ARTICLES

Long-term motor cortex plasticity induced by an electronic neural implant

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It has been proposed that the efficacy of neuronal connections is strengthened when there is a persistent causal relationship between presynaptic and postsynaptic activity. Such activity-dependent plasticity may underlie the reorganization of cortical representations during learning, although direct *in vivo* evidence is lacking. Here we show that stable reorganization of motor output can be induced by an artificial connection between two sites in the motor cortex of freely behaving primates. An autonomously operating electronic implant used action potentials recorded on one electrode to trigger electrical stimuli delivered at another location. Over one or more days of continuous operation, the output evoked from the recording site shifted to resemble the output from the corresponding stimulation site, in a manner consistent with the potentiation of synaptic connections between the artificially synchronized populations of neurons. Changes persisted in some cases for more than one week, whereas the output from sites not incorporated in the connection was unaffected. This method for inducing functional reorganization *in vivo* by using physiologically derived stimulus trains may have practical application in neurorehabilitation after injury.

Learning is associated with a long-term reorganization of sensory and motor representations in the neocortex[1–3]. Acquisition of motor skills can alter the somatotopic map of limb movements in sensorimotor areas[4,5], and plastic changes have been implicated in the recovery from disorders such as stroke[6] and incomplete spinal cord injury[7]. Hebb[8] postulated that synaptic efficacy between two neurons is strengthened if the first repeatedly contributes to firing the second; since then, long-term potentiation of motor cortical synapses[9–11] and associated expansion of movement representations[12,13] have been induced with tetanic stimulus trains delivered to individual sites. Long-term potentiation is widely assumed to reflect a learning mechanism, but its physiological relevance and relationship to hebbian plasticity are often inferred indirectly[14]. More recently, spike timing-dependent plasticity consistent with Hebb's criterion of a causal relationship between presynaptic and postsynaptic firing has been described at the cellular level[15,16]. However, it remains to be shown that such a mechanism can cause stable, functional reorganization of cortical maps *in vivo* under normal behavioural conditions.

We are developing implantable electronic circuits[17] (or Neurochips; Supplementary Fig. 1) for neural recording and stimulation in freely behaving animals that could provide prosthetic connections to replace or augment damaged pathways in the nervous system[18]. A Neurochip creates an artificial connection between two sites by using action potentials recorded on one electrode to trigger electrical stimuli delivered to another (Fig. 1a). Once configured with appropriate recording and stimulation parameters, the Neurochip operates autonomously, allowing connections to function continuously over days of unrestrained behaviour. Because the Neurochip creates a causal relationship between neural activities at connected sites, its long-term operation could also induce changes mediated by hebbian

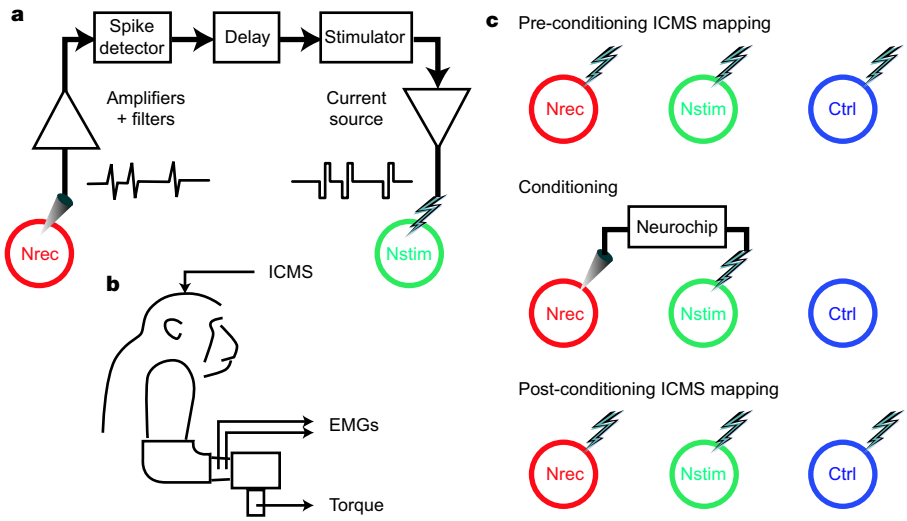

Figure 1 | Conditioning protocol and experimental design. a, Diagram of the artificial connection. Action potentials detected in the signal recorded from the Nrec electrode triggered electrical stimuli delivered to the Nstim electrode after a predefined delay. **b**, Experimental setup for testing output effects of ICMS on the right wrist. **c**, Experimental sequence of ICMS testing and conditioning with the Neurochip.

