

# Restoration of grasp following paralysis through brain-controlled stimulation of muscles

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Patients with spinal cord injury lack the connections between brain and spinal cord circuits that are essential for voluntary movement. Clinical systems that achieve muscle contraction through functional electrical stimulation (FES) have proven to be effective in allowing patients with tetraplegia to regain control of hand movements and to achieve a greater measure of independence in daily activities<sup>1,2</sup>. In existing clinical systems, the patient uses residual proximal limb movements to trigger pre-programmed stimulation that causes the paralysed muscles to contract, allowing use of one or two basic grasps. Instead, we have developed an FES system in primates that is controlled by recordings made from microelectrodes permanently implanted in the brain. We simulated some of the effects of the paralysis caused by C5 or C6 spinal cord injury<sup>3</sup> by injecting rhesus monkeys with a local anaesthetic to block the median and ulnar nerves at the elbow. Then, using recordings from approximately 100 neurons in the motor cortex, we predicted the intended activity of several of the paralysed muscles, and used these predictions to control the intensity of stimulation of the same muscles. This process essentially bypassed the spinal cord, restoring to the monkeys voluntary control of their paralysed muscles. This achievement is a major advance towards similar restoration of hand function in human patients through brain-controlled FES. We anticipate that in human patients, this neuroprosthesis would allow much more flexible and dexterous use of the hand than is possible with existing FES systems.

Worldwide, over 130,000 people each year survive spinal cord injury (SCI) but sustain extensive paralysis<sup>4</sup>. Approximately half of these injuries occur above the sixth cervical vertebra, thereby affecting all four limbs. Most of these patients indicate that regaining the ability to grasp objects would provide the greatest practical benefit compared to regaining other lost functions<sup>5</sup>.

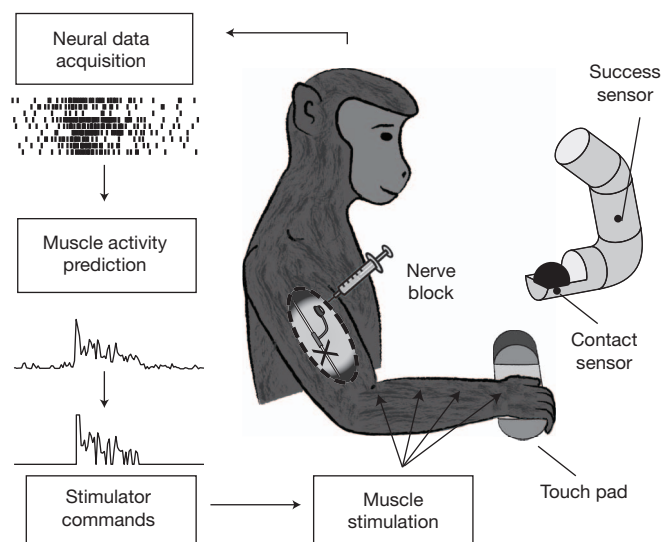
For this reason, considerable effort has been devoted to the development of FES systems to restore voluntary grasp<sup>1,2,6</sup>. These systems rely on residual movement or muscle activity to control electrical activation of hand muscles. Because of the complexity of the necessary patterns of muscle activation, current FES systems produce only one or two grasps using pre-programmed stimulus trains that must be customized for each user<sup>7</sup>. This is effective because many objects can be grasped adequately with only palmar or pinch grasp. However, normal hand use is much more complex than this. Furthermore, using the motion of one body part to control that of another inevitably increases the associated cognitive burden. If FES is to provide hand movements that are close to normal, a more natural control signal of higher dimension than that available through residual motion will be necessary.

Fortunately, the rapid development of the brain machine interface (BMI) provides promising new means by which more flexible and dexterous movements might be controlled. However, despite the initial demonstration of strong force-related discharge in the primary motor

cortex (M1)<sup>8</sup>, virtually all existing BMIs extract only kinematic information from the brain. This bias is ironic, as the first study to decode signals from simultaneously recorded neurons found that force was more strongly represented than movement in M1 (ref. 9).

Only a small number of groups have pursued the possibility of using kinetic (force-related) information as a real-time control signal for a BMI, through the prediction of grasp force<sup>10,11</sup>, joint torque<sup>12</sup> or muscle activity<sup>10,13,14</sup>. We showed previously that despite paralysis produced by peripheral nerve block, monkeys could accurately modulate the magnitude of isometric flexion and extension wrist torque using cortically controlled FES<sup>15,16,17</sup>. Related results were also reported by a group that operantly conditioned monkeys to modulate the activity of one or two individual neurons whose discharge directly controlled stimulation of individual muscles<sup>18</sup>.

