Title: Environment symmetry drives a multidirectional code in rat retrosplenial cortex

Ningyu Zhang[1,2], Roddy M. Grieves[1,3] and Kate J. Jeffery[1]*

Affiliations

[1]Institute of Behavioural Neuroscience, Division of Psychology & Language Sciences, University College London, 26 Bedford Way, London WC1H 0AP, United Kingdom

[2] Institute of Neuroscience, State Key Laboratory of Neuroscience, CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai, 200031, China

[3] Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH, USA

*For correspondence:

k.jeffery@ucl.ac.uk (K.J.J)

One Sentence Summary:

Retrosplenial directionally tuned neurons encode global environment symmetry even in local sub-compartments.

Abstract:

A class of neurons showing bidirectional tuning in a two-compartment environment was recently discovered in dysgranular retrosplenial cortex (dRSC). We investigated here whether these neurons possess a more general environmental symmetry-encoding property, potentially useful in representing complex spatial structure. We report that directional tuning of dRSC neurons reflected environment symmetry in onefold, twofold and fourfold-symmetric environments: this was the case not just globally, but also locally within each sub-compartment. Thus, these cells use environmental cues to organize multiple directional tuning curves, which perhaps sometimes combine via interaction with classic head direction cells. A consequence is that both local and global environmental symmetry are simultaneously encoded even within local sub-compartments, which may be important for cognitive mapping of the space beyond immediate perceptual reach.

Main text:

Self-localization and navigation require construction of a stable directional signal that orients the brain's map of space so as to be in register with the actual environment. Retrosplenial cortex (RSC) is a brain region where internal and external orientation signals combine, as evidenced by the long-established existence of head direction cells (*1*) which are compass-like, directionally tuned neurons that fire according to the animal's facing direction. Recent findings revealed that in addition to these "classic" head direction (HD) cells, in dysgranular RSC (dRSC) there are also landmark-sensitive "bidirectional cells" which were found to express a bipolar firing pattern if recorded in a two-compartment space having twofold rotational symmetry (*3*). This bidirectional pattern was surprising, having not been noted previously, and we hypothesized that it arose from experience in the unusual environment structure, and reflects a general propensity for the cells to detect and acquire encoding of environment symmetry. To test this, we recorded RSC neurons in environments having symmetries varying between onefold, twofold and fourfold. We found that a subpopulation of electrophysiologically and anatomically distinct directionally tuned neurons showed multidirectional tuning that accorded with the environment's symmetry, not just globally, when considered across the whole environment, but also sometimes locally within each sub-compartment. This pattern persisted in the dark and was not due to occult egocentric boundary encoding. Global multidirectional encoding indicates tuning of the neurons to the local environment polarities (and hence is only multifold when all the compartments are considered together), while local encoding of global symmetry means that the global multifold symmetry experienced after exploration has been captured by the network and is re-expressed locally. This enables spatial encoding of the environment beyond immediate perceptual reach, which may be important in building a cognitive map of a multi-compartment space.

Results:

RSC neurons were recorded from 18 rats (Table S1) foraging in environments having onefold symmetry (1-box), twofold symmetry (2-box) or fourfold symmetry (4-box). Every cell was recorded in one of the two 1-boxes and in either the 2-box or the 4-box (**Fig.1**; Fig. S1). We first present the 2-box data, then the 4-box, and then finally the 1-box results which flanked the multifold box trials.

In the 2-box, we recorded 478 RSC cells from 14 rats (Table S1). As well as classic HD cells (27/478, 6%, **Fig. 2A-B**) and consistent with our previous work (*3*), we found directionally tuned cells with bidirectional tuning curves: a twofold-symmetric firing pattern with a 180º offset between two tuning curves (**Fig. 1A, Fig. 2C**; see Fig. S2 for more examples). This was quantified with a bidirectionality score and angle-doubled Rayleigh vector length (see **Methods**); 48/478 cells (10%) passed the criteria for bidirectionality. These cells displayed three main firing patterns. First, the so-called between-compartment bidirectional cells (BC-BD, n = 9/48, 19%, **Fig. 2C**; Fig. S1A) lost their bidirectionality in the local sub-compartments (**Fig. 2D**), as shown by the fact that BD scores were not significantly different from 0 (mean, lemon = 0.15, vanilla = -0.12, $p > 0.3$ in all cases); however they maintained unidirectional firing (median Rayleigh vector length: lemon = 0.22; vanilla = 0.23), as the within-compartment autocorrelations were single-peaked at zero and significantly different from a shuffle (KS test, lemon, D = 0.65, $p < .001$; vanilla, D = 0.59, $p < .001$). Thus, for these cells only the global pattern was bidirectional (**Fig. 2E**, cross-correlations significantly different from shuffle, KS test, D = 0.58, $p < .001$; peaked at 174°, circular v-test against 180°, V = 4.76, $p = 0.012$).

