Experience-dependent rescaling of entorhinal grids

Caswell Barry[1–4], Robin Hayman[3,4], Neil Burgess[1,2] & Kathryn J Jeffery[3,4]

The firing pattern of entorhinal 'grid cells' is thought to provide an intrinsic metric for space. We report a strong experience-dependent environmental influence: the spatial scales of the grids (which are aligned and have fixed relative sizes within each animal) vary parametrically with changes to a familiar environment's size and shape. Thus grid scale reflects an interaction between intrinsic, path-integrative calculation of location and learned associations to the external environment.

'Grid cells' in dorsolateral medial entorhinal cortex (dlMEC) of freely moving rats show regular grid-like patterns of firing across the environment[1] (**Fig. 1**). These are thought to provide an absolute metric whereby an animal can update its own location using self-motion information ('path integration')[2–6]. Accordingly, grid cells may provide the path-integrative component to the representation of self-location shown by hippocampal place cells[2–4]. Despite their apparent intrinsic metric, grid cell firing is reproducible across trials[1], indicating an association to environmental information possibly mediated by feedback from place cells whose unitary firing locations facilitate association to location-specific sensory information[2]. Contrary to this proposition, although place cell firing responds parametrically to deformations of the environment[7–9], initial reports suggest that grid cell firing does not[1].

Here we show that grid cell firing patterns do distort parametrically in response to deformation of a familiar enclosure. We recorded grid cells from the superficial and deep layers of dlMEC (**Supplementary Figs. 1** and **2** online) while rats foraged in a rectangular enclosure formed by moveable walls, situated within a cue-rich laboratory. (All work was conducted according to institutional and national ethical guidelines as outlined in the UK Animals (Scientific Procedures) Act, 1986.) Animals experienced a familiar configuration (100 × 100 cm square for three animals, 70 × 100 cm rectangle for three animals) for at least 20 min on three separate days before recording. Each recording session consisted of five 20-min trials: one in the familiar configuration, then three probe trials with the enclosure shortened or extended along one or both dimensions, and finally one in the familiar configuration again. We calculated the 'horizontal' (dimension 1) and 'vertical' (dimension 2) transformation required to match each probe trial firing rate map onto the combined baseline firing rate map (**Fig. 1**; **Supplementary Methods** online).

Grid cells in rats familiar with the large square ($n = 28$) or vertical rectangle ($n = 10$) changed in response to environmental deformation, by rescaling in the same direction but by a lesser amount (**Fig. 1**; **Supplementary Fig. 3** online). For deformation along both dimensions, grids showed horizontal and vertical changes simultaneously. When the environment was deformed along one dimension, there was a hint that, as well as rescaling along that dimension, grids also showed a reaction in the opposite direction along the orthogonal dimension (**Fig. 2**).

To establish its overall magnitude in each rat, we normalized rescaling along each dimension to a percentage of the environmental change along that dimension, and averaged over all cells and manipulations. Averaged over the six rats (**Supplementary Table 1** online), grids rescaled by 47.9% of the change made to the enclosure ($t_5 = 4.96$, $P = 0.004$) and also rescaled by 7.9% in the opposite direction along the unchanged dimension ($t_5 = -2.92$, $P = 0.033$). Consistent with the

