Three-dimensional spatial selectivity of hippocampal neurons during space flight

James J. Knierim[1,2], Bruce L. McNaughton[1] and Gina R. Poe[1]

[1] *University of Arizona, Arizona Research Laboratories Division of Neural Systems, Memory & Aging, 384 Life Sciences North Bldg., Tucson, Arizona, 85724, USA*

[2] *University of Texas-Houston Medical School, Department of Neurobiology & Anatomy and the W. M. Keck Center for the Neurobiology of Learning and Memory, P.O. Box 20708, Houston, Texas 77225, USA*

Correspondence should be addressed to B.L.M. (bruce@nsma.arizona.edu)

'Place' cells of the hippocampus and 'head-direction' (HD) cells of the thalamus and limbic cortex derive their spatial and directional specificity from a combination of idiothetic (self-motion) cues and external landmarks, which normally reinforce each other to generate a robust neural code for location and direction[1]. In weightlessness, however, three-dimensional navigation can cause the idiothetic and landmark cues to conflict. Nonetheless, neural recordings on the space shuttle demonstrated that the hippocampus can create a robust spatial code for three orthogonal surfaces in the weightless environment of space flight.

The firing properties of place cells and HD cells are coupled[2], and one function of the HD system may be to orient the 'cognitive map' in the hippocampus[3]. As an animal explores a novel environment, vestibular input and other idiothetic cues are thought to keep the HD system aligned with external landmarks long enough for the landmarks to form stable associations with, and thereby exert control over, place and HD cells[2–7]. In normal gravity, HD cells are sensitive to only the horizontal component of head direction; although changes in pitch and roll attitude are not signaled directly by these cells[8,9], calculation of head direction in the horizontal plane may involve compensation for such changes. Because the otolith organs—normally, a major source of information about static pitch and roll attitude—are rendered useless in zero gravity, the HD system would be deprived of this input in compensating for changes in pitch and roll (although the semicircular canals would still detect angular accelerations in all three dimensions). Three-dimensional navigation in microgravity might thus lead to inconsistent associations between HD and landmark information and a consequent inconsistency in the hippocampal place code. In light of the disorientation frequently reported by astronauts during space flight[10], it was of interest to determine whether the hippocampus can create a stable representation of space during three-dimensional movement in the absence of gravity.

During the Neurolab Space Shuttle mission of April, 1998, ensembles of place cells were recorded from three rats implanted with a multi-electrode recording array[11,12]. The rats were trained to negotiate a three-dimensional track (the 'Escher staircase') in which 3 turns of 90° in yaw were interleaved with 3 turns of 90° in pitch (**Fig. 1**). As a result, the rat completed a full circuit of the track and returned to its starting location/direction after having made only 3 right turns (270° total yaw). The spatial information provided by external landmarks was thus presumably in conflict with the direction information from HD cells, which under normal conditions require a fourth 90° turn (360° total yaw) to signal a return to the starting direction. Nonetheless, place cells eventually demonstrated normal, spatially specific firing properties.

Spatial firing patterns of 16 active place cells from rat 2 were recorded on the ninth day of flight (FD9; **Fig. 2a**), which was the second day in which the rats had been exposed to the Escher staircase track in flight. For comparison, we show the spatial firing patterns of 12 representative place cells from the same rat recorded 4 days before launch as the rat ran clockwise on a flat, rectangular track (**Fig. 2b**). An index of spatial tuning specificity, which quantifies the amount of information about the rat's position transmitted by the firing of a single spike[13], did not significantly differ between cells recorded preflight and those recorded on FD9 (for active cells, defined as having a mean firing rate > 0.05 Hz on the track; mean information per spike ± s.e. preflight, 1.12 ± 0.08 bits, $n = 19$; FD9, 1.13 ± 0.09 bits, $n = 16$; not significant by Mann-Whitney). We also determined the spatial tuning of 21 active cells from rat 1 on FD9 (**Fig. 2c**). The mean spatial-information content for these cells (1.19 ± 0.09) did not significantly differ from that rat's preflight data (1.37 ± 0.10; $n = 28$).

The mean spatial-information content for all 7 active place cells from rat 3 on the fourth day of flight (FD4) was 1.12 ± 0.27 bits (**Fig. 3a**), which was not different from the information content measured for this rat's place cells before the flight (1.48 ± 0.11 bits; $n = 24$). Another recording session followed immediately, and most cells maintained the same firing fields in both sessions (**Fig. 3b**), demonstrating that the spatial tuning was stable across different exposures to the track.