We performed the current experiments with two monkeys trained to pick up weighted rubber balls and to convey them to an opening at the top of a dispenser (Fig. 1). After training, each monkey was implanted with a multi-electrode recording array in the hand area of M1. In a separate surgical procedure, we implanted intramuscular electrodes for recording and stimulation of hand and forearm muscles. Figure 2a shows the neural discharge recorded under normal conditions from a representative session. Most of these 104 neuronal signals



**Figure 1 | Brain-controlled FES.** The monkeys' forearm and digit flexor muscles were temporarily paralysed by a peripheral nerve block. Recordings from the motor cortex were used to infer the monkeys' attempted patterns of muscle activity and thereby control electrical stimulation that restored the monkeys' ability to perform a functional grasping task. The ball-grasp device was equipped with a contact sensor and a task-success sensor that were activated when the monkeys initially touched the ball and dropped it into the tube, respectively.

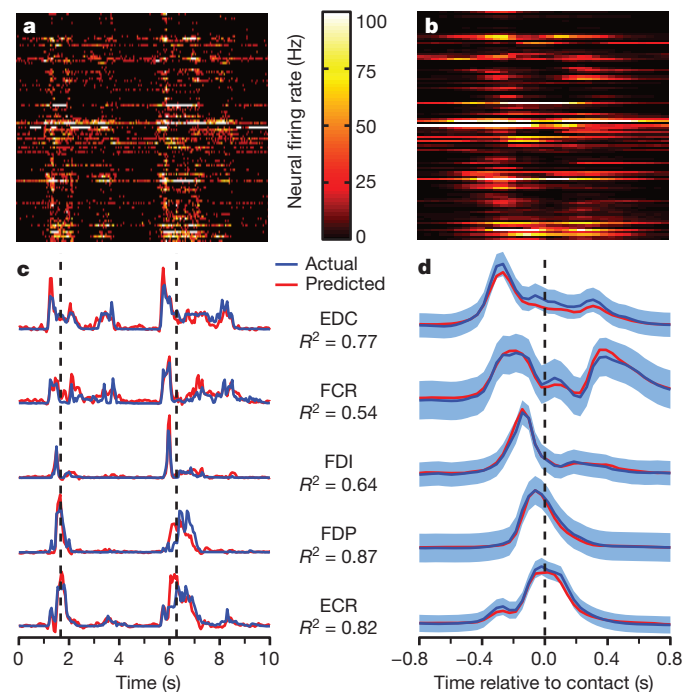
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were well-modulated during at least some portion of the task. Offline, typically 50–75% of the neuronal signals could be discriminated as single neurons, on the basis of the consistency of their waveform shape and inter-spike interval histogram distribution. However, under real-time conditions, only about one-third of the inputs were well-discriminated single units; the remainder were signals that included action potentials from more than one neuron. Figure 2b shows the discharge of these neurons averaged over 229 trials, aligned to the time of contact with the ball. The varied phasing of the different neurons is evident.

We recorded from flexor and extensor muscles of the hand and forearm simultaneously with the neural recordings (Fig. 2c, d). There was considerable variation both in the magnitude and duration of electrical activity that occurred from trial to trial (Fig. 2c), and in the average timing and patterns of activation of the different muscles (Fig. 2d).

We were able to predict electromyographic (EMG) activity with very high accuracy, typically from approximately 100 neural signals (Fig. 2c, d; red traces), using Wiener cascade decoders. These decoders consisted of multiple-input, linear-impulse response functions between the neural inputs and each muscle, followed by a static non-linearity. Each impulse response was composed of ten lags spanning 500 ms. At the beginning of each week, we collected 20 min of data under normal conditions, and we used this to compute the coefficients for the decoder that were then used for the remainder of the week. Accuracy was represented by  $R^2$ , calculated using a multi-fold cross-validation procedure described in the Supplementary Information.