Figure 1 Rescaling of grid cell firing in response to environmental deformation. (**a,b**) Action potentials (colored dots) superimposed on the animal's path (black) reveal the spatial periodicity characteristic of grid cells. Trials 1 and 5 were recorded in a familiar baseline configuration (red outline: large square, **a**, or vertical rectangle, **b**). (**c–f**) Firing rate maps (**c,e**) were constructed from **a** and **b** (red, high; blue, low). The baseline rate maps (red outline) combine trials 1 and 5. Numeric labels show, for each dimension, the transformation of the rate map relative to baseline (>1 = expansion, <1 = contraction). Spatial autocorrelograms (**d,f**) were constructed from rate maps **c** and **e**; the six peaks around the origin in the baseline (and corresponding peaks in probe trials) are indicated for comparison.
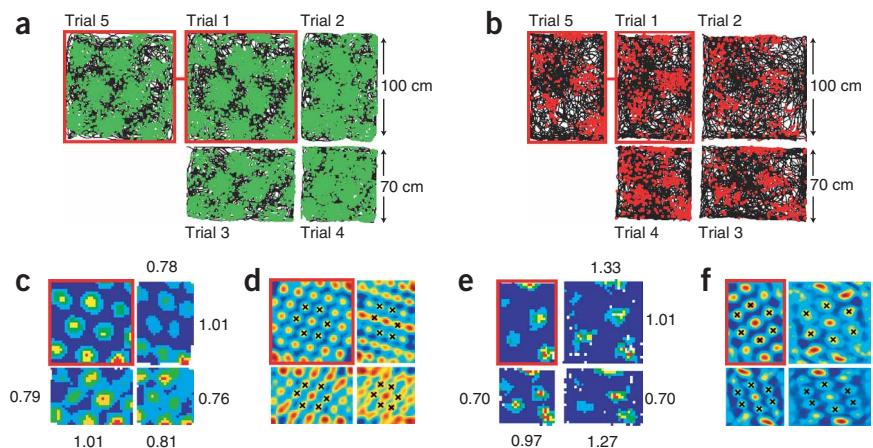
[1]Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. [2]Department of Anatomy, University College London, Gower St., London WC1E 6BT, UK. [3]Institute of Behavioural Neuroscience and [4]Department of Psychology, University College London, 26 Bedford Way, London WC1H 0AP, UK.
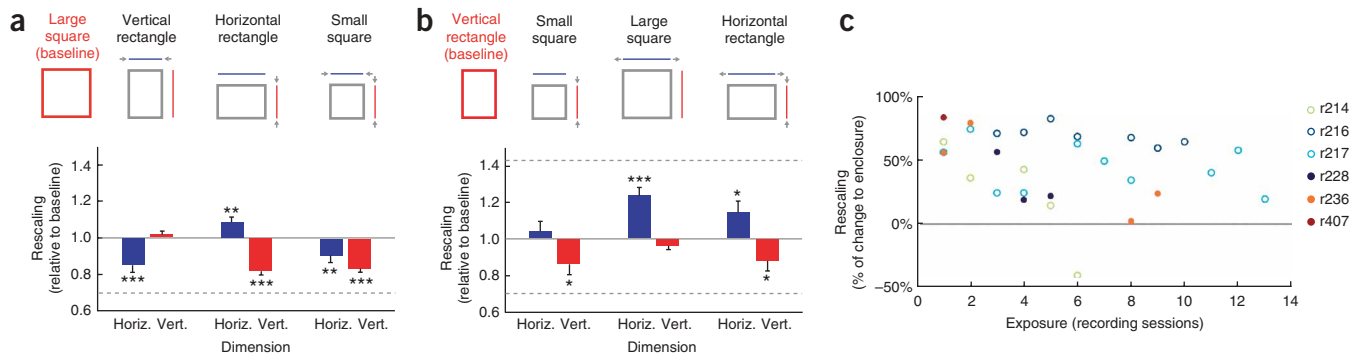
Figure 2 Magnitude of rescaling and effect of experience. (**a,b**) The magnitude of grid rescaling is shown for each dimension for each transformation in rats familiar with the large square (**a**) or vertical rectangle (**b**) (mean over cells ± s.e.m.; dotted line, magnitude of environmental rescaling). Colors indicate individual rats. t-tests compare observed values to an expected mean of 1 (one-tailed along the transformed dimension, two-tailed otherwise; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). (**c**) Decrease in rescaling with experience of probe trials. Mean normalized rescaling values (percentage of change to environmental size) per rat are shown for each recording session against the number of sessions experienced.

range of superficial to deep recording sites[5], grid cell firing showed a range of modulation by direction ($n = 14$ non-directional, $n = 24$ directional; **Supplementary Methods**). Extent of rescaling was unrelated to either directionality ($t_{36} = -0.94$, $P = 0.356$) or recording site ($t_{36} = -0.57$, $P = 0.573$). Similarly, grid scale does not simply reflect different running speed in the two dimensions; there was no relationship between grid scale and speed in the baseline rate maps (horizontal: $t_{37} = 0.247$, $P = 0.808$; vertical: $t_{37} = -0.722$, $P = 0.475$).