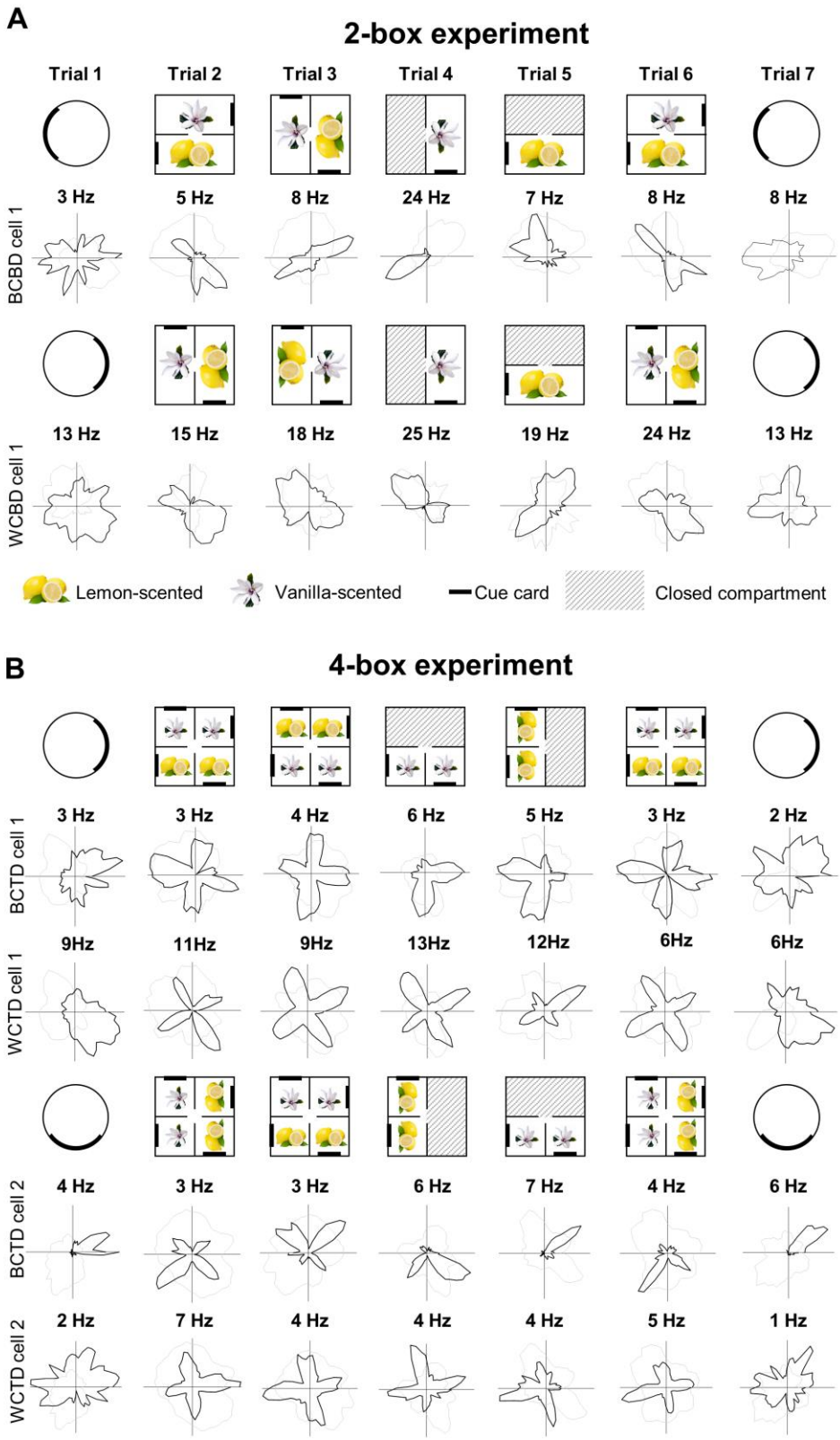

Fig. 1. Directional tuning of BD-pattern cells in the 2-box experiment and TD-pattern cells in the 4-box experiment. (A) One between-compartment (BC) BD cell (top) and one within-compartment (WC) BD cell recorded in two different

sessions. Polar plots show the standard seven-trial recording sessions, the box orientation was sometimes different from that in the baseline (see Fig.S1 for full procedures). (B) Four TD cells: example between-compartment (BC) TD cells and within-compartment (WC) TD cells recorded simultaneously from different tetrodes in one session (upper two rows) and another two co-recorded cells from a different session (lower two rows). Plots show cell activity in standard seven-trial recording sessions. Note that co-recorded cells have different PFDs within the same session. The decoupled HD tuning of co-recorded cells strongly supports that the firing symmetry is unlikely due to merely movement-related factors of the animal during recordings.

Second, the within-compartment bidirectional cells (WC-BD; n = 22/48, 46%, **Fig. 1A, Fig. 2C**, Fig. S2B), expressed a bidirectional pattern even within single sub-compartments (BD scores above shuffle control, mean lemon = 0.80; vanilla = 0.68; within-compartment autocorrelations significantly differed from a shuffle: KS test, lemon, D = 0.52, p <.001; vanilla, D = 0.52, p <.001; **Fig.2D**). Where the two within-compartment tuning curves were asymmetric, the direction of the large/small peaks rotated by ~180° between the two sub-compartments (**Fig.2E**, between-compartment correlations significantly different from shuffle: KS test, D = 0.51, p <.001; mean ΔPFD = 188°, circular v-test against 180°: V = 6.54, p = 0.024). A third category of BD-pattern cells (17/48, 35%) fell below the statistical threshold for directionality in the sub-compartment analysis, and remained unclassified.