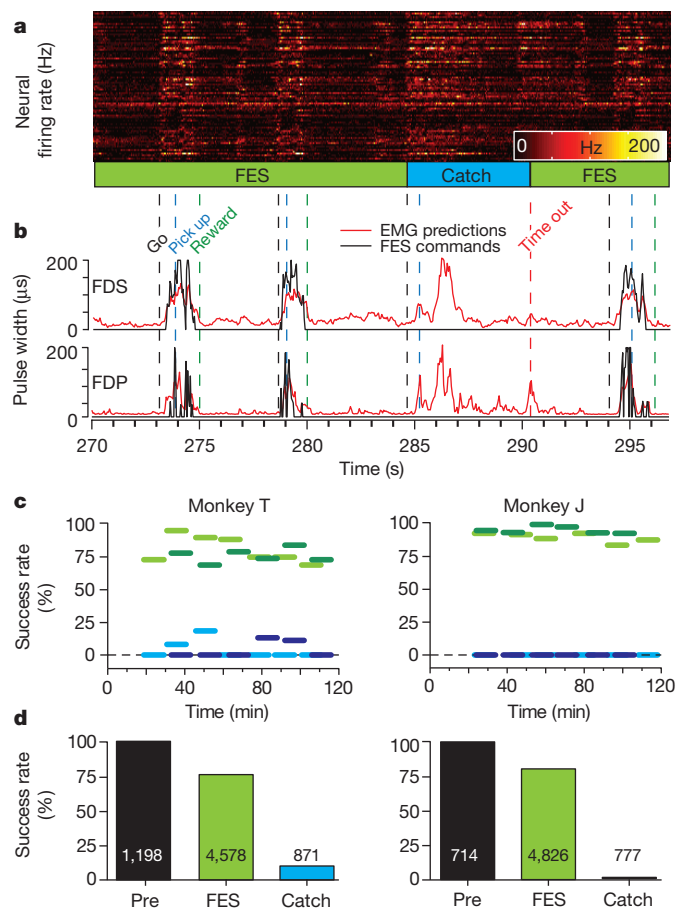
Using these real-time predictions of muscle activity, we stimulated up to five electrodes in three different muscles (flexor carpi radialis



**Figure 2 | Grasp-related raw data collected during normal conditions.** **a**, Firing rates of 104 neuronal signals recorded during series of two grasps. **b**, Ensemble average of 229 trials aligned to the time of ball contact. **c**, Actual and predicted EMG during the same period as (a), with the muscles ordered by the relative times of their onset, including extensor digitorum communis (EDC), flexor carpi radialis (FCR), first dorsal interosseous (FDI), flexor digitorum profundus (FDP), and extensor carpi radialis (ECR). Predicted EMG was computed using multiple-input linear-impulse response decoders built from data collected earlier in the session. Vertical dashed lines mark the times of ball contact.  $R^2$  values indicate prediction accuracy for the 20-min data file. **d**, Ensemble averages of EMG activity, aligned to the time of initial contact. Blue shaded regions,  $\pm 1$  s.d. around the mean.

(FCR), medial and lateral sites in the flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP)). By these means, we have restored in two monkeys the ability to pick up and move objects despite complete paralysis of the flexor muscles in the forearm and hand. We began each FES experimental session by collecting data under normal conditions to establish baseline performance. Following these baseline recordings, we injected lidocaine through nerve cuffs implanted proximal to the elbow that blocked the median and ulnar nerves. After 15–20 min the nerve block was complete, as determined by the loss of flexor muscle EMG activity (see Supplementary Information and Supplementary Fig. 1), and the onset of profound motor deficits. We made periodic tests of nerve-block effectiveness throughout each session (Supplementary Fig. 2), and we used a standardized stimulus train to evaluate the level of fatigue induced by the stimulation (Supplementary Fig. 2).

A series of four trials is shown in Fig. 3a, b, showing typical neural discharge, predicted EMG and stimulus commands, as well as markers of the monkey's performance. Although the common digit flexors (FDS and FDP) are normally activated nearly synchronously, FDS activation tended to be more sustained, whereas FDP was more phasic. The pulse widths of the stimulus trains used to activate a given muscle



**Figure 3 | Grasp performance during four consecutive brain-controlled FES trials.** **a**, Neural data. **b**, Predicted EMG signals (red traces) transformed into stimulus commands (black traces). Vertical dashed lines: go tone (Go), time of initial ball contact (Pick up) and successful task completion (Reward). **c**, Horizontal lines show average success rates for sequential 10-min blocks during two separate experimental sessions (indicated by light and dark horizontal lines, respectively). Each session included both FES trials (green lines) and catch trials without stimulation (blue lines). The neuroprosthesis markedly improved the monkeys' ability to grasp the ball despite paralysis. **d**, Average success rates for pre-block (Pre), FES and catch (Catch) trials across all sessions (100%, 76% and 10% for Monkey T; 99%, 80% and 1% for Monkey J). The total number of trials (successful and failed) is displayed on the bars for each condition.

were determined from the predicted EMG for that muscle using a mapping procedure described in the Supplementary Information and Supplementary Fig. 3. The distribution of these pulse widths throughout the full range from 0 to 200  $\mu$ s suggests that the monkey was able to grade the strength of contraction continuously (Supplementary Fig. 4). During the FES trials, the monkey grasped and moved the ball reliably. The movements did not differ sufficiently from normal to be obvious to casual observation (see Supplementary Movies 1 and 2 for representative examples from both monkeys). On occasional 'catch' trials, we turned off the neuroprosthesis at the beginning of the trial, to test the ability of the monkey without FES. In the example of a catch trial illustrated here (note the flat stimulus trace in Fig. 3b), the monkey was unable to grasp the ball despite the considerable effort apparent in the neural discharge and predicted EMG.

