

# Cortical-based neuroprosthetics: when less may be more

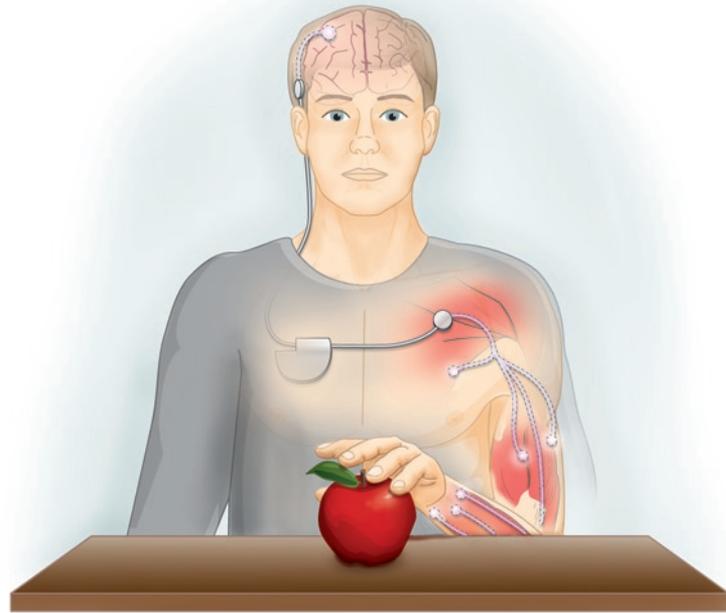
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Combined population activity is usually used to control neural prosthetics. A recent study in *Nature* finds that a single primary motor cortex neuron can control the artificial stimulation of paralyzed wrist muscles to move a computer cursor.

We take for granted the ease with which we can walk, reach out and grab a cup of coffee, or type on a computer. Yet these basic motor skills become impossible following severe neurological insults such as spinal cord injuries. Neural regeneration to repair the damage remains a distant goal, but artificial means to bypass the injury and re-animate paralyzed limbs are a more plausible short-term goal for helping these individuals (Figure 1 shows what this system might look like implemented in humans). A paper by Moritz *et al.*<sup>1</sup> in *Nature* moves us a step closer toward this goal of moving paralyzed limbs by bypassing the injury. This study demonstrates that neural activity from the primary motor cortex of non-human primates can be used to artificially stimulate paralyzed muscles to control wrist function. Although this study is admittedly the latest in a long series of studies extending and improving cortical-based neuroprosthetics, it provides several new twists to the saga.

Studies on non-human primates have shown that the activity of a large population of neurons in the primary motor cortex (and elsewhere) can predict movement features such as the direction of hand movement (ref. 2; but see ref. 3). Cortical-based neuroprosthetics capitalize on these findings by isolating the activity patterns from many neurons and then using a mathematical algorithm to convert these noisy spike trains into a signal that controls the movement of a computer cursor or robotic arm. To date, neuroprosthetic research has focused on increasing the number of recorded neurons and developing faster and more accurate algorithms to convert spike trains into useful control signals<sup>4–6</sup>. Of particular interest is the recent demonstration that a human subject who was paralyzed from a spinal-cord injury was able to directly control the movement of a computer cursor, driven by neural activity in his motor cortex<sup>7</sup>.

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**Figure 1** Potential design of a cortical-based prosthetic to re-animate a paralyzed limb. Neural activity is recorded in cortical regions, such as the primary motor cortex. The timing of action potentials from each neuron are transferred transcutaneously to a processor that converts these patterns of cell activity into patterns of muscle stimulation for arm muscles. These signals are passed transcutaneously to electrodes or cuffs surrounding muscle nerves to artificially stimulate each muscle, permitting voluntary control over limb movements.

For pragmatic reasons, such neuroprosthetic research has focused on directly controlling computer cursors or robotic devices. Ideally, however, neuroprosthetics should re-animate the paralyzed limb by artificially stimulating muscles of the limb, commonly called functional electrical stimulation (FES). The problem is that the conversion from muscle activity into purposeful limb movement is extremely complex, depending on the mechanical properties of the muscle and the physics of multi-segmented limbs, including intersegmental dynamics. An added challenge of FES is fatigue and course control of muscle activation caused by the nonphysiological recruitment pattern of motor units from electrical stimulation. Although FES has been used in some prosthetic systems based on electromyograms of nonparalyzed muscles or recorded body movements<sup>8</sup>, the use of cortical signals to directly control FES has not been attempted.

Moritz *et al.*<sup>1</sup> attempt just such an experiment by testing whether neural activity in the primary motor cortex of non-human primates could control FES of wrist muscles. The basic task required the monkey to move a computer cursor to targets presented on the computer screen. Cursor motion was controlled by modulating wrist torque. The first step was to quantify the activity of a neuron as the nonparalyzed monkey performed this behavioral task under normal conditions without FES. Some neurons were broadly tuned to the direction of wrist torque, with maximal activity for one particular direction and correspondingly less activity for directions progressively away from this preferred direction. Other primary motor cortex neurons turn out not to have a preferred direction during this behavioral task.

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<sup>9,10</sup>. 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<sup>11</sup>.

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.

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## 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<sub>v</sub>1.8* 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.

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