Is grid deformation experience dependent? Deforming the environment along one dimension produced an asymmetry in grids not present when the same configuration was familiar (**Fig. 1**). Thus, grids in the large square showed significant asymmetry in rats familiar with the vertical rectangle ($t_9 = 3.684$, $P = 0.005$), but not in those familiar with the large square ($t_{27} = -1.605$, $P = 0.120$). Conversely, grids were asymmetrical in the vertical rectangle in the three rats familiar with the large square ($t_{27} = -5.682$, $P < 0.0001$) but symmetrical in the rectangle familiar to the other three rats ($t_9 = 0.035$, $P = 0.973$). In both cases, asymmetry was significantly greater in the unfamiliar than in the familiar configuration (squares: $t_{36} = -3.851$, $P < 0.001$; rectangles: $t_{36} = 3.280$, $P = 0.002$; see **Fig. 3a** and **Supplementary Methods**). Thus, grid structure in the deformed environments reflects experience rather than the shape of the current environment. We also examined each rat's rescaling score as a function of continued exposure to the protocol. In all five animals with cells recorded in multiple sessions, rescaling extent correlated negatively with session (binomial, $P = 0.031$; **Supplementary Table 2** online), but showed differential rates of reduction in each rat (so that a single correlation over all points is not quite significant, $\rho = -0.311$, $P = 0.095$, **Fig. 2c**).

Our results suggest that in a familiar environment, grids become associated with environmental features such as boundaries[7–9], so that subsequent deformation of the environment causes parametric deformation of the grid. Mediation of this association by place cells would be consistent with the similar

response of place cells to environmental deformation[7,10] and also with computational considerations[2–4], coincident remapping of place cells and realignment of grids[11], and bidirectional connectivity between similar regions of entorhinal cortex and hippocampal field CA1 (ref. 12). The slow, rat-specific reduction of rescaling with repeated experience of the probe configurations suggests a tendency of the system to revert to an intrinsic grid scale. Notably, it occurs on a timescale similar to that of the slow transition from deformation to remapping shown by place cells repeatedly exposed to configurations of different shape[13]. Similarly, the small but significant reaction to rescaling along one dimension by an opposing change along the other may also indicate a propensity to preserve overall grid scale.

Significantly for models of grid cell function, the set of grids recorded from each rat seemed to share a common orientation, including those of different sizes (Rayleigh test, $P = 0.002$; **Supplementary Fig. 4** online; ref. 11). The scale of grids recorded from different dorsoventral
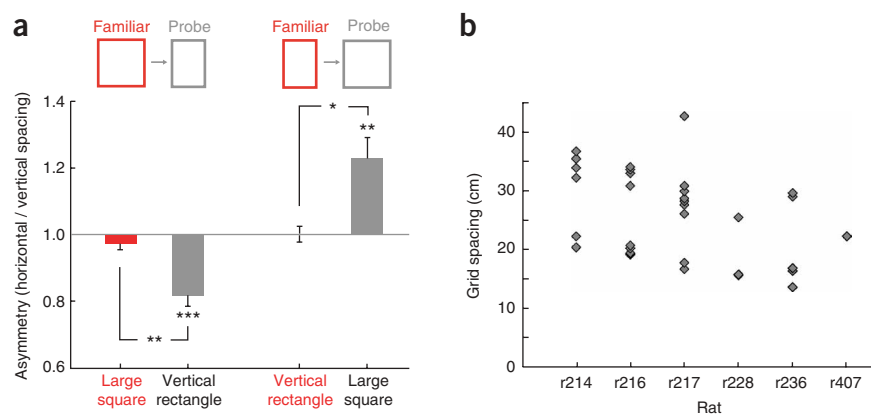
Figure 3 Grid asymmetry is experience dependent and grid sizes are clustered within rat. (**a**) Induced grid asymmetry as a product of experience. Asymmetry (see **Supplementary Methods**) was assessed for recordings made in the large square and vertical rectangle (mean ± s.e.m.). Grids are symmetrical in the familiar enclosure regardless of its shape. Asymmetry was induced when grids were recorded in the probe enclosures. t-tests compare observed values to a mean of 1 (where 1 indicates no asymmetry; two-tailed; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). (**b**) Grid scale, measured in the familiar enclosure, in individual rats. The lengths of grids recorded from different dorsoventral locations in each rat show a tendency to cluster. In each rat the ratio of the shortest and second-shortest cluster is a fixed non-integer ratio approximately equal to 1.7 ($P = 0.008$, see **Supplementary Fig. 5**).

