Furthermore, how are peripheral signals such as insulin, leptin, ghrelin, and cholecystokinin affecting hypothalamic synaptic plasticity? While Crosby et al. (2011) focused on GABAergic synapses, it is important to know whether glutamatergic synapses in the DMH can also undergo activity-dependent plasticity and whether food-deprivation can trigger changes in DMH excitatory transmission. Ultimately, the balance of excitatory and inhibitory synaptic transmission determines DMH output. The DMH sends direct projections to the paraventricular nucleus (PVN), a major homeostatic workhorse for the hypothalamus and brain. Stimulating different areas of the DMH causes different PVN outputs (Ulrich-Lai and Herman, 2009). Because PVN neurons ultimately trigger CORT release into the blood from the adrenal cortex, which prepares virtually every cell in the body for an ensuing stressor, it is important for researchers to determine how the synaptic plasticity described by Crosby et al. (2011) affects downstream hypothalamic nuclei such as the PVN. CORTs are also known to promote eCB signaling in the hypothalamus (Tasker, 2006), and eCBs are key regulators of food intake and energy balance. As a result, eCBs have garnered much attention in the fight against eating disorders (Di Marzo and Matias, 2005). In this context, the study by Crosby et al. (2011) may provide a window on how food intake can be controlled by targeting synaptic function in the hypothalamus. Future studies to test this exciting possibility are warranted.

REFERENCES

Bellinger, L.L., and Bernardis, L.L. (2002). Physiol. Behav. *76*, 431–442.

Berthoud, H.R. (2002). Neurosci. Biobehav. Rev. *26*, 393–428.

Castillo, P.E., Chiu, C.Q., and Carroll, R.C. (2011). Curr. Opin. Neurobiol. *21*, 328–338.

Chiu, C.Q., Puente, N., Grandes, P., and Castillo, P.E. (2010). J. Neurosci. *30*, 7236–7248.

Crosby, K.M., Inoue, W., Pittman, Q.J., and Bains, J.S. (2011). Neuron *71*, this issue, 529–541.

Di Marzo, V., and Matias, I. (2005). Nat. Neurosci. *8*, 585–589.

Heifets, B.D., and Castillo, P.E. (2009). Annu. Rev. Physiol. *71*, 283–306.

Kano, M., Ohno-Shosaku, T., Hashimotodani, Y., Uchigashima, M., and Watanabe, M. (2009). Physiol. Rev. *89*, 309–380.

Kleppisch, T., and Feil, R. (2009). Handb Exp Pharmacol *191*, 549–579.

Lafourcade, M., Larrieu, T., Mato, S., Duffaud, A., Sepers, M., Matias, I., De Smedt-Peyrusse, V., Labrousse, V.F., Bretillon, L., Matute, C., et al. (2011). Nat. Neurosci. *14*, 345–350.

Nugent, F.S., Penick, E.C., and Kauer, J.A. (2007). Nature *446*, 1086–1090.

Tasker, J.G. (2006). Obesity (Silver Spring) *14* (*Suppl 5*), 259S–265S.

Ulrich-Lai, Y.M., and Herman, J.P. (2009). Nat. Rev. Neurosci. *10*, 397–409.

Wamsteeker, J.I., Kuzmiski, J.B., and Bains, J.S. (2010). J. Neurosci. *30*, 11188–11196.

Woodin, M.A., and Maffei, A., eds. (2011). Inhibitory Synaptic Plasticity (New York: Springer).

New Insights into Motor Cortex

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An exciting new experiment on the motor cortex of monkeys, by Shenoy and colleagues, begins to elucidate how the neuronal ensemble travels in a systematic fashion through state space. This trajectory through state space may help to explain how the motor cortex sets up and then triggers arm movements.

Imagine that you live on a hilly plain. You are rolling a large spherical boulder around the terrain in hopes of crushing an enemy. The way to crush him is to roll the boulder to the right spot on the right hill and to wait for the opportune moment. Then you can push the rock over the crest of the hill, passing a threshold on the terrain. If you have found a good initial location, the rock will follow a specific trajectory down the hill and smash through your enemy. Action accomplished. To smash another enemy at the same spot, you will have to roll your boulder around and up the back of the hill to the same preparatory location, and then wait for the next opportunity. To smash an enemy at a different location, you will have to find another hill. The concept is simple and intuitive. According to the article by Afshar et al. (2011) (this issue of *Neuron*), the same intuitive concept may be able to explain how neurons in the motor cortex of monkeys prepare for specific reaching movements of the arm.

The network within the motor cortex, with its fluctuating activity levels of millions of neurons, defines a state space and moves along trajectories through that space like a boulder rolling around a hilly terrain, albeit a multidimensional terrain. The movement through state space can be measured, at least approximately, by monitoring the activity of a sample of neurons using an electrode array. To prepare for a specific arm movement, the network moves to and pauses in a restricted region of state space. To produce the movement, the network then leaves that restricted region of state space and moves in a particular direction as if pushed over the cusp of a hill, a threshold from which the "stone" rolls along a stereotyped trajectory. In following that trajectory through state space, the network causes the arm movement. To prepare for another arm movement, the network then travels through state space up the back of the hill so to speak, and is parked once again in the preparatory location. In performing repeated trials of the reaching task, the network therefore moves in a repeating loop around state space.

