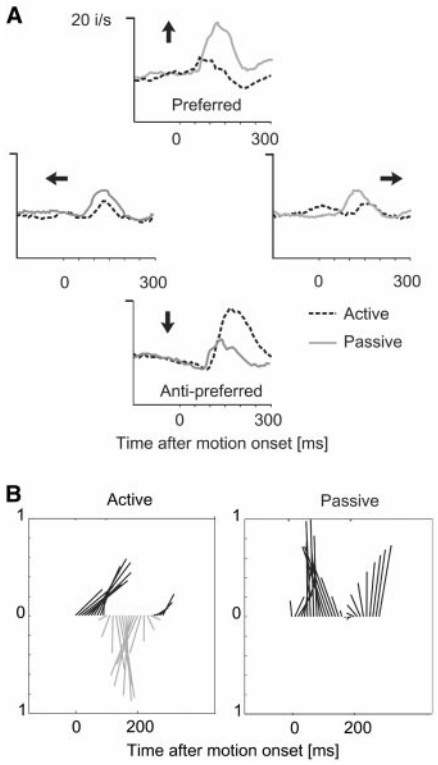


Fig. 4. Population response to saccade-induced and external motion. (**A**) Response of MST directionally selective cells as a function of direction of motion and task condition. Preferred directions of all cells are aligned and presented as upwards. Black curves show the activity when image motion was due to a saccade, gray curves the image motion when it was due to external image motion. (**B**) Time-resolved "preferred direction population vector." For each cell that contributed to (A), the preferred direction vector was calculated in 10-ms bins for the active and passive condition [supplementary note S8 (*18*)] and plotted relative to the preferred direction as determined independently [supplementary note S5 (*18*)]. The angular difference between the preferred direction assessed independently [supplementary note S5 (*18*)] and the preferred direction in the active (passive) condition determined the appearance of the direction vector in the plot. When the difference was zero the vector was plotted upwards; when it was 180° it was plotted downwards [supplementary note S8 (*18*)]. *x* axis: time (in ms) with respect to saccade (motion) onset.

movements. The activity of these neurons can be used to annul the retinal motion signal; consequently, saccade-induced motion is not perceived and external motion perception shortly after saccades is likely to be distorted (*28*). In addition, the sudden reversal of preferred motion direction demonstrates that tuning properties of cortical neurons are not necessarily static, but can be modified in the millisecond range.

References and Notes

1. B. Bridgeman, D. Hendry, L. Stark, *Vision Res.* **15**, 719 (1975).
2. E. Holt, *Harvard Psychol. Stud.* **1**, 3 (1903).
3. E. von Holst, H. Mittelstaedt, *Naturwissenschaften* **20**, 464 (1950).
4. R. W. Sperry, *Vision Res.* **16**, 1185 (1950).
5. D. MacKay, *Nature* **255**, 90 (1970).
6. E. Matin, A. B. Clymer, L. Matin, *Science* **178**, 179 (1972).
7. E. Matin, *Psychol. Bull.* **81**, 899 (1974).
8. F. W. Campbell, R. H. Wurtz, *Vision Res.* **18**, 1297 (1978).
9. D. C. Burr, M. C. Morrone, J. Ross, *Nature* **371**, 511 (1994).
10. J. Ross, D. Burr, C. Morrone, *Behav. Brain Res.* **80**, 1 (1996).
11. M. R. Diamond, J. Ross, M. C. Morrone, *J. Neurosci.* **20**, 3449 (2000).
12. D. C. Burr, J. Holt, J. R. Johnstone, J. Ross, *J. Physiol.* **333**, 1 (1982).
13. U. J. Ilg, K.-P. Hoffmann, *Vision Res.* **33**, 211 (1993).
14. K. H. Britten, M. N. Shadlen, W. T. Newsome, J. A. Movshon, *J. Neurosci.* **12**, 4745 (1992).
15. S. Celebrini, W. T. Newsome, *J. Neurosci.* **14**, 4109 (1994).
16. S. Treue, J. H. R. Maunsell, *Nature* **382**, 539 (1996).
17. A. Thiele, C. Distler, K.-P. Hoffmann, *Eur. J. Neurosci.* **11**, 2044 (1999).
18. Supplementary Web material is available on *Science* Online at www.sciencemag.org/cgi/content/full/295/5564/2460/DC1.
19. D. Commenges, F. Pinatel, J. Seal, *Comput. Methods Prog. Biomed.* **23**, 123 (1986).
20. D. Commenges, J. Seal, *Stat. Med.* **4**, 91 (1985).
21. S. J. Judge, R. H. Wurtz, B. Richmond, *J. Neurophysiol.* **43**, 1133 (1980).
22. D. C. Burr, J. Ross, *Vision Res.* **22**, 479 (1982).
23. W. H. Fischer, M. Schmidt, V. Stuphorn, K.-P. Hoffmann, *Exp. Brain Res.* **110**, 435 (1996).
24. H. Noda, *J. Physiol.* **250**, 579 (1975).
25. A. M. Derrington, F. Felisberti, *Vis. Neurosci.* **15**, 875 (1998).
26. D. A. Leopold, N. K. Logothetis, *Exp. Brain Res.* **123**, 341 (1998).
27. W. Bair, L. P. O'Keefe, *Vis. Neurosci.* **15**, 779 (1998).
28. J. Park, J. Lee, C. Lee, *Vision Res.* **41**, 3751 (2001).
29. We are grateful to F. Bremmer and A. Welchman for valuable discussions and comments on the paper. The research was supported by Deutsche Forschungsgemeinschaft grant SFB509.