We next increased the level of environment symmetry from twofold to fourfold (the 4-box; Fig. S1). To avoid possible carry-over effects from the 2-box, we used four new rats, plus four rats that had previously had nine sessions in the 2-box (total rats, n = 8; cells, n = 660; Table S1). In the 4-box, in addition to HD cells (n = 75/660, 11%) we saw a fourfold-symmetric 'four-leafed clover' firing pattern, with a 90º offset between four directional tuning peaks (**Fig. 1B**). These also occurred in 3 out of 4 of the animals with previous 2-box experience (n cells = 15), suggesting pattern formation through learning of the new environment (Fig. S3). This fourfold directionality was quantified as a tetradirectional (TD) score, and 67/660 (10%) met the criteria for tetradirectionality (**Methods**).

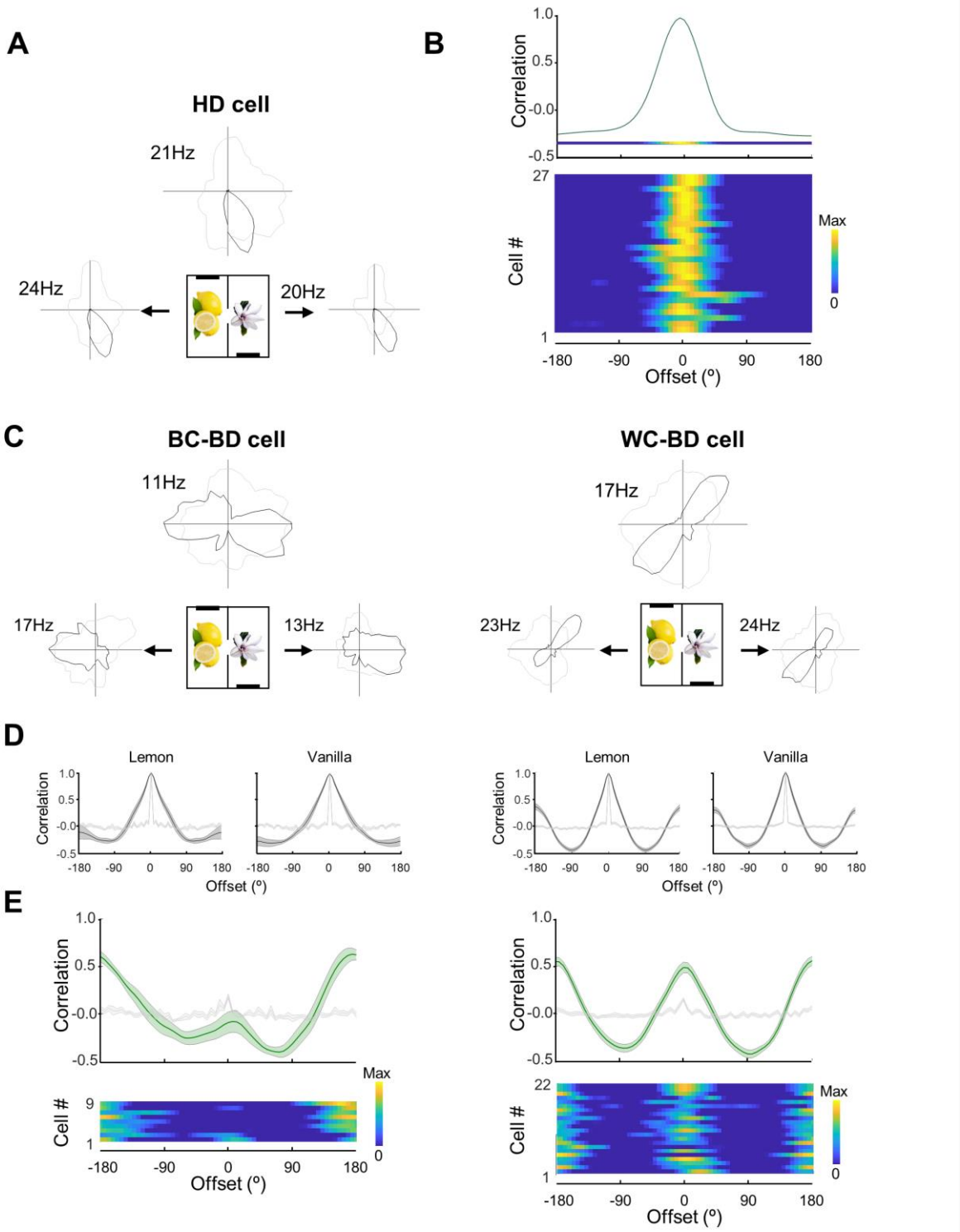

Fig. 2. Multiple directional firing symmetries in the 2-box. (A-B) Classic HD cells. (A) Top polar plot: unipolar directional tuning curve for the whole apparatus (dark line) and directional behavioral sampling (pale line). Numbers show peak firing rates. Side plots: Tuning for each sub-compartment showing globally consistent direction. (B) Top: example tuning curve cross-correlation between sub-compartments, shown as a line and also as a heatplot. Bottom: heatplots of the

cross-correlograms for individual cells, sorted by Rayleigh vector lengths; maximum at the top. (C) Global and compartment-specific polar plots of a between-compartment bidirectional cell (BC-BD; left) and a within-compartment cell (WC-BD; right). (D) Single-compartment autocorrelograms for the cells in (C) (mean +/- s.e.m.) showing a single peak for the BC-BD cell and double (second peak at 180 deg.) for the WC-BD cell. Shuffle control data are shown as pale gray. (E) Population cross-correlograms shown as line plot (top; shuffle controls as pale gray) and heatplots (bottom), again showing single peaks for the BC-BD cells and double for the WC-BD cells.