The rats occasionally turned around on the track and moved counterclockwise for short periods. Some cells demonstrated place fields when the rat was moving only counterclockwise through a single location, thus demonstrating the direction selectivity that is seen on such tracks under normal terrestrial conditions[14]. Hippocampal EEG activity was also

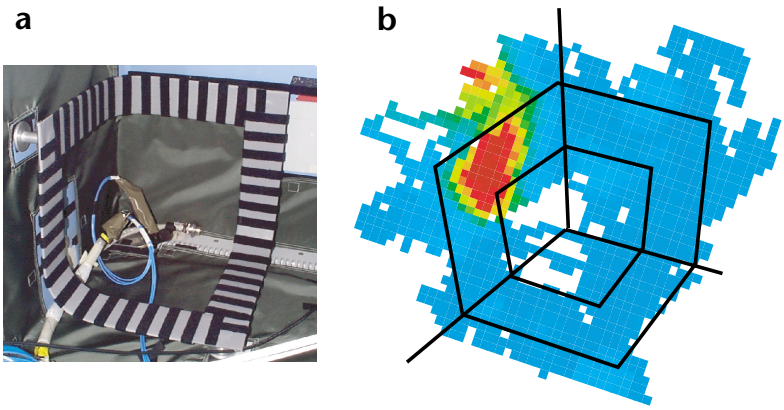

Fig. 1. Escher staircase track. (**a**) To obtain stimulation of the medial forebrain bundle as a reward, the rat moved along the track by grasping the edges of the track and propelling itself forward. (**b**) Normal place field recorded from rat 3. Red indicates maximal firing rate (> 5 spikes per s), and blue indicates positions sampled for which the cell never fired. Locations indicated outside the black outline of the Escher staircase were sampled when the rat's head moved off the track. Although all statistical analyses included these off-track data, they were deleted in the remaining figures for clarity of illustration.

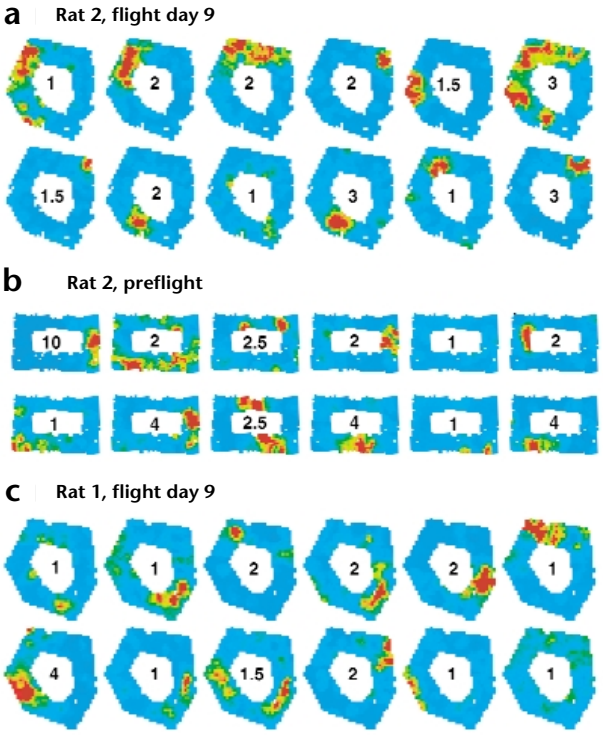

Fig. 2. Representative place fields. (**a**) Normal place fields from rat 2 recorded on FD9. The number inside each map indicates the firing rate coded by red (for instance, > 1 spike per s for the first cell). (**b**) Preflight place fields from rat 2 as the rat ran on a rectangular track. (**c**) Normal place fields from rat 1 on FD9.

recorded during baseline and behavioral sessions in all rats on FD4 and FD9. Although the small number of subjects precluded a statistical analysis, they showed normal theta rhythm during active locomotion and normal sharp waves and ripples[15] during quiet inactivity in the sleeping pouch on both flight days.

It is interesting to note that on the first experience on the Escher staircase on FD4, firing of place cells showed abnormal patterns of spatial selectivity that differed between rats 1 and 2 (J.J.K., B.L.M. and G.R.P., unpublished observations). Thus hippocampal cells can form unique, reliable representations of position on three orthogonal surfaces in microgravity, but they may require either a period of adaptation to microgravity or more experience with the environment than is typically required in normal gravity. It remains to be determined whether the hippocampal code in microgravity can fully represent three dimensions, or whether the system adapts by developing independent two-dimensional representations for each orthogonal surface. It is also unknown what cues drive the firing of place cells under these conditions. Although the eventual formation of stable fields suggests that the visual landmarks may be primary, other contributing factors may include adaptive mechanisms that alter the efficacy of idiothetic cues during extended exposure to microgravity (for instance, changes in the vestibular system or learned ability to path integrate in three dimensions). Despite these unanswered questions, our recordings of CNS neurons from freely moving mammals in space demonstrate the feasibility of performing such complex neurophysiological and behavioral experiments in the microgravity environment. Further experimentation in the international space station may yield a better understanding of the effects of prolonged space flight on various components of the nervous system as well as insight into their normal function on Earth.

