncontrolled movements (called chorea) in the early stages of the disease[1]. Woody Guthrie, the famed folk singer, died of Huntington's disease. Over two decades ago, it was discovered that this disease is caused by the expansion of a CAG repeat domain in the huntingtin (*Htt*) gene. The resulting dysfunction has long been thought to be strictly neuronal in nature. However, in this issue of *Nature Neuroscience*, Tong *et al.*[2] provide compelling evidence that mutant huntingtin (mHtt) triggers downregulation of a key potassium channel in striatal astrocytes, potentially driving excitotoxic damage to neuronal circuits. This insight reframes our understanding of the pathogenesis of this disease.

Although huntingtin is ubiquitously expressed in the cells of the brain, the pathology in patients with Huntington's disease is most prominent in the striatum, a part of the brain that is involved in the control of volitional movement and habits[3,4]. Because the principal neurons of the striatum, spiny projection neurons (SPNs), wither and die in patients, they have been the focus of researchers in the field from the beginning. Although it is clear that the accumulation of mHtt in SPNs could be responsible for their atrophy and ultimate death, there have been hints that glia might be abetting this process rather than simply being innocent bystanders. There are three main classes of glia: oligodendrocytes, microglia and astrocytes. Microglia are highly mobile immune cells in the brain, ridding it of debris and helping to remodel neural circuits. Astrocytes are the ubiquitous 'glue' that holds the tissue together and keep it working properly. For example, astrocytes regulate the concentration of ions and neurotransmitters in the extracellular space to prevent the products of neural activity from building up and interfering with network function, a bit like a housekeeper who vacuums and washes the dishes after a party.

Studies some years ago had shown that astrocytes in patients accumulate mHtt, just like neurons, and that expressing mHtt in them compromises their ability to remove glutamate from the extracellular space, leading to the proposition that they could be promoting striatal excitotoxicity—long thought to drive pathogenesis in Huntington's disease[5–7]. But what has been lacking is a demonstration that astrocytes contribute to pathogenesis in mouse models that mimic the human condition. This fundamental gap is filled by the work of Tong *et al.*[2]. In the most extensively studied Huntington's disease model, the R6/2 mouse[8], the authors found that the onset of motor symptoms was tightly correlated with depolarization of striatal astrocytes. Surprisingly, given the widespread expression of the mHtt fragment in this model, the change in astrocyte physiology appeared to be specific to the striatum, as it was not seen in hippocampus. The authors traced the depolarization back to a reduction in current through a constitutively active astrocytic potassium channel (Kir4.1) that is thought to help keep extracellular K^+ low and neurons hyperpolarized (**Fig. 1**). As predicted from this deficit, extracellular K^+ in the striatum of R6/2 mice was elevated and SPNs were depolarized. The depolarization was not dramatic, but it was enough to substantially increase their excitability.

What is the connection between mHtt and astrocyte expression of Kir4.1? One of the

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