As with the BD cells, in single sub-compartments we identified three subgroups of TD-pattern cells: unidirectional, multidirectional and non-directional. First, the between-compartment TD cells (BC-TD; n = 9/67, 13%, **Fig. 1B**, **Fig. 3A**, Fig. S3A) expressed unidirectional but not tetradirectional tuning curves in individual sub-compartments (**Fig. 3B**). Unidirectionality was shown by a high Rayleigh vector score (median, vanilla1 = 0.27, vanilla2 = 0.22, lemon1 = 0.25, lemon2 = 0.32) and within-compartment autocorrelations significantly different from a shuffle in every sub-compartment (KS test, vanilla1, D = 0.67, p <.001; vanilla2, D = 0.66, p <.001; lemon1, D = 0.72, p <.001; lemon2, D = 0.52, p <.001.). Loss of tetradirectionality was shown by within-compartment TD scores near zero (mean, vanilla1 = 0.00, vanilla2 = -0.02, lemon1 = -0.03, lemon2 = 0.03, p > 0.6 in all cases). The global preferred firing direction in each sub-compartment rotated by 90° in successive sub-compartments: cross-correlations of tuning curves from adjacent sub-compartment pairs differed from a shuffle (**Fig. 3C**, KS test, D = 0.68, p <.001) and peaked at ~90° (circular v-test against 90°: V = 7.98, p <.001). These BC-TD cells also did not show a bidirectional pattern in single compartments, having BD scores not significantly different from zero (mean, vanilla1 = 0.07, t(8)= 0.51, p = 0.62; vanilla2 = 0.08, t(8)= 0.40, p = 0.70; lemon1 = 0.04, t(8)= 0.29, p = 0.78; lemon2 = -0.09, t(8)= -0.45, p = 0.67).

A second subgroup of TD-pattern cells, the within-compartment cells (WC-TD; n = 29/67, 43%, **Fig. 1B, Fig. 3A**, Fig. S3A) exhibited a multidirectional pattern (usually

fourfold, though occasionally one peak was smaller) even in single sub-compartments. The within-compartment fourfold symmetry was quantified as follows. TD scores were significantly greater than the shuffle control: mean, vanilla1 = 0.41, t(28)= 6.03, p <.001; vanilla2 = 0.36, t(28)= 4.04, p <.001; lemon1 = 0.35, t(28)= 5.31, p <.001; lemon2 = 0.23, t(28)= 1.70, p = 0.05. Also, the coefficient of within-compartment autocorrelations was significantly different from shuffle: KS test, vanilla1, D = 0.49, p <.001; vanilla2, D = 0.47, p <.001; lemon1, D = 0.52, p <.001; lemon2, D = 0.50, p <.001; **Fig. 3B**. The tuning curve peaks varied in size, and the direction of the largest peak usually rotated 90º between successive sub-compartments. This was quantified using cross-correlograms of tuning curves from adjacent sub-compartment pairs, which significantly differed from a shuffle (**Fig. 3C**; KS test, D = 0.47, p <.001) and peaked at ~90° (circular v-test against 90°: V = 13.69, p < .001). The third group (29/67, 43%) were not directional in individual sub-compartments and remained unclassified. We rarely saw cells with only two or three peaks in the whole 4-box. Moreover, we did not see any cells that were directionally stable across similarly-scented sub-compartments but that rotated between lemon and vanilla (i.e., there was no apparent hierarchy of sub-compartment encoding).

We also recorded the firing activity of TD-pattern cells in the dark in the 4-box (Fig. S4), finding that 75% maintained their four-way pattern in the first dark trial (n = 21/28), 64% in the second dark trial (n = 16/25), and 44% in both (n = 11/25). Together with previous findings of a preserved BD pattern in the dark (*3*), the results suggest that the multidirectional cells were not solely dependent on vision, and that multimodal sensory information could help maintain their directional tuning.