7 December 2001; accepted 18 February 2002

Cortical Neurons Encoding Path and Place: Where You Go Is Where You Are

Michael T. Froehler and Charles J. Duffy*

We recorded neuronal activity in monkey medial superior temporal (MST) cortex during movement on a motorized sled. Most neurons showed a preferred heading direction, but some responded only when that heading was part of a particular path. Others responded only when the animal was at a certain place in the room, regardless of its path to that place. Video simulations of the self-movement scene evoked path, but not place, responses. Stationary positioning in the room revealed location preferences that matched place preferences recorded during movement. We conclude that MST encodes heading, path, and place information to support visuospatial orientation.

The visual motion of optic flow (*1*) is processed by MST neurons (*2–6*) to derive the heading of self-movement (*7*). Adjacent cortical areas (*8–10*) project to hippocampal (*11*, *12*) place cells that build a cognitive map of the environment (*13–15*). This network may serve the path integration of parietal self-movement responses (*16*) involved in spatial orientation (*17*) and disorientation (*18*). We now show that MST integrates heading and location to encode the path and place of self-movement, potentially serving spatial cognition.

Natural heading sequences were presented as translational movement on a circular path in front of a stationary array of small white lights viewed during straight-ahead gaze (Fig. 1A) (*19*).

Departments of Neurology, Neurobiology and Anatomy, Ophthalmology, Brain and Cognitive Sciences, and the Center for Visual Science, The University of Rochester Medical Center, Rochester, NY 14642, USA.

*To whom correspondence should be addressed. E-mail: cjd@cvs.rochester.edu

Most MST neurons (73%, 46/63) showed significant direction tuning (Fig. 1B), identified by the circular net vector (Z of circular distribution $P \leq 0.05$) (*20*, *21*).

Clockwise (CW) and counterclockwise (CC) circular paths presented the same headings in reversed sequences with identical headings on opposite sides of the room. Nevertheless, many neurons had similar heading preferences on CW and CC paths (Fig. 1C), although 40% (25/63) showed at least a twofold difference (*22*) between CW and CC response amplitudes (Fig. 1D).

Most neurons with comparable CW and CC response amplitudes preferred the same heading on both paths (Fig. 2A), but some preferred opposite headings. The neuron in Fig. 2B preferred rightward CW headings and leftward CC headings with both responses corresponding to the front of the room. This neuron was more affected by place-during-movement than by heading or path.