locations varied in size, as reported previously[1], but were tightly clustered rather than evenly distributed (**Fig. 3b**). Notably, the ratio of grid sizes seemed to be constant across rats, such that the grids in each rat varied in size by a fixed, non-integer ratio ($P = 0.008$, **Supplementary Fig. 5** online)—consistent with the efficient coding of location by quantized grid scales[14,15].

Why was rescaling not seen in a previous study[1]? There, the large and small environments were physically different boxes which were both already very familiar to the rats (E. Moser, personal communication). Thus the switch from one box to the other would have acted more like a change to a new environment than a deformation of the same environment (possibly causing grids to shift and place cells to remap[11] rather than deforming). Indeed, qualitative observations suggest that grid asymmetry induced by deformation of a familiar environment disappears in a new environment of the deformed shape, and can then be induced in the reverse direction by morphing the new environment into the initial (pre-deformation) shape of the original environment (**Supplementary Fig. 6** online).

In conclusion, our results suggest that the interaction between sensory and path-integrative information that is needed for accurate self-localization may be mediated by the entorhinal grid cells. Observed parallels in phenomenology and time course between grid cells and place cells suggest that this mediation may result from experience-dependent interactions between hippocampus and entorhinal cortex. Understanding the interactions between these regions is likely to be critical to understanding spatial memory and, more generally, human episodic memory.

1. Hafting, T., Fyhn, M., Moser, M. & Moser, E.I. *Nature* **436**, 801–806 (2005).
2. O'Keefe, J. & Burgess, N. *Hippocampus* **15**, 853–866 (2005).
3. Fuhs, M.C. & Touretzky, D.S. *J. Neurosci.* **26**, 4266–4276 (2006).
4. McNaughton, B.L., Battaglia, F.P., Jensen, O., Moser, E.I. & Moser, M.B. *Nat. Rev. Neurosci.* **7**, 663–678 (2006).
5. Sargolini, F. *et al. Science* **312**, 758–762 (2006).
6. Hargreaves, E.L., Roa, G., Lee, I. & Knierim, J.J. *Science* **308**, 1792–1794 (2005).
7. O'Keefe, J. & Burgess, N. *Nature* **381**, 425–428 (1996).
8. Hartley, T., Burgess, N., Lever, C., Cacucci, F. & O'Keefe, J. *Hippocampus* **10**, 369–379 (2000).
9. Barry, C. *et al. Rev. Neurosci.* **17**, 71–97 (2006).
10. Muller, R.U. & Kubie, J.L. *J. Neurosci.* **7**, 1951–1968 (1987).
11. Fyhn, M., Hafting, T., Treves, A., Moser, M.B. & Moser, E.I. *Nature* **446**, 190–194 (2007).
12. Kloosterman, F., Van Haeften, T. & Lopes da Silva, F.H. *Hippocampus* **14**, 1026–1039 (2004).
13. Lever, C., Wills, T.J., Cacucci, F., Burgess, N. & O'Keefe, J. *Nature* **416**, 90–94 (2002).
14. Brookings, T., Burak, Y. & Fiete, I.R. Preprint at ⟨http://www.arxiv.org/abs/q-bio/0606005⟩ (2006).
15. Gorchetchnikov, A. & Grossberg, S. *Neural Netw.* **20**, 182–93 (2007).