The next step was to inject a local anesthetic into catheters or cuffs surrounding the nerves that innervate wrist muscles, temporarily, but reversibly, paralyzing these muscles. During paralysis, changes in cell activity were used to control the current level of FES applied through electrodes implanted in the paralyzed wrist muscles. Similar to pre-injection trials, the monkey was rewarded when the cursor reached the spatial targets, but in this case, it was the activity of the single neuron in the primary motor cortex that was controlling FES of the wrist muscles. The monkey's performance was relatively poor at the beginning with FES, with only about four successful targets reached in a minute, but with practice, the monkey was able to successfully acquire about 14 targets per min, with relatively few errors. Admittedly, FES only provided control of flexor or extensor wrist torques, but it does demonstrate the principle that cortical signals can be used to re-animate a paralyzed limb.

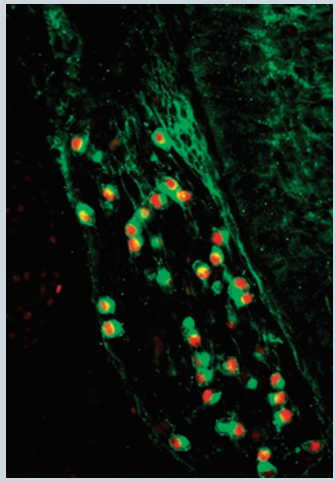
What is surprising in this study is that FES was controlled using the discharge rate of a single cortical neuron, rather than a large population of neurons. Moreover, it did not seem to matter whether or not the neuron used to control FES current levels had modulated its activity earlier in the experiment, when the monkey generated wrist torques with the nonparalyzed muscles. That is, neurons that did not modulate their activity under normal conditions started to modulate their activity when they were used to control FES.

These results raise two questions. First, how can the discharge pattern of a single neuron successfully control wrist motor function when the prevailing view is that one needs to record from a large population of neurons? The second question is even more perplexing: why should a neuron that is normally inactive when a monkey moves a cursor suddenly modulate its activity when it is driving FES of the same muscle group to perform essentially the same task? These questions are puzzling if one assumes that the activity of all of the neurons in the primary motor cortex is specifying some parameter of movement and that the goal of neuroprosthetics is to read out this signal. It is less of a surprise if the primary motor cortex is seen as a part of a flexible control system that converts motor goals (for example, moving a cursor on a screen) into coordinated patterns of muscle activity. The most impressive aspect of the voluntary motor system is the breadth of motor skills that we can perform, from playing a piano to juggling while riding a unicycle. One theory suggests that the brain develops specialized control policies or feedback laws that are unique for each behavioral task[9,10]. Learning a new motor skill reflects a process of developing a new control policy that is appropriate for that task. The use of cell activity to control FES of wrist muscles that move a cursor is simply a new skill that the monkey's brain must learn. The result is that neurons that are not tuned during normal wrist movements can become modulated if this facilitates the goal of the task. This latter observation is reminiscent of a previous study on operant conditioning between the primary motor cortex and limb muscle activity[11].

The success of the present study in using a single neuron to control FES should generate healthy debate about the best strategy for creating a cortical-based neuroprosthetic. The assumption has been to record from as many neurons as possible and to put one's faith into developing more sophisticated mathematical algorithms to convert all of these spike trains into purposeful control signals. However, this approach limits the potential use of the brain to adapt and improve control, as it is unlikely that any algorithm will ever be as clever as the brain for solving motor control problems. A better strategy would be to take advantage of the brain's enormous processing power, which permits learning and adaptation, to solve a new motor problem, whether it is moving a computer cursor, a robotic aid or controlling FES of muscles to permit these subjects to re-use their paralyzed limb.

1. Moritz, C.T., Perlmutter, S.I. & Fetz, E.E. *Nature* advance online publication, doi:10.1038/nature07418 (15 October 2008).
2. Georgopoulos, A.P., Kettner, R.E. & Schwartz, A.B. *J. Neurosci.* **8**, 2928–2937 (1988).
3. Scott, S.H., Gribble, P.L., Graham, K.M. & Cabel, D.W. *Nature* **413**, 161–165 (2001).
4. Wessberg, J. *et al. Nature* **408**, 361–365 (2000).
5. Musallam, S., Corneil, B.D., Greger, B., Schergerger, H. & Andersen, R.A. *Science* **305**, 258–262 (2004).
6. Santhanam, G., Ryu, S.I., Yu, B.M., Afshar, A. & Shenoy, K.V. *Nature* **442**, 195–198 (2006).
7. Hochberg, L.R. *et al. Nature* **442**, 164–171 (2006).
8. Peckham, P.H. *et al. J. Hand. Surg. (Am.)* **27**, 265–276 (2002).
9. Todorov, E. & Jordan, M.I. *Nat. Neurosci.* **5**, 1226–1235 (2002).
10. Scott, S.H. *Nat. Rev. Neurosci.* **5**, 532–546 (2004).
11. Fetz, E.E. & Finocchio, D.V. *Exp. Brain Res.* **23**, 217–240 (1975).

A master regulator of nociceptor differentiation



Nervous system development is orchestrated by transcription factors acting in sequence and in networks. The effectors that actually execute the steps leading to early specification or later phenotypic maturation of developing neurons are largely unknown. On pp. 1283–1293, Sun *et al.* identify some of these effectors, using the transcription factor Islet1 and its role in sensory neuron development as their model system.

The authors genetically excised Islet1 from the early mouse neural crest and dorsal neural tube. Dorsal root and trigeminal ganglia formed normally, but, from E12.5 onwards, most pain- and touch-sensitive neurons, as identified by TrkA, TrkB or Runx1 expression, died. Proprioceptive neurons were far less affected. The figure shows surviving proprioceptors, identified by Runx3 (red) and TrkC (green), in an E14.5 dorsal root ganglion (DRG) lacking Islet1.

How could the absence of Islet1 cause such specific apoptosis? The time course of Islet1 expression offered a partial explanation. Nearly all wild-type sensory neurons expressed Islet1 from approximately E10 onwards, but the proprioceptive cells had downregulated it by E14.5. Thus, they may not require Islet1-dependent pathways for differentiation and survival.

By immunostaining and gene expression analysis, Sun *et al.* reveal a complicated picture of how Islet1 functions in sensory neuron subtype differentiation. In the nociceptive lineage, initial induction of the receptor TrkA was independent of Islet1, whereas expression of the transcription factor Runx1 required it. The mRNA levels of several nociceptor-specific genes were substantially reduced in E12.5 DRG that lacked Islet1, among them the channels $Na_v1.8$ and TRPV1. In the proprioceptive lineage, onset of TrkC expression was delayed, but expression of Runx3 was unaffected. Several mRNAs coding for transcription factors involved in earliest neuron specification or in hindbrain and spinal cord development were abnormally expressed in Islet1-null DRG. Thus, a major function of Islet1 seems to be the repression of inappropriate genetic programs.

One important question remains unanswered: how does Islet1 enable the survival of certain sensory neurons past E12.5? Future work, undoubtedly, will tell.

Annette Markus