We used circular statistics (*21*) to describe heading, path, and place-during-movement selectivity. The sample's distribution of direction-

ality showed no predominant heading preference. About half (46%, 21/46) of the neurons showed significant directionality on only the CW or the CC path. The remaining neurons (54%, 25/46) showed significant directionality on both paths, most (35%, 16/46) with similar preferred headings (CW-CC difference <50°) but many (20%, 9/46) with opposite preferred headings (CW-CC difference >100°). This creates the discontinuous distribution of directional differences separating heading and place preference neurons during movement (Fig. 2C).

We assessed the contributions of visual motion and translational movement by recording responses under three conditions (*23*): optic flow video simulations presented while the monkey was stationary, optic flow presented with matching CW or CC translational movement, and translational movement presented in darkness (no optic flow). Fig. 3, A to C, shows a neuron's preference for leftward headings on the CC path with optic flow alone (3A) or with translational movement (3B), but not with movement alone (3C); a typical response pattern (*24*).

Optic flow with movement evoked a continuum of CW/CC response amplitude differences (Fig. 3D) like that seen during movement past the room-mounted lights (Fig. 1D). In contrast, CW/CC directional differences were always <90° during simulated optic flow with movement (Fig. 3E), with no place-during-movement preferences (differences ~180°) like those seen during movement past the room-mounted lights (Fig. 2C). We used optic flow simulating movement in front of a wall or through a cloud of dots (*24*), both evoked the heading-path response continuum without place-during-movement effects.

The source of selectivity for place-during-movement was explored by positioning the monkey at four stationary locations on the circular path while it viewed the room-mounted lights (*19*). Neuronal activity varied with the monkey's stationary position in

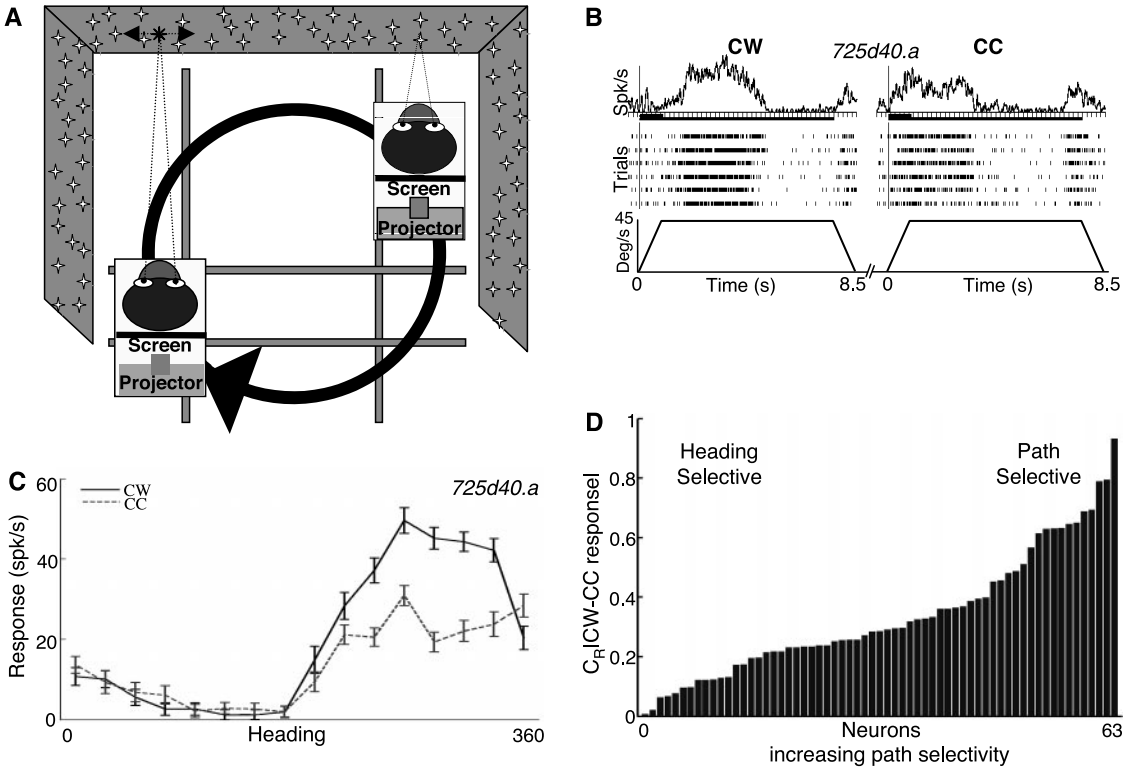
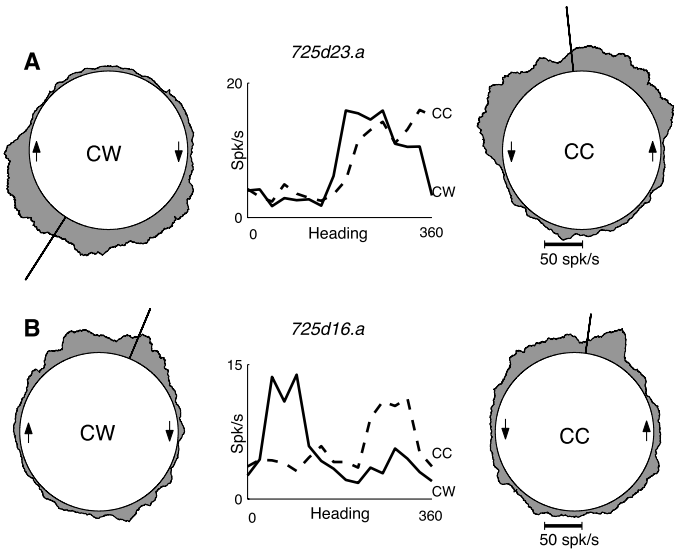