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mechanisms. Here we describe stable reorganization of movement representations in the wrist area of the primary motor cortex (M1) in monkeys resulting from artificial connections between pairs of electrodes in a chronically implanted array. We found that the motor output elicited from recording sites shifted towards the output evoked from stimulation sites. These changes occurred only when stimuli were delivered within 50 ms of recorded spikes. The output evoked from neighbouring control electrodes was unchanged. This shows that natural patterns of cortical spiking *in vivo* during normal behaviour can lead to input-specific hebbian plasticity when paired with appropriate stimulation. Plastic changes arising from these artificial connections could have clinical applications in rehabilitation after motor injury.

Conditioning with an artificial connection

The output effects in the contralateral wrist evoked from cortical electrodes before, during and after conditioning with the artificial connection were tested with daily intracortical microstimulation (ICMS, Fig. 1b, c). Figure 2a shows the pre-conditioning average trajectories of isometric wrist torque (dashed lines) for 200 ms after a train of stimuli delivered separately to each of three electrodes, designated Neurochip recording (Nrec), Neurochip stimulation (Nstim) and control (Ctrl). The mean torque, indicated by solid arrows, was towards the flexion direction for Nrec and Ctrl, and in the radial-extension direction for Nstim. Figure 2b shows average rectified electromyogram (EMG) responses to ICMS in three wrist muscles: extensor carpi radialis (ECR), flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU).

The Neurochip was then programmed to deliver a single stimulus pulse to Nstim 5 ms after every action potential detected at Nrec (Supplementary Fig. 2a). The cell at this site fired preferentially with flexion during torque-tracking and its activity was correlated with both wrist flexor and extensor muscles during free behaviour (Supplementary Fig. 2f, g). The stimulus intensity (40 μA) was below the movement threshold for a single pulse but was sufficient for occasional bursts of cell activity to elicit small muscle twitches while the monkey sat at rest. This connection produced no noticeable disruption of the control of active movements, probably because the effect of stimulation was weak in comparison with neural activity generating volitional movement. The artificial connection operated continuously for two days while the monkey moved unrestrained about the home cage. During this period, the Neurochip also recorded the stimulation rate over consecutive 1-s bins (Supplementary Fig. 2b). The mean rate of stimulation was 19 Hz during daytime behaviour and 9 Hz during the night. This pattern was consistent with our observations of robust correlations between the firing rate of M1 neurons and muscle activity during natural behaviour, and cycles of activity and quiescence during sleep[19].

After two days of conditioning, the mean torque generated by ICMS at Nrec had shifted to the radial direction, towards the output effect produced from Nstim (Fig. 2c). The torque now followed a curved trajectory aligned initially with the Nstim trajectory, before returning to the flexion direction. This curved path was produced by a new pattern of muscle responses (Fig. 2d), which included initial activation of the extensor muscle ECR (black arrows), previously elicited only by ICMS at Nstim. The output from the control electrode was unaffected, indicating that the plastic change was caused by the pairing of neural activity at the Nrec site with the stimulation of Nstim. In this case, the response from the Nstim site had also increased slightly (Supplementary Fig. 3), but this was not generally so (see Supplementary Information). Figure 2e plots the angle of mean torque produced by ICMS at each site for the days before, during and after conditioning. The changes at the Nrec site developed gradually over the two days of conditioning and subsequently remained stable for one week.

