

Disrupting the grid cells' need for speed

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Abstract

Hinman et al., demonstrate the presence of two speed signals in the rodent medial entorhinal cortex (mEC) that are differentially affected by muscimol inactivation of medial septum. The results reveal important constraints on several computational models of grid cell firing.

The ability to accurately determine spatial location is a vital process for mobile organisms. Sensory perception of immediately available environmental features, be they visual landmarks or olfactory signals, are sufficient to guide navigational behaviour. Indeed, it is possible to predict the responses of a broad range of spatial cells to the manipulation of such cues. In conditions where external sensory information is unreliable or absent it is possible to estimate changes in self-location on the basis of vestibular, proprioceptive and motor efference signalling of self-motion. This process, often referred to as 'path integration' (PI) or spatial updating, represents changes in spatial location based on a cumulative estimate of the distance and direction moved.

Since their discovery over a decade ago, grid cells in the medial entorhinal cortex (mEC; Hafting et al., 2005) have been proposed as a possible neural substrate for PI. Grid cells are defined by spatial firing fields organised into a regular triangular lattice that uniformly covers an environment. The grid can be quantified by its orientation with respect to the environment, the distance between the firing fields (scale) and the spatial offset (or phase) of the firing fields with respect to the environment. In addition to the regular periodic firing patterns, the consistent phase relationship between pairs of grid cells when the animal is moved to a new environment (Yoon et al., 2013) strongly hints that an internally generated mechanism underlies the generation of the grid pattern.

Many computational models of grid cell firing explicitly involve path integration mechanisms to create the characteristic spatial distribution of firing fields. The source of directional information used in these models is usually derived from the firing of head direction cells (HDCs) found in many brain structures (including the mEC) which signal the orientation of the animals head in the horizontal plane. In parallel to translational path integration, head-direction cells appear to combine integration of angular velocity signals with environmental cues to orientation, such as visual landmarks. The angular offset between pairs of HDCs is consistent across different environments, similarly to the spatial phases of grid cells, again implying an internally generated mechanism.

There is a broad consensus that the stability of the relative spatial tuning with populations of HDCs and with populations of grid cells reflects the presence of recurrent connectivity. The effect of this connectivity is to create a single coherent 'bump' of activity across the population (if imagined as topographically laid out), as captured by the 'continuous attractor' theory (Zhang, 1996). For HDCs, the circuit performing angular path integration is reasonably well established, see Taube (2007) for a review. However, for grid cells the circuit performing translational path integration remains a

topic of much interest, and this is addressed by Hinman et al.

Computational models of grid cell firing based on PI require an input conveying the speed of motion, as well as its direction, so velocity can be integrated to give displacement. Speed information has long been known to be present in the wider hippocampal network, and most attention has focussed on neurons whose firing rate increases with running speed. For example, the deeper layers of mEC contain 'conjunctive' grid cells whose firing is modulated by both head-direction and running speed (Sargolini et al., 2006). These cells provide the perfect substrate to shift the activity bump in a continuous attractor network to track the movement of the animal, and interneurons whose firing rate increases with running speed have been reported in the mEC (Kropff et al., 2015) as the source of the speed signal. The information on running speed is likely to arise from the medial septum, where cells have been found whose activity causally controls running speed (Fuhrmann et al., 2015).

However, a second possible source of velocity information is the movement-related theta rhythm. This is a 4-10Hz oscillation in the hippocampal local field potential (LFP) seen whenever the animal is in motion, and whose frequency increases with running speed. The generation of this signal depends on the medial septum and the entorhinal cortex. Of potential functional importance, place and grid cells fire bursts of action potentials at a slightly higher frequency, so that the LFP phase of firing reliably signals distance travelled through the firing field, an effect referred to as 'theta phase precession' (Hafting et al., 2008).

Hinman et al., followed up the finding that inactivation of the medial septum specifically disrupts the firing patterns of grid cells in mEC (Brandon et al., 2011). To identify the specific medial septal signal required by the grid cells, they studied the effect of medial septal inactivation on both types of speed signal in the mEC. Here, under normal conditions, running speed correlates with both the firing rates and with the theta-band frequency of modulation of firing rates in many mEC cell types. Both types of speed signal were present in all the cell types analysed (grid cells, HDCs, conjunctive grid cells and interneurons) and both signals could be present in the same cell. Critically, these two signals were affected differently by muscimol inactivation of medial septum, a manipulation known to result in the break-down of grid cell firing (Brandon et al., 2011). While the firing rate to running speed signal increased in strength, the intrinsic theta frequency / running speed relationship significantly decreased.

Thus the results suggest that the medial septum provides a speed signal to the grid cells whose interruption during medial septum inactivation causes the break-down in grid cell firing patterns, and that the critical speed information may be carried by theta rhythmicity rather than firing rate. Accordingly, it may be that coding of speed and direction by subtle changes in burst frequency allows a natural integration into a phase code for location (Burgess, 2008). This model predicts 'velocity-controlled oscillators' whose burst frequency has a linear dependence on running speed and cosine dependence on direction, with evidence that 'theta cells' found throughout the hippocampal system provide this signal (Welday et al., 2011). This 'oscillatory interference' model explains the presence of theta phase precession, and the correlation between grid cell firing and theta rhythmicity during medial septal inactivation. Importantly, grid cell firing results from coincident firing caused by systematic changes in the relative phases of firing, and so may generalise to bats and humans in which a strong constant frequency 'theta' oscillation is not seen.

In continuous attractor models, the bump of activity is shifted by the conjunctive (grid, speed and head-direction) cells to perform translational path integration. The existence of these conjunctive cells is powerful evidence for the attractor models, but they do not explain the dependence of grid cell firing on theta rhythmicity during medial septal inactivation, the non-linear dependence of firing rate with running speed (Hinman et al.) or the discrepancy between head-direction and

movement direction.

In conclusion, Hinman et al., provide a fascinating and provocative first insight into the detail of what it is that the medial septum does for grid cells, focussing on speed signalling, and raises plenty of more general questions for future research.

Acknowledgements. We thank the Wellcome Trust for funding this work.

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