Fig. 1. Path-dependent heading selectivity. (**A**) The monkey viewed either a light-array or a video projection screen during translational sled movement on a circular path. (**B**) Spike-density histograms and raster displays of a neuronal response showing a left-forward heading preference that is stronger with CW motion (left). (**C**) A neuron's responses to 16 heading intervals revealing greater CW heading selectivity. (**D**) Contrast ratios of CW and CC response amplitudes at the neuron's preferred heading, 73% showed significant directionality (Z statistic) on at least one path.



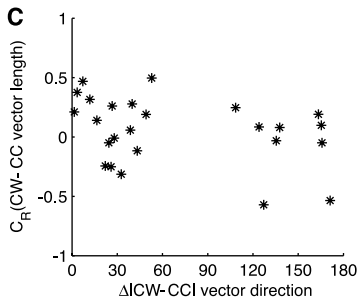


Fig. 2. Heading and place preferences. (**A** and **B**) Spike-density polar plots (spikes/s) and net vectors (radial lines) with respect to heading (*22*). (A) Responses of a neuron with similar heading preferences on both paths (CW = 237°, CC = 276°). (B) A neuron with opposite heading preferences (CW = 67°, CC = 262°); a place preference for the right front of the room. (**C**) Heading and place preferences on a scatter plot of CW and CC response contrast (ordinate, C_R) versus the difference between CW and CC preferred directions (abscissa) for the 25 neurons with significant CW and CC responses.

the room (Fig. 4A) and was not attributable to ocular vergence (*25*) or disparity (*26*) effects: there was no relationship to distance from the wall (Fig. 4B), and all light stimuli were on the plane of fixation (*27*).

Stationary location effects were related to place-during-movement preferences in two ways. First, significant stationary location effects were more common (78%, 7/9) in neurons with place-during-movement preferences (CW/CC directional differences >100°) than in neurons (38%, 6/16) with heading preferences (CW/CC directional differences <50°). In addition, the preferred stationary location was close to the preferred place-during-movement (Fig. 4C).

These experiments reveal that MST encodes both instantaneous heading direction and the path to that heading. Path-dependent heading responses from simulated optic flow show the influence of the context (*16*, *28*) created by heading sequences. The absence of context effects with other stimuli (*29*) suggests a critical role for heading sequences that represent a naturalistic path.