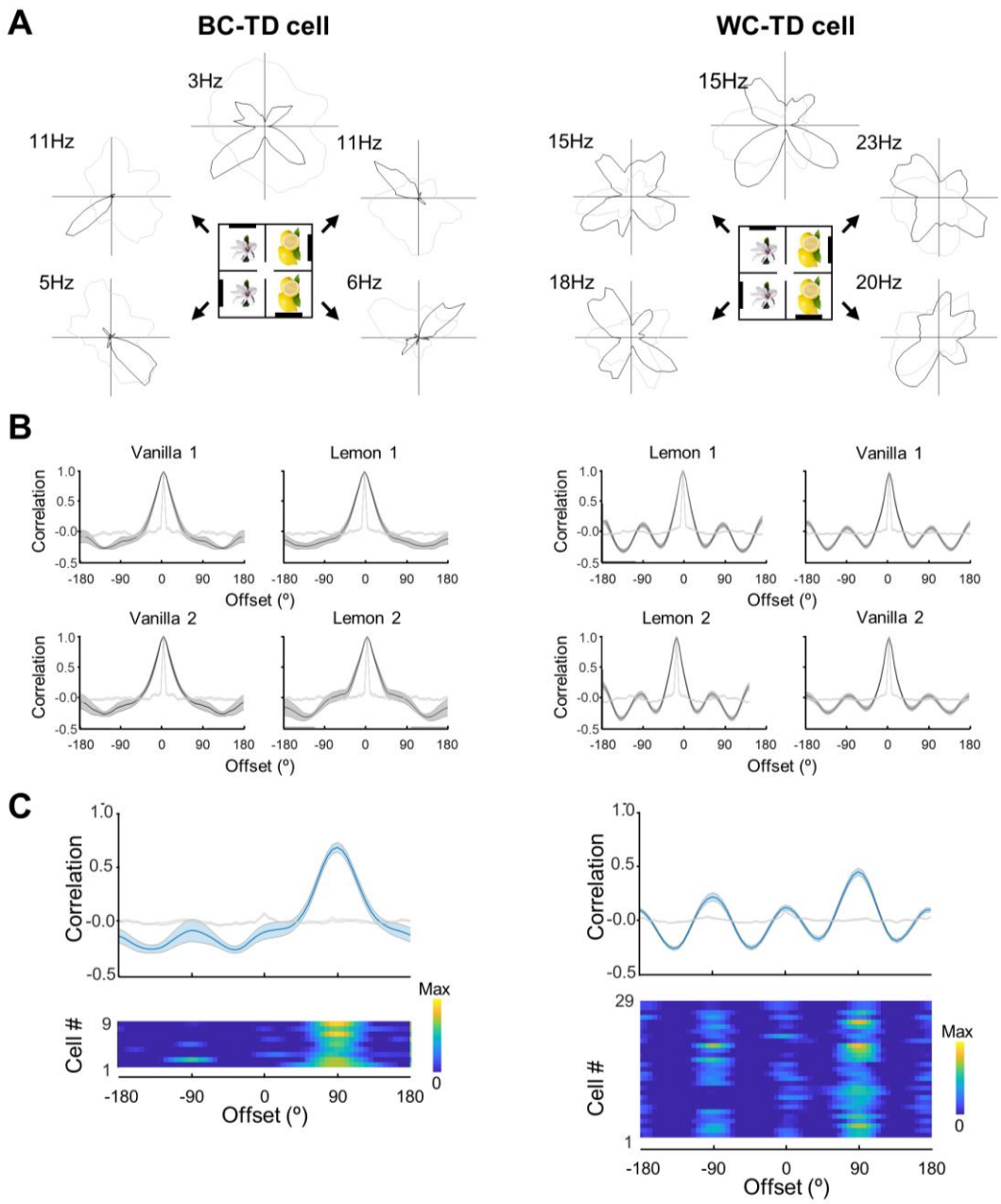

Fig. 3. Multiple directional firing symmetries in the 4-box. (A) A between-compartment tetradirectional cell (BC-TD; left) and a within-compartment tetradirectional cell (WC-TD; right); illustrations as in Fig. 2. Note the occurrence of fourfold (90°) symmetries for the global pattern alone for the BC-TD cells, and for both global and local patterns in the WC-TD cells. (B) Rotational autocorrelograms of the tuning curves in each sub-compartment (mean ± s.e.m. = dark gray), compared with the shuffled data (light gray). The BC-TD cell has onefold symmetry (single peak) in each compartment while the WC-TD cell has fourfold symmetry (four peaks). (C) Population cross-correlograms (each compartment compared with the one clockwise adjacent): note peak at +90 degrees, reflecting rotation of the tuning curves to follow the rotation of the compartment layouts.

So far, we have shown that multidirectional cells are driven by a multifold environment symmetry, how might they behave in environments with no repeating components? We then looked at the onefold-symmetry trials (the 1-boxes: the open arena and cylinder, Fig. S1), which flanked the multi-compartment trials. We found that while some cells lost directionality, a significant proportion became unidirectional: this was the case in both the open arena and the cue-controlled cylinder for cells that previously had been either BD or TD cells.

In the open arena, for cells that were BD in the 2-box (n = 32; **Fig. 4A**, Fig. S2), we found that overall, the cross-correlation between the two baselines had a tall central peak that significantly differed from the shuffle (KS test, D = 0.63, p <.001; **Fig. 4B**), indicating above-chance directionality at the population level. To quantify this at the level of individual cells, the Rayleigh vector length was compared with the cell's shuffle in both baseline 1-box trials: 14/32 cells (were BD, 44%) passed the criteria in both baseline trials (median, baseline 1 = 0.12, baseline 2 = 0.13), showing broad unidirectional pattern, leaving 56% lost directional specificity. They did not show bidirectional pattern either, only 3/32 cells had BD scores higher than the shuffle.