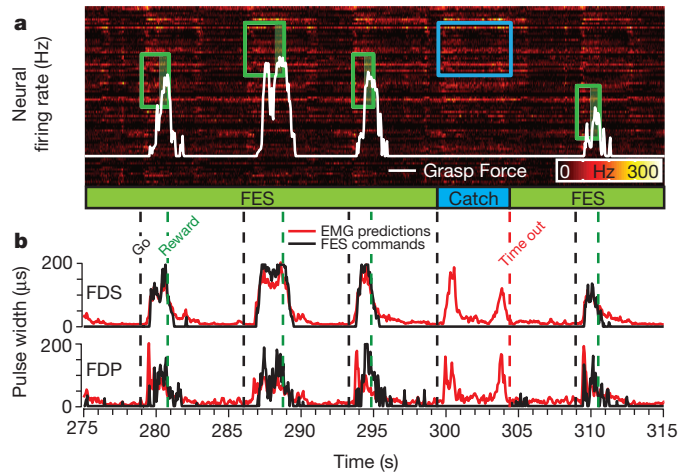
After the onset of paralysis, each experimental session consisted of a series of 10-min sets of trials like those in Fig. 3, in which the monkey attempted to complete the grasp task either with or without FES assistance. Two complete sessions for both monkeys are summarized by the horizontal light and dark lines in Fig. 3c. The success rate in these sessions using the neuroprosthesis was approximately 80% and 90% for the two monkeys, respectively (green lines). In contrast, the average catch-trial success rate was 5% for monkey T and 0% for monkey J (blue lines). The average number of trials per session varied substantially across sessions, with a mean of  $272 \pm 84$  for monkey T, and  $208 \pm 112$  for monkey J. Although we tried different types of balls, we did not systematically examine the effects of size, weight or texture on the monkeys' performance. It is likely that the FES success rate would have been lower if balls that were substantially heavier or more slippery had been used. We chose to use balls that in size and weight mimicked objects grasped in routine human tasks (for example, eating an apple).

Figure 3d summarizes both monkeys' overall success rate across all sessions, both with the FES neuroprosthesis and during catch trials. Both monkeys achieved a success rate of approximately 80% using the neuroprosthesis, a level that was highly significantly different ( $P < 0.0001$ ) from that of the catch-trial condition. In addition to resulting in a greatly improved success rate, the FES neuroprosthesis also significantly increased the speed at which the monkeys completed successful trials (not shown;  $P < 0.0001$  for both monkeys, two-tailed Mann-Whitney test).

To test force control more systematically we conducted a second set of experiments with monkey J, who was trained to control the vertical displacement of a cursor that moved in proportion to palmar grasp force. Using the neuroprosthesis, the monkey was able to squeeze a pneumatic tube, and to track up to three different targets ranging from 15 to 80% of his normal maximum voluntary contraction (MVC), each target having a width of approximately 20% of MVC. To be successful, the monkey needed to maintain the target force for 0.5 s. Figure 4 shows a short sequence of data during this target tracking task. One of these four trials was a catch trial. The monkey was unable to generate any force during the catch trial despite two attempts that are evident in the predicted EMG signals.

We quantified this performance by measuring the mean force and stimulation pulse width during the target-hold periods of the initial and final 10 min of the session. Despite considerable FES-induced fatigue, the monkey remained able to achieve the required force throughout the session by voluntarily increasing the mean stimulus pulse width (see Supplementary Fig. 5). The increased pulse width reflects an increase in cortical activity and resultant EMG predictions. The monkey seemed to overcome the fatigue in a manner similar to that of normal conditions, increasing its effort to regulate force accurately.