The heading-path response continuum must be separate from place preferences, because they are double-dissociated: Optic flow simulations yield path, but not place-during-movement, preferences; and stationary positioning yields location effects without a path. Nevertheless, path and place effects might interact. Stimulus sequence effects could support path integration and update position in the hippocampal place map (*14*, *15*, *30*). Hippocampal place information might feed back to create location effects when the monkey is stationary and path effects when the monkey is moving. Such reciprocal interactions may transform self-movement signals into a cognitive map; converting where you go, to where you are.

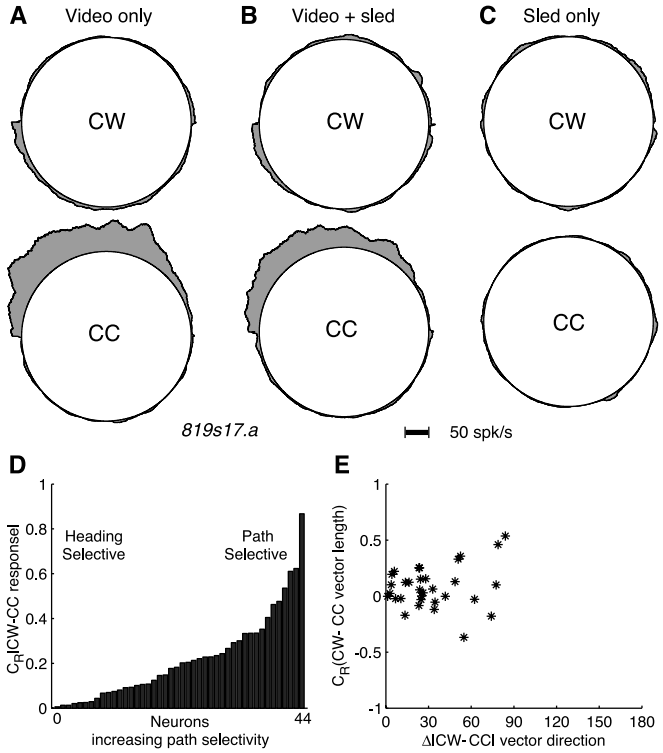


Fig. 3. Path, but not place, preferences with simulated optic flow. (**A** to **C**) A neuron that showed rightward CC heading preferences in response to optic flow (A) regardless of translational movement (B), and no response to movement in darkness (C). (**D**) CW/CC response contrast ratios showing path preferences, format as in Fig. 1D, 16% (7/44) showed at least a twofold difference. (**E**) Neurons with CW and CC responses showed heading, but not place, preferences, (format as in Fig. 2C).