Summary of conditioning sessions

We investigated the effect of creating artificial connections between 17 different pairs of electrodes over separate conditioning sessions in two monkeys (Y, eight sessions; K, nine sessions). Conditioning lasted for 1–4 days (mean 1.6 days) with Nstim currents in the range 25–80 μA (mean 48 μA) and delays of 0, 1 and 5 ms interposed between spike and stimulus (Supplementary Table 1). ICMS effects were quantified by the angle of mean wrist torque relative to the pre-conditioning direction of Nstim effect. Control electrodes were chosen to have similar ICMS effects to those of the Nrec pre-conditioning. Figure 3a summarizes the direction of mean torque produced by ICMS before and after each session. Points lying on the dashed line of identity represent ICMS effects that were unaffected by conditioning; points lying below the line represent effects that moved towards the output effect of Nstim. Conditioning had no significant effect on the separation of Ctrl site effects from the Nstim direction, which changed by 2.1° ± 2.3° (mean ± s.e.m., two-tailed

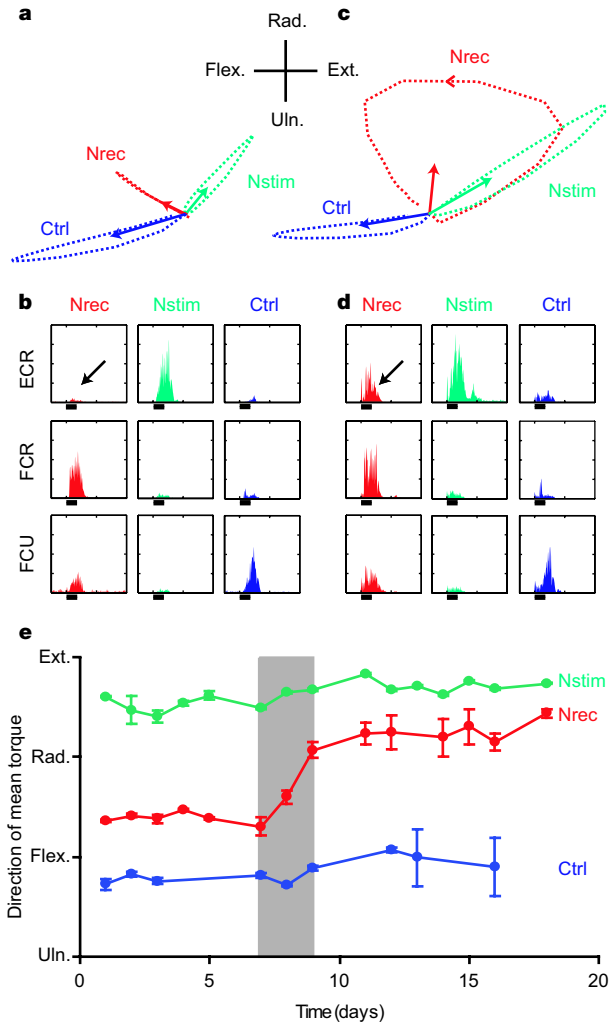

Figure 2 | Reorganization of motor output after conditioning. **a**, Average wrist torque responses to ICMS before conditioning. Arrows show the means of each 200-ms trajectory (dashed lines). Calibration bars are ±0.02 N m (Nrec and Ctrl) and ±0.08 N m (Nstim). **b**, Peristimulus averages of the rectified EMG response. The full axis lengths are 250 ms (*x*) and 0.4 mV (*y*). The bar indicates the ICMS train. **c, d**, Data after two days of conditioning with an artificial connection. Arrows indicate increased ECR response from Nrec after conditioning. **e**, Angle of torque response over 18 days. Shading indicates the conditioning period. Error bars show s.e.m. ICMS, 13 pulses at 300 Hz; current, 30 μA (Nrec), 40 μA (Nstim) and 50 μA (Ctrl). The data are given in session 3 of Supplementary Table 1 and are averages of 20 stimulus trains.

paired *t*-test, $P = 0.4$). In contrast, Nrec effects moved towards the Nstim direction by 38° ± 9° (mean ± s.e.m., $P = 0.0005$). In 13 of 17 individual sessions, Nrec effects rotated by an angle greater than the 95th centile of the Ctrl distribution (15°). The angular shift per day of conditioning was comparable for both animals (Y, 24° ± 8°; K, 25° ± 7°; mean ± s.e.m.). Figure 3b shows average angular separations of Nrec and Ctrl effects from the Nstim direction before, just after and one day after the end of the conditioning period. Supplementary Fig. 4 shows example torque trajectories from these experiments. Supplementary Fig. 5 shows the one session in which the change at the Nstim site gradually wore off, six to eight days after the end of conditioning.