We undertook a similar analysis for the cue-controlled cylinder 1-box trials (**Fig.** 1, **Fig. 4A**, Fig. S3, Fig. S5). Eight cells were formerly BD and 65 were formerly TD: we pooled these as "multidirectional". As a population, the cells' cross-correlations between the two 1-box baselines were significantly different from shuffle (KS test: n = 73 D = 0.67, p <.001; **Fig. 4B**). At the single-cell level, 28/73 (38%) cells (26 were TD, 2 were BD) had the Rayleigh vector lengths higher than its shuffle in both baseline trials (median, baseline 1 = 0.17, baseline 2 = 0.18), while 45/73 (62%) cells lost the directional specificity. They did not show multidirectional pattern either in 1-box trials, only 1/8 had the BD score higher than shuffle, and 3/65 cells had the TD score higher than the shuffle in both trials.

Some cells showed sensitivity to cue rotation (**Fig. 4C**) although this was inconsistent, perhaps due to familiarity of the rats with the room context. To assess whether this narrow onefold pattern is comparable with the unidirectional classic HD cells in the cylinder, we compared their peak firing rate, tuning width, and Rayleigh vector length, finding that these values were significantly different (Fig. S5): multidirectional cells showed a lower firing rate, lower Rayleigh vector score and broader tuning curves, suggesting that although they had become unidirectional, these cells were not the same as HD cells (see more extensive comparison below).

We then looked to see whether the multi-directional pattern we saw could be explained by occult tuning to the egocentric direction of boundaries, as has been previously suggested (*4*). Arguing against this possibility, we found that the allocentric directional tuning of retrosplenial cells was homogeneously distributed in the multifold environments, and therefore dissociated from the boundary directions which aligned along four distinct directions (Fig. S6A). Additionally, by applying established egocentric analyses (*4*) to the multidirectional cells, we found no selective egocentric boundary tuning in either the simple or complex environments: multidirectional cells generally showed multiple and uniformly dispersed egocentric firing fields (Fig. S6B-E).

We finally investigated whether multidirectional cells may be a physically separate neuronal sub-class from classic HD cells. First, and similar to previous results (*3*), more multidirectional cells were anatomically distributed in the dysgranular rather than granular RSC (Fig. S7; Table S1). Second, waveform analyses found that multidirectional cells in general had significantly higher peak amplitudes (ANOVA, $F(2, 101.87) = 7.84$, $p = 0.001$), longer peak-trough latencies ($F(2, 100.98) = 159.73$, $p<.001$) and longer latencies to the inter-spike-interval half-peak ($F(2, 94.87) = 33.64$, $p<.001$). Moreover, HD cells were significantly burstier than

multidirectional cells ($F(2, 140.61) = 24.81$, $p<.001$). The results thus indicated an electrophysiological distinction between multidirectional cells and HD cells (Fig. S8, see summary in Table S2).