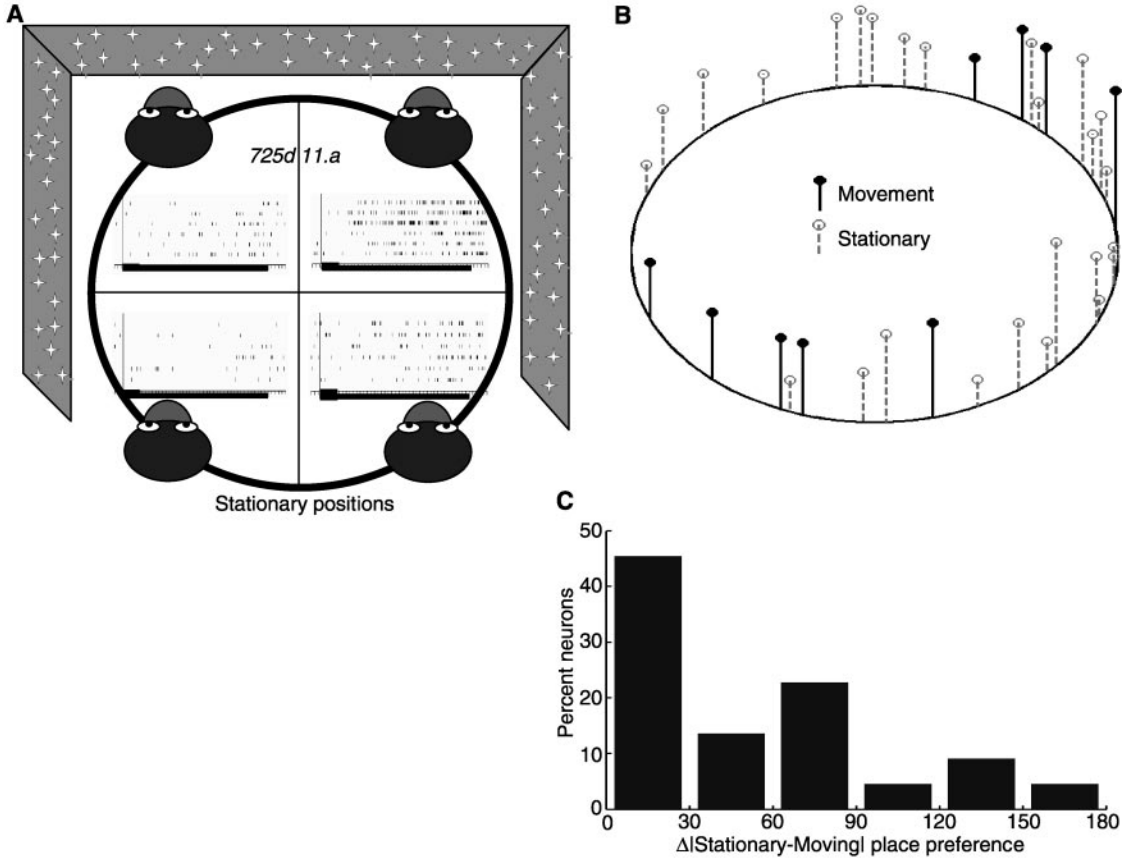


Fig. 4. Stationary location and place-during-movement preferences. (**A**) A neuron recorded at four stationary locations and preferring the right-forward location. (**B**) Preferred stationary locations (open, $n = 26$) and places-during-movement (filled, $n = 9$) on the circular path. (**C**) Similarity of preferred stationary locations and places-during-movement for the 22 neurons with significant location effects and significant responses on both CW and CC paths.