Dependence on spike–stimulus delay

The absence of conditioning effects at control sites suggests that the timing of stimulation relative to cell activity had a crucial function in inducing plasticity. Neurons distributed widely throughout the motor cortex exhibit correlated firing on the timescale of movements (typically several hundred milliseconds[19,20]; Supplementary Figs 2g and 6a). The site specificity of our results therefore indicates that a more precise coincidence between spikes and stimulation was required to induce plastic changes. We tested this hypothesis in a further series of experiments with monkey K by introducing longer delays of 20–2,000 ms between the spike and stimulation pulse (see Supplementary Information). Figure 4 summarizes these data by plotting the angular shift of the Nrec effect towards the Nstim direction per day of conditioning as a function of stimulus delay. Significant shifts ($P < 0.05$, two-tailed *t*-test) were obtained for intervals up to 50 ms, indicating that a coincidence of spike and stimulus within this window was required for inducing plasticity. The average angular shift for delays of 20 and 50 ms (35° ± 5°) was slightly greater than had been obtained with the shorter delays (24° ± 5°), but this difference was not significant ($P = 0.25$, two-tailed unpaired *t*-test).

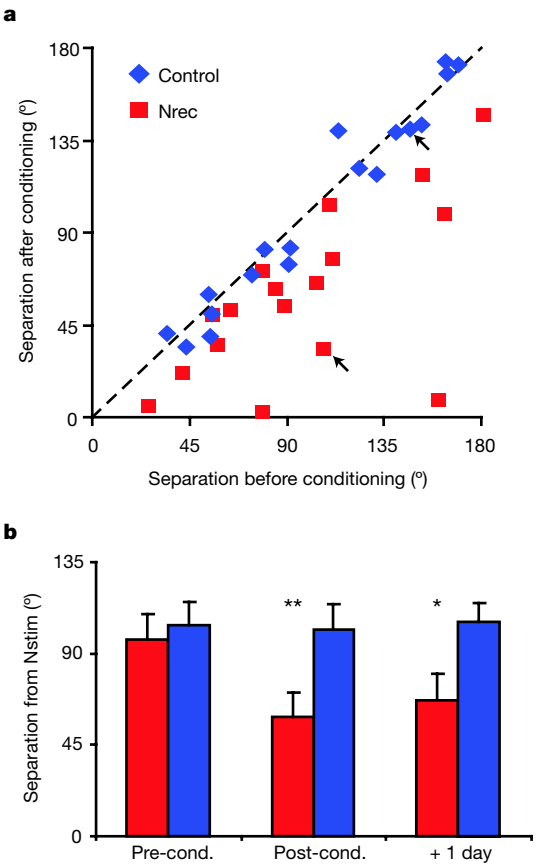

Figure 3 | Summary of conditioning results. **a**, Angular separation of Nrec and Ctrl ICMS effects from the pre-conditioning Nstim direction before and after conditioning for 17 sessions. Control data (blue) cluster around the dashed line of identity. Nrec data (red) fall below the line, indicating that the mean torque shifted towards the response elicited from Nstim. Arrows indicate data in Fig. 2. **b**, Average angular separation of Nrec (red bars) and Ctrl (blue bars) effects from the Nstim direction before conditioning. Error bars show s.e.m. '+1 day' describes one day after the end of conditioning. Asterisk, $P = 0.001$; two asterisks, $P = 0.0005$ ($n = 17$, two-tailed paired *t*-test relative to pre-conditioning data).