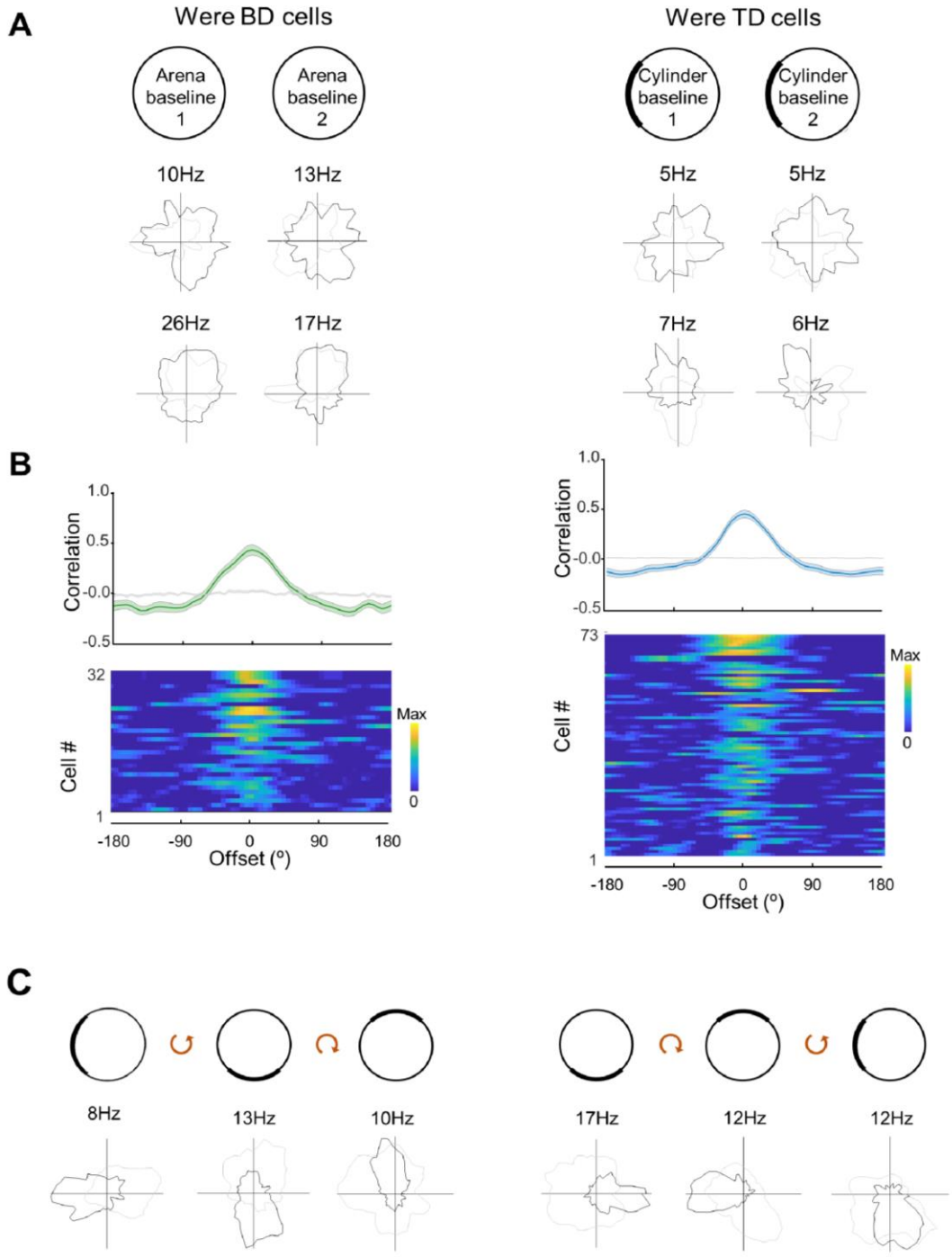

Fig. 4. Variable uni-directional firing symmetries in the 1-box. (A) Two cells that had been BD cells in the 2-box (left) and two that were TD cells in the 4-box (right) showing varying directionality in the arena (left) vs. cylinder (right), either

non-directional (upper cells in both examples) or unidirectional (lower cells). (B) Population data from former BD cells (left) and former TD cells (right) ordered top-to-bottom by Rayleigh vector; format as described in Fig. 2(E), prominent central stripe indicates preserved uni-directionality. (C) Two cells, a former BD-pattern cell (left) and former TD-pattern cell (right), which developed singular tuning curves in the 1-box that followed cue rotation (denoted by the rotation mark).

Discussion:

Our data show that a subpopulation of directionally tuned RSC neurons express an experience-dependent multi-directional code that captures the rotational symmetries of the extended environment. In addition to the well-known classic HD cells with globally unipolar, narrow directional tuning, some electrophysiologically distinct directionally tuned cells had firing patterns that matched the overall environmental symmetry, being one-directional in a single compartment but bidirectional in a twofold-symmetric environment and tetradirectional in a fourfold-symmetric environment. Furthermore, while some cells expressed these multidirectional patterns globally (being unidirectional in single compartments but multidirectional overall), others expressed them locally, expressing the global environment symmetry in local sub-compartments. These neurons thus provide an instantaneous readout of the global symmetry from within each of the sub-compartments.

Two questions arise from these findings: what generates these symmetries, and what, if anything, are they for? Clearly they are not intrinsic, because fourfold symmetric firing was not seen in the 2-box, and four- and twofold symmetry has not previously been observed in naïve animals in simple environments. However, some cells that later became multi-directional expressed onefold directional tuning in the first 1-box baseline, suggesting a pre-configured responsiveness to local environment layout. Multidirectional firing was also found not to be due to egocentric boundary vector coding, and instead driven by allocentric environmental cues. The symmetries therefore evidently arise from experience of the different environment symmetries.

However, they frequently persist in the onefold-symmetric sub-compartments afterwards, suggesting a learning process that was initially informed by the global exploration but then came to affect local activity.

Within-compartment expression of an across-compartment symmetry could potentially arise from plastic interactions with the HD system (*5*). Canonical HD cells use self-motion information to establish their globally stable directional orientation (*6*), while the non-canonical directional cells are sensitive to environment layout (*3*), developing multiple tuning curves if the environment has multiple identical but differently oriented sub-compartments. A consequence of this multi-directionality is that different populations of HD neurons become co-active with these neurons, depending on the global orientation of a given sub-compartment, and this co-activation could allow new HD inputs to form by Hebbian association.

Interestingly, the four tuning peaks in the fourfold-symmetric environment exceeds a proposed theoretical threshold (*5*) because previous computational modelling predicted that while the BD pattern would become tri-directional in a trifold-symmetric environment, the directional specificity should break down altogether with higher symmetries, due to the tuning curves overlapping (*5*). The fact that we saw fourfold symmetry suggests potential constraints on the parameters of the ring attractor that underlies the head direction signal (such as more narrowly dispersed interconnections).