References and Notes

1. J. J. Gibson, *The Perception of the Visual World* (Houghton Mifflin, Boston, 1950).
2. H. Saito *et al.*, *J. Neurosci.* **6**, 145 (1986).
3. K. Tanaka, Y. Fukuda, H. Saito, *J. Neurophysiol.* **62**, 642 (1989).
4. C. J. Duffy, R. H. Wurtz, *J. Neurophysiol.* **65**, 1346 (1991).
5. G. A. Orban *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 2595 (1992).
6. M. S. A. Graziano, R. A. Andersen, R. J. Snowden, *J. Neurosci.* **14**, 54 (1994).
7. C. J. Duffy, R. H. Wurtz, *J. Neurosci.* **15**, 5192 (1995).
8. S. J. Schaafsma, J. Duysens, *J. Neurophysiol.* **76**, 4056 (1996).
9. F. Bremmer, U. Ilg, A. Thiele, C. Distler, K.-P. Hoffmann, *J. Neurophysiol.* **77**, 944 (1997).
10. R. M. Siegel, H. L. Read, *Cereb. Cortex* **7**, 327 (1997).
11. K. S. Rockland, G. W. Van Hoesen, *Cereb. Cortex* **9**, 232 (1999).
12. D. M. Clower, R. A. West, J. C. Lynch, P. L. Strick, *J. Neurosci.* **21**, 6283 (2001).
13. J. O'Keefe , L. Nadel, *The Hippocampus as a Cognitive Map* (Clarendon, Oxford, UK, 1978).
14. T. Ono, K. Nakamura, H. Nishijo, E. A. Eisenhauer, *J. Neurophysiol.* **70**, 1516 (1993).
15. H. Nishijo, T. Ono, S. Eifuku, R. Tamura, *Neurosci. Lett.* **226**, 57 (1997).
16. B. L. McNaughton *et al.*, *Cereb. Cortex* **4**, 27 (1994).
17. E. T. Rolls, in *The Hippocampal and Parietal Foundations of Spatial Cognition*, N. Burgess, K. J. Jeffery, J. O'Keefe, Eds. (Oxford, New York, 1999), chap. 17.
18. H. L. O'Brien *et al.*, *Cereb. Cortex* **11**, 1083 (2001).
19. The animals received water reward for fixating a projected light-emitting diode (LED), either on the wall in front of the monkey or on the rear-projection screen. Eye position was monitored using the magnetic search coil technique (*31*, *32*). The room was illuminated by ~1000, small, incandescent lights (1.9 cd/m^2 on a black background) covering the three walls that were visible through the monkey's 90° × 90° field of view. The monkey faced the wall while the computer-controlled motorized sled either moved it along a circular path 127 cm in diameter, or positioned it at one of four stationary locations at 90° intervals on the circular path. All 63 neuronal responses were characterized by averaging across a pseudorandom sequence of four starting positions and six repetitions of each trial type. Each trial began with the illumination of the room-mounted light array, and the centered fixation point with recording started after 250 to 500 ms of centered fixation. Movement trials consisted of: 1 s of acceleration at 45°/s^2, followed by 7.5 s of movement at 45°/s around 360° at a speed of 47 cm/s. The sled would then decelerate for 1 s at 45°/s^2, the room light array was extinguished, and the monkey's reward was delivered. Stationary position trials required the monkey to maintain centered fixation in front of the room-mounted light array. After 8.5 s, the light array and fixation point were extinguished, and the reward was delivered. The position of the fixation point tracked sled movement so that the monkey maintained neutral, straight-ahead gaze throughout all trials.
20. We recorded 107 neurons from four cerebral hemispheres in two rhesus monkeys. All studies presented are based on data sets that include neurons from both monkeys. All procedures were approved by the University of Rochester Committee on Animal Research and were consistent with Society for Neuroscience policy on the care and use of laboratory animals. Bilateral recording cylinders were placed over trephine holes in the parietal calvarium (stereotaxic coordinates: AP –2 mm, ML ± 15 mm, angle 0) above area MST. Microelectrode penetrations were made using epoxy-coated tungsten microelectrodes (FHC, Inc.) that were passed through transdural guide tubes into cortex (*33*). The location of recording sites on the anterior bank of the superior temporal sulcus was confirmed by magnetic resonance imaging with selected electrodes in place. MSTd neurons were identified by physiologic criteria: large receptive fields (>20°× 20°), which included the fovea with direction-selective responses that prefer large moving patterns rather than moving bars or spots (*7*, *2*, *34*). Single neuron discharges were isolated by using a dual-window discriminator and stored through the REX experimental control system (*35*).
21. E. Batschelet, *Circular Statistics in Biology* (Academic Press, New York, 1981).
22. The significance of effects on neuronal responses was tested by two-way ANOVAs having main effects of heading and path direction (CW or CC). Visual and translational movement responses were characterized by using 16 movement intervals around the CW and CC circular paths, and stationary location responses were characterized by four positions around the room. Circular statistics (*20*, *36*) were implemented in Matlab v.5 to derive a net vector for each neuron's averaged responses to CW, CC, and stationary trials. The angle of the net vector indicated the location at which the preferred heading occurred and the length of the net vector indicated the strength of that preference. A Z statistic was used to identify net vectors that reflected significant selectivity in unimodal response profiles.
23. In optic flow video simulation experiments, the monkey viewed a 90° by 90° rear-projection screen while maintaining neutral gaze by fixating on a red LED image at the center of the screen. Randomly interleaved trials consisted of computer-generated optic flow simulations, translational sled movement, or both. The optic flow video displays averaged ~1000 white dots (2.6 cd/m^2) on a black background moving to simulate the visual motion pattern seen during observer movement in front of a stationary array of dots. The distance cue in the video simulation was either dot density or motion parallax (*24*). Accompanying translational movement matched the direction and speed of the optic flow video simulations and was identical to CW and CC circular translational movement presented when the monkey viewed the room-mounted lights. All 44 neuronal studies included a pseudorandom sequence of six repetitions of each stimulus type.
24. Supplementary figures and details of video stimuli are available on *Science* Online at www.sciencemag.org/cgi/content/full/295/5564/2462/DC1
25. Y. T. A. Inoue, K. Kawano, T. Kitama, F. A. Miles, *Exp. Brain Res.* **121**, 135 (1998).
26. J. P. Roy, H. Komatsu, R. H. Wurtz, *J. Neurosci.* **12**, 2478 (1992).
27. Ocular vergence effects were considered as a possible explanation for heading-path and place-during-movement preferences. However, the monkey's viewing distance in the room was always >1 m, beyond the range of most vergence effects. Also, identical vergence states exist on opposite sides of the circle so that vergence responses would occur on both sides. However, there were no biphasic place effects, and there was an even distribution of preferred places-during-movement and stationary locations (Fig. 4B). Vergence may still have some affect on these responses, but oculomotor afferent information alone does not explain place selectivity.
28. C. J. Duffy, R. H. Wurtz, *Exp. Brain Res.* **114**, 472 (1997).
29. M. Paolini, C. Distler, F. Bremmer, M. Lappe, K.-P. Hoffmann, *J. Neurophysiol.* **84**, 730 (2000).
30. B. L. McNaughton, B. Leonard, L. L. Chen, *Psychobiology* **17**, 230 (1989).
31. D. A. Robinson. *IEEE Trans. Bio.-Med. Eng.* **10**, 137 (1963).
32. S. J. Judge, B. J. Richmond, F. C. Chu, *Vision Res.* **20**, 535 (1980).
33. C. F. Crist, D. S. Yamasaki, H. Komatsu, R. H. Wurtz, *J. Neurosci. Methods* **26**, 117 (1988).
34. H. Komatsu, R. H. Wurtz, *J. Neurophysiol.* **60**, 580 (1988).
35. A. V. Hays, B. J. Richmond, L. M. Optican, *WESCON Conf. Proc.* **2**, 1 (1982).
36. K. V. Mardia, *Statistics of Directional Data* (Academic, London, 1972).