Discussion

These results may be explained by the potentiation of horizontal pathways within the motor cortex[10] such that ICMS delivered, after conditioning, to Nrec activates additional muscle groups through Nstim (Fig. 5). Alternatively, plasticity could occur at other cortical or subcortical targets of converging projections from Nrec and Nstim sites. Repetitive high-frequency stimulation has been shown to expand movement representations in the motor cortex of rats[12,13], but a general expansion of local Nstim effects cannot account for the changes we saw at Nrec sites for several reasons. First and foremost, outputs from neighbouring control electrodes were unaffected by conditioning. There was no significant difference in either the distance from the Nstim site (Nrec, 1.09 ± 0.16 mm; Ctrl, 0.95 ± 0.12 mm; mean ± s.e.m.; two-tailed unpaired *t*-test, $P = 0.5$) or ICMS currents used (Nrec, 68 ± 10 μA, Ctrl, 60 ± 7 μA, $P = 0.5$). Second, the angular shift of ICMS effects evoked from Nrec was not correlated with distance from the Nstim site (Pearson's $r = -0.0007$). Last, no shifts occurred when stimuli were delayed by more than 50 ms relative to the Nrec spikes, although the temporal pattern of stimulation was equivalent. These observations all indicate that the relative timing of Nrec spikes and Nstim stimulation was the critical factor for inducing plasticity.

Cellular studies of spike timing-dependent plasticity have shown that plasticity at individual synapses is triggered by Ca^{2+} influx, requiring both presynaptic glutamate release and postsynaptic depolarization to release the Mg^{2+} block of *N*-methyl-D-aspartate channels[16]. We propose that in our experiments the depolarization of local or downstream neurons by stimulation at Nstim induced the potentiation of synapses concurrently activated by spikes arriving from the Nrec site. Inputs from other sites (namely Ctrl electrodes) were not potentiated because the timing of this presynaptic activity had no consistent correlation with postsynaptic depolarization. Previous studies have shown that synaptic inputs activated after postsynaptic depolarization can be depressed[15,16], so although some fraction of spikes from control sites would have arrived during the window for synaptic potentiation, these could be cancelled by a comparable

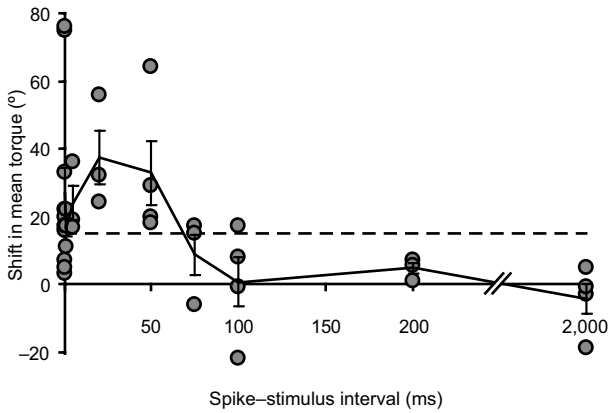

Figure 4 | Dependence of conditioning effects on delay between spikes and stimuli. The graph shows angular shift of Nrec effects towards Nstim effects per day of conditioning for different spike–stimulus intervals. The solid line connects the group means for each interval. Error bars show s.e.m. The dashed line indicates the 95th centile for control electrodes obtained from the previous experiment.