Shenoy and colleagues have been steadily building this insightful new understanding of the dynamics of motor cortex (Churchland et al., 2006; 2010). The key addition in the present study concerns the latency of the movement. Intuitively, the closer you park the stone to the crest of the hill, the faster you can get it over the crest and on its way when called to do so. The same relationship to latency was found in the motor cortex. While the monkey is preparing to make the arm movement, the network moves into its preparatory position. By random variation, sometimes it is moved a little farther, sometimes a little less far, along the path that it will ultimately take to trigger the arm movement. If the preparatory state is farther along that trajectory, and the monkey is then signaled to make the movement, the latency to move is shorter. The importance of the study is that it lends specific, quantitative support for the new view of motor cortex.

The approach taken by Afshar et al. (2011) does not so much overturn previous conceptions of motor cortex as open a new door. The emphasis is not on how muscles are controlled, but on how the neuronal network in the motor cortex operates. The potential generality of the result is also of interest. The same concepts might be applicable to any cortical area as it sends control signals to other neural structures.

For more than a century a simple conception of motor cortex dominated the literature. In that traditional view, motor cortex contains output neurons that project down the pyramidal tract to the spinal cord, synapse on motor neurons, and thereby affect muscles. Activity of the pyramidal tract neurons translates directly to muscular force. This view was perhaps most fully articulated by Evarts (1968) and Asanuma (1975). But what pulls the marionette strings? What decides which muscles to combine into meaningful ensembles and how to shape the timing of the activity? How are movements planned, and what stops the plan from being executed prematurely? These questions are not easily approached in the traditional view of cortical output wires.

A more sophisticated picture was provided by the work of Cheney and Fetz (1985), who found that individual neurons in the motor cortex showed evidence of a direct pathway to a large set of muscles. One neuron in cortex could in principle coordinate a pattern of activity among a set of muscles. Yet even this description says nothing about the dynamics of the network in motor cortex. Though the marionette strings are more complex, each string branching to attach to many parts of the marionette, the question remains: what is the nature of the cortical network that pulls the strings?

An epic, twenty-year battle was fought over the cortical representation of movement. Do motor cortex neurons represent the direction of the hand during reaching, or do they represent other features of movement such as joint rotation or muscle output (Georgopoulos et al., 1986; Kakei et al., 1999; Scott and Kalaska, 1995; Todorov, 2000)? As vigorous as this debate may have been, it still did not address the nature of the network within the motor cortex. Indeed, it tended to emphasize the properties of individual neurons rather than network properties. If a neuron does represent some higher order aspect of movement, how is the representation constructed by the network in which the neuron is embedded, and how does a representation of a movement ultimately cause a movement? The battles over the cortical representation of movement never satisfactorily addressed those questions.

One of the more unexpected modern findings in motor cortex is that electrical stimulation on a behavioral time scale can evoke complex, ethologically relevant movements, and that different classes of movement are evoked from different subregions of cortex (Graziano et al., 2002; Stepniewska et al., 2009). For example, the subregion studied by Afshar et al. (2011), when stimulated, tends to evoke an outward projection of the arm and a shaping of the hand, consistent with an emphasis on the control of reaching. Other subregions, when stimulated, evoke feeding-type movements, defensive-type movements, climbing-type movements, digital manipulation-type movements, and so on. Yet these results, informative about the overarching topography of the motor cortex (Graziano and Aflalo, 2007), revealed little about the mechanism—about the network properties that cause movement to occur.

Other major lines of research on motor cortex could be cited here, many of them useful and informative. Yet almost all of these previous approaches sidestep the issue of cortical mechanism. How does the network of cortical neurons function? What are its dynamics? Under what conditions does it cause movement, withhold movement, or plan movement, and how does it transition from one state to another? The work of Afshar et al. (2011) is valuable precisely because it steps into the gap and addresses questions about the cortical network. For the first time the behavior of the network itself is being elucidated.

REFERENCES

Afshar, A., Santhanam, G., Yu, B.M., Ryu, S.I., Sahani, M., and Shenoy, K.V. (2011). Neuron *71*, this issue, 555–564.

Asanuma, H. (1975). Physiol. Rev. *55*, 143–156.

Cheney, P.D., and Fetz, E.E. (1985). J. Neurophysiol. *53*, 786–804.

Churchland, M.M., Yu, B.M., Ryu, S.I., Santhanam, G., and Shenoy, K.V. (2006). J. Neurosci. *26*, 3697–3712.

Churchland, M.M., Cunningham, J.P., Kaufman, M.T., Ryu, S.I., and Shenoy, K.V. (2010). Neuron *68*, 387–400.

Evarts, E.V. (1968). J. Neurophysiol. *31*, 14–27.

Georgopoulos, A.P., Schwartz, A.B., and Kettner, R.E. (1986). Science *233*, 1416–1419.

Graziano, M.S.A., and Aflalo, T.N. (2007). Neuron *56*, 239–251.

Graziano, M.S.A., Taylor, C.S.R., and Moore, T. (2002). Neuron *34*, 841–851.

Kakei, S., Hoffman, D.S., and Strick, P.L. (1999). Science *285*, 2136–2139.

Scott, S.H., and Kalaska, J.F. (1995). J. Neurophysiol. *73*, 2563–2567.

Stepniewska, I., Fang, P.C., and Kaas, J.H. (2009). J. Comp. Neurol. *517*, 765–782.

Todorov, E. (2000). Nat. Neurosci. *3*, 391–398.