37. This work was supported by grants from the National Eye Institute (EY10287) and the National Institutes on Aging (AG17596). M.T.F. is a trainee in the Medical Scientist Training Program (T32-GM07356) and is additionally supported by an NIH training grant to The University of Rochester Center for Visual Science (T2-EY07125C). The authors are grateful to J. Postle for technical support, W. Vaughn for computer support, and to W. K. Page and V. Kavcic, and to M. J. Dubin and D. J. Logan for comments on an earlier draft of the manuscript.

25 October 2001; accepted 29 January 2002

Molecular Determinants for the Tissue Specificity of SERMs

Yongfeng Shang and Myles Brown*

Selective estrogen receptor modulators (SERMs) mimic estrogen action in certain tissues while opposing it in others. The therapeutic effectiveness of SERMs such as tamoxifen and raloxifene in breast cancer depends on their antiestrogenic activity. In the uterus, however, tamoxifen is estrogenic. Here, we show that both tamoxifen and raloxifene induce the recruitment of corepressors to target gene promoters in mammary cells. In endometrial cells, tamoxifen, but not raloxifene, acts like estrogen by stimulating the recruitment of coactivators to a subset of genes. The estrogen-like activity of tamoxifen in the uterus requires a high level of steroid receptor coactivator 1 (SRC-1) expression. Thus cell type– and promoter-specific differences in coregulator recruitment determine the cellular response to SERMs.

Tamoxifen and raloxifene are selective estrogen receptor modulators (SERMs) that bind the estrogen receptor (ER) and modulate ER-mediated gene transcription. Tamoxifen is an effective treatment for all stages of hormone-responsive breast cancer and can prevent breast cancer in high-risk women (*1*). However, tamoxifen has partial estrogenic activity in the uterus and is associated with an increased incidence of endometrial hyperplasia and cancer. Raloxifene, approved for the prevention and treatment of osteoporosis in postmenopausal women, also appears to prevent

Department of Adult Oncology, Dana-Farber Cancer Institute, 44 Binney Street, and Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA.

*To whom correspondence should be addressed. E-mail: myles_brown@dfci.harvard.edu