What might this symmetry-influenced firing pattern be for? On the one hand it may be a byproduct of having explored a space with multiple similar-looking but differently-oriented compartments, forcing an unusual plasticity between the visual layout and the HD cells which " confused" the system. However there may be a deeper functional consequence, in which a global symmetry experienced when exploring multiple compartments can be re-expressed

locally, for use in constructing an internal representation of a multi-compartment space. Such a construction, the so-called "cognitive map" of space, relies on recruitment of information beyond immediate perceptual reach. The ability of multidirectional RSC neurons to capture structural elements of the whole space (and their orientation) and then re-express them locally suggests that they may form part of such a mapping, perhaps as part of a compression process to more efficiently store complex structural information. In a more naturalistic environment, assuming that different cells are sensitive to different structural elements and that any repeating elements (such as corners, doors etc) would be irregularly distributed in directional space, the resultant population activity might look rather heterogeneous to an experimenter and yet contain a detailed plan of the global layout that could be use by other cognitive mapping neurons.

Overall, our results show that the subset of RSC directional neurons that become multi-directional in spaces with higher order rotational symmetries form a different subpopulation than classic head direction cells, and may play a role in mediating between the perception of local spatial features and construction of a cognitive map.

References and Notes:

1. J. Cho, P. E. Sharp, Head direction, place, and movement correlates for cells in the rat retrosplenial cortex. *Behav Neurosci*. **115** (2001), pp. 3–25.

2. J. S. Taube, R. U. Muller, J. J. B. Ranck, Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J. Neurosci.* **10**, 436–447 (1990).

3. P.-Y. Jacob, G. Casali, L. Spieser, H. Page, D. Overington, K. Jeffery, An independent, landmark-dominated head-direction signal in dysgranular retrosplenial cortex. *Nat. Neurosci.* **20**, 173–175 (2017).

4. A. S. Alexander, L. C. Carstensen, J. R. Hinman, F. Raudies, G. W. Chapman, M. E. Hasselmo, Egocentric boundary vector tuning of the retrosplenial cortex. *Sci Adv*. **6**, eaaz2322 (2020).

5. H. J. I. Page, K. J. Jeffery, Landmark-Based Updating of the Head Direction System by

Retrosplenial Cortex: A Computational Model. *Front. Cell. Neurosci.* **12**, 1–17 (2018).

6. J. S. Taube, H. Burton, Head direction cell activity monitored in a novel environment and during a cue conflict situation. *J. Neurophysiol.* **74**, 1953–1971 (1995).

7. K. D. Harris, D. A. Henze, J. Csicsvari, H. Hirase, G. Buzsáki, Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements. *J. Neurophysiol.* **84**, 401–414 (2000).

8. N. Schmitzer-Torbert, J. Jackson, D. Henze, K. Harris, A. D. Redish, Quantitative measures of cluster quality for use in extracellular recordings. *Neuroscience*. **131**, 1–11 (2005).

9. M. S. Fee, P. P. Mitra, D. Kleinfeld, Automatic sorting of multiple unit neuronal signals in the presence of anisotropic and non-Gaussian variability.[Erratum appears in J Neurosci Methods 1997 Feb;71(2):233]. *J. Neurosci. Methods*. **69**, 175–188 (1996).

10. P. Berens, CircStat: A Matlab Toolbox for Circular Statistics. *J. Stat. Softw.* **31**, 1–21 (2009).

11. L. M. Giocomo, T. Stensola, T. Bonnevie, T. Van Cauter, M. B. Moser, E. I. Moser, Topography of head direction cells in medial entorhinal cortex. *Curr. Biol.* **24**, 252–262 (2014).

12. L. Landler, G. D. Ruxton, E. P. Malkemper, Circular data in biology: advice for effectively implementing statistical procedures. *Behav. Ecol. Sociobiol.* **72** (2018), doi:10.1007/s00265-018-2538-y.

13. J. R. Hinman, G. W. Chapman, M. E. Hasselmo, Neuronal representation of environmental boundaries in egocentric coordinates. *Nat. Commun.* **10**, 1–8 (2019).

14. K. D. Harris, H. Hirase, X. Leinekugel, D. A. Henze, G. Buzsáki, Temporal interaction between single spikes and complex spike bursts in hippocampal pyramidal cells. *Neuron*. **32**, 141–149 (2001).

15. R. M. Grieves, S. Jedidi-Ayoub, K. Mishchanchuk, A. Liu, S. Renaudineau, K. J. Jeffery, The place-cell representation of volumetric space in rats. *Nat. Commun.* **11**, 789 (2020).

Acknowledgements

Funding: This work was supported by a Wellcome Trust Investigator Award (WT103896AIA), a grant from the Biotechnology and Biological Sciences Research Council (BB/Joo9792/1) to K.J.J, and a China Scholarship Council Research Excellence Scholarship for PhD programme to N.Z. (201608000007). **Author contributions:** Ningyu Zhang: Conceptualization, Methodology, Software, Investigation, Formal analysis, Data curation, Visualization, Writing – Original Draft, Review & Editing; Roddy Grieves: Conceptualization, Software, Writing - Review & Editing; Kate Jeffery: Conceptualization, Methodology, Data curation, Supervision, Resources, Funding acquisition, Writing – Review & Editing. **Competing interests**: The authors declare the following competing interests: K.J.J is a non-shareholding director of Axona Ltd.

Data and materials availability

A raw dataset can be requested from the authors. Summarized data and analysis code are documented in an online repository available upon publication.

Supplementary materials

Materials and Methods
Figs. S1 to S8
Tables S1 and S2