The monkey's ability to control both a well-regulated palmar grasp as well as to execute the unconstrained natural grasp is powerful evidence of the impact that this FES neuroprosthesis could have in eventual clinical application. Our neuroprosthesis makes use of patterns of activity in M1 that reflect the patterns that occur naturally during grasp. By matching patterns of neuronal activity to those muscles with



**Figure 4 | FES used to produce controlled palmar grasp force during the palmar grasp task.** **a**, Colour-coded neural discharge recorded during a series of five trials. The rectangles indicate times of target appearance and disappearance, as well as their upper and lower force bounds. The white trace is the force generated by the monkey, resulting from stimulation of FDS and FDP (Stim commands). **b**, There were four successful trials with FES (green targets) and one unsuccessful catch trial (blue target). During the catch trial, the monkey made two unsuccessful attempts to squeeze the tube, as seen in the EMG predictions (also evident in the neural discharge (a)).

which they are normally most closely correlated, we hope to maintain the natural coupling between cortical activity and motor output.

It is important to note that this process in no way limits the ability of the brain to adapt further, to compensate for inaccuracies in the decoded signals or the stimulus-evoked contractions. Even with adaptation, it is difficult to imagine how a small number of individually conditioned, randomly selected neurons could yield an adequate level of control without the type of pre-programming that is necessary with existing FES systems. Indeed, there is no evidence that it is possible to learn to associate the simultaneous activity of two, three or more neurons with independent patterns of muscle activity. Even if possible, the cognitive load associated with this effort would presumably be rather high, whereas the reliability of a neuroprosthesis relying on a small number of conditioned neurons would be quite low.

Our model of paralysis avoided many of the complications of actual spinal cord injury, including muscle denervation and spasticity<sup>19,20</sup>. Furthermore, it was limited to the forearm and digit flexors. Patients with C5 and C6 spinal cord injury retain voluntary control of proximal arm muscles while losing full control of the more distal limb. Many patients retain or regain some level of voluntary wrist extension<sup>21</sup>. As we did not paralyse the monkeys' extensor muscles in this experiment, it is important to recognize the good coordination between the remaining natural muscle control and that achieved through the neuroprosthesis. We routinely obtained extensor EMG predictions that were in fact slightly more accurate than those of the flexors. In future experiments, we intend to expand our control to these muscles.

This technology may offer even greater advantages to patients with more severe injuries, who have a greater need for replaced function but possess even fewer available sources of control<sup>22</sup>. In addition to the ability to predict the reach-related activity of distal limb muscles considered in this study, we have previously showed the same ability in relation to proximal limb muscles, suggesting the possibility of extending this control to these muscles<sup>13</sup>. As well as offering patients greater independence, FES is also established as an effective means for exercising the muscles of paralysed patients, bringing a range of health benefits: stronger muscles and bones, improved metabolism, cardiorespiratory health and reduced propensity to pressure sores<sup>23,24</sup>. It may be that drawing on a conscious process to restore natural movement will bring the additional benefit of improved psychological health<sup>25</sup>.



## METHODS SUMMARY

**Experimental subjects and task.** Two monkeys were trained to perform a ball-grasp task (Fig. 1) and one of the monkeys was also trained to perform a controlled-force palmar grasp task. The monkeys were allowed 5 s to grasp one of several balls (ranging in size from 25–40 mm in diameter and 55–130 g) and place it into the top of a dispenser tube. The palmar grasp task required the monkey to squeeze a pneumatic tube that controlled movement of a cursor. Force targets were chosen from a set of two or three non-overlapping levels. All procedures were approved by the Institutional Animal Care and Use Committee of Northwestern University, Illinois, USA.

**EMG prediction.** Inputs consisted of roughly 100 single and multi-unit signals from a 100-electrode array (Blackrock Microsystems) implanted within the hand area of M1. Decoders consisted of multiple-input impulse response functions between the neural inputs and each muscle, subsequently transformed by a second-order static nonlinearity to reduce the baseline noise in the predictions and to increase the gain near the EMG peaks<sup>13,16</sup>. We computed decoders at the beginning of each week, which were used in daily sessions for the remainder of the week. We conducted 20 sessions with 7 decoders across 7 weeks for monkey T and 27 sessions with 6 decoders across 11 weeks with monkey J.

**Stimulation.** All muscles were stimulated at a single, fixed rate of either 25 or 30 Hz to achieve nearly fused contractions. The EMG predictions were transformed into stimulus pulse widths by mapping the predicted EMG noise floor to the stimulus force threshold, and the maximum predicted EMG to the maximum pulse width (200  $\mu$ s; see Supplementary Fig. 3). The current, typically 2–8 mA, was chosen independently for each electrode, to yield forces of approximately 50% of the maximal evocable force at 200- $\mu$ s pulse width.

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**Supplementary Information** is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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**Author Contributions** L.E.M. conceived, designed and supervised the basic experiments. C.E. and E.R.O. performed the experiments. M.J.B. carried out software development. C.E. analysed the data and prepared figures. L.E.M. and C.E. wrote the manuscript.

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