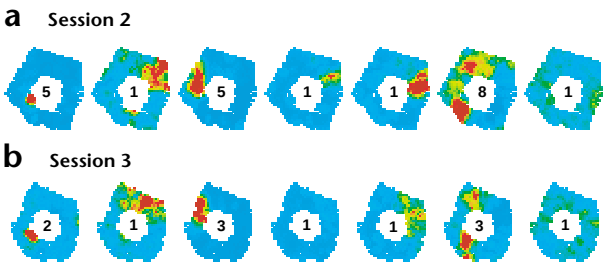

Fig. 3. Stability of place fields across sessions. (**a**) Normal place fields from rat 3 on FD4 recorded on second exposure to the track. (Data from the first exposure were lost because of technical problems.) (**b**) Place fields for the same seven cells on a third run shortly after the second. Most place cells maintained the same firing locations, although the fourth cell lost its field and a few other cells (not shown) gained a field in session 3; such changes in responses of a minority of place cells are not uncommon.

Acknowledgements

We thank the crew of STS-90 (Scott Altman, Jay Buckey, Alex Dunlap, Kay Hire, Rick Linnehan, Chiaki Mukai, Jim Pawelczyk, Rick Searfoss and Dave Williams), Bryan Roberts, Lisa Baer, Mike Eodice, Laurie Dubrovin, Tom Howerton, Louis Ostrach, Chris Maese, Justine Grove, Ali Werner, Dave Bergner, Tom McCarthy, George Swaiss, Steve Carmen, Jim Cockrell and others at NASA-Ames. We also thank Casey Stengel (who designed and built the recording system), Krzystof Jagiello (who designed and wrote the data acquisition software), Kathy Dillon, Shanda Roberts, Shane Smith, Vince Pawlowski, Carol Barnes, Katalin Gothard, Veronica Fedor-Duys, Mark Bower, Karen Reinke, Chris Duffield, Luann Snyder, Doug Wellington and others at the University of Arizona. Additionally, we thank Bill Skaggs and Matt Wilson, who wrote much of the data analysis software, and science and engineering support and management teams at Johnson Space Center and Kennedy Space Center. Supported by grants NAG 2-949 from NASA; NS33471 and NS20331 from NIH; and N0014-98-1-0180 and N0014-96-1-1082 from ONR.

RECEIVED 3 SEPTEMBER 1999; ACCEPTED 1 FEBRUARY 2000

1. Redish, A. D. *Beyond the Cognitive Map* (MIT Press, Cambridge, Massachusetts, 1999).
2. Knierim, J. J., Kudrimoti, H. S. & McNaughton, B. L. *J. Neurosci.* **15**, 1648–1659 (1995).
3. O'Keefe, J. & Nadel, L. *The Hippocampus as a Cognitive Map* (Clarendon, Oxford, 1978).
4. Muller, R. U. & Kubie, J. L. *J. Neurosci.* **7**, 1951–1968 (1987).
5. Goodridge, J. P., Dudchenko, P. A., Worboys, K. A., Golob, E. J. & Taube, J. S. *Behav. Neurosci.* **112**, 749–761 (1998).
6. McNaughton, B. L. *et al. J. Exp. Biol.* **199**, 173–185 (1996).
7. Jeffery, K. J. & O'Keefe, J. M. *Exp. Brain Res.* **127**, 151–161 (1999).
8. Taube, J. S., Muller, R. U. & Ranck, J. B. Jr. *J. Neurosci.* **10**, 420–435 (1990).
9. Taube, J. S. *Prog. Neurobiol.* **55**, 225–256 (1998).
10. Oman, C. M. in *Proceedings of the Symposium on Vestibular Organs and Altered Force Environment* (eds. Igarashi, M. & Nute, K.) 25–37 (NASA Space Biomedical Research Institute, Houston, Texas, 1988).
11. Wilson, M.A. & McNaughton, B. L. *Science* **261**, 1055–1058 (1993).
12. Gothard, K. M., Skaggs, W. E., Moore, K. M. & McNaughton, B. L. *J. Neurosci.* **16**, 823–854 (1996).
13. Skaggs, W. E., McNaughton, B. L., Wilson, M. A. & Barnes, C. A. *Hippocampus* **6**, 149–172 (1996).
14. McNaughton, B. L., Barnes, C. A. & O'Keefe, J. *Exp. Brain Res.* **52**, 41–49 (1983).
15. Buzsaki, G. *Brain Res.* **398**, 242–252 (1986).