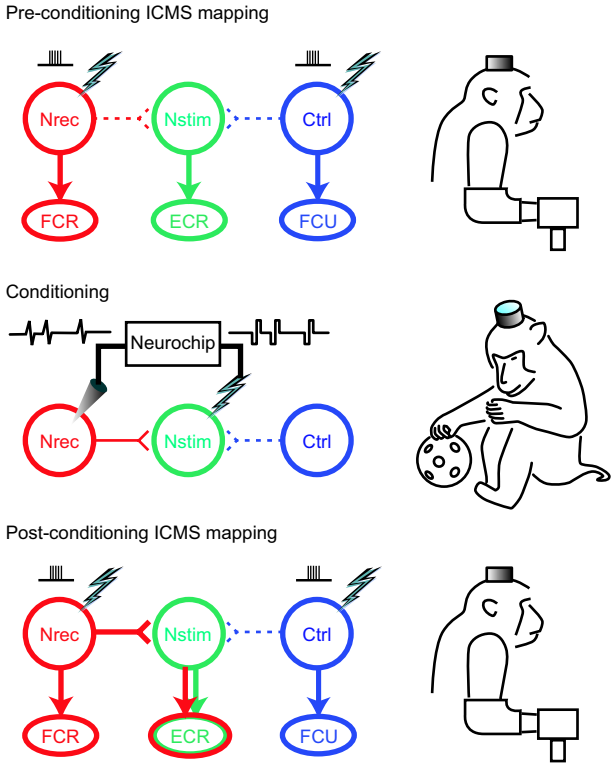

Figure 5 | Suggested mechanism for the conditioning effect documented in Fig. 2. Pre-conditioning ICMS predominantly activates distinct descending projections from Nrec to FCR, from Nstim to ECR, and from Ctrl to FCU. Conditioning during unrestrained behaviour induces a strengthening of horizontal connections between Nrec and Nstim. Post-conditioning ICMS now activates ECR by means of horizontal projections to Nstim, as well as activating FCR by means of the direct projection.

number of inputs arriving during the window for synaptic depression. This would also explain why delays of about 20 ms tended to produce the strongest conditioning effects. With shorter delays more Nrec spikes would have arrived after stimulation, during the window for synaptic depression.

Associative plasticity has been demonstrated previously with the use of paired stimulation of two input pathways in the cerebellum[21], hippocampus[22] and motor cortex[23]. In contrast with those studies, we induced a functional reorganization by using *in vivo* spike activity at one site to trigger the stimulation of a second site. This constitutes a relatively direct test of Hebb's postulate, showing that natural patterns of neuronal firing can lead to input-specific plasticity when paired with appropriate postsynaptic depolarization during normal behaviour. It seems unlikely that the magnitude of this reorganization can be accounted for by altered projections only from the recorded neuron, because ICMS delivered to Nrec presumably activated populations of cells by means of local circuitry and temporal summation[24]. However, neighbouring M1 neurons with similar output projections exhibit the maximal degree of synchronous discharge[25–27] (Supplementary Fig. 6b), so during conditioning many spikes from this population will be temporally correlated within the coincidence window for synaptic potentiation.

Our method for inducing plasticity shares similarities with cellular conditioning protocols *in vivo* in sensory areas that pair spontaneous or evoked neuronal activity with appropriate sensory stimulation[28–30]. However, the changes seen at the cellular level in those studies typically lasted for a few hours at most and were reversed by normal activity. The continuous conditioning over long periods of natural behaviour implemented by our Neurochip system may account for the strength and stability of the effects described here; they are consistent with the finding that multiple sessions are required to induce stable long-term potentiation in rats *in vivo*[11]. Furthermore, conditioning was associated with volitional movements rather than externally imposed activation and was continued during natural sleep, including rapid eye movement phases when motor cortical neurons can be highly active[19]. Sleep has been implicated in the consolidation of motor memory[31], but the relative contributions of waking and sleeping periods to our results remain to be determined.

Artificial connections could provide a neural prosthesis to replace damaged pathways in the nervous system after injury[18]. Our results suggest that an additional rehabilitative consequence in cases of partial injury may be the strengthening of surviving projections between sites connected by the prosthesis. Functional reorganization is thought to be important in recovery from numerous movement disorders[6,7], and new stimulation protocols are being developed to aid this process[32–34]. Stimulation in real time triggered from neural recordings during volitional movements could provide an effective method of selectively strengthening specific neural pathways during rehabilitation.

METHODS

See Supplementary Information for additional methods.

Subjects. Experiments were performed with two male *Macaca nemestrina* monkeys: Y (3 years old; weight 4.3 kg) and K (3 years old; weight 4.6 kg). All procedures were approved by the University of Washington Institutional Animal Care and Use Committee.

Neurochip implant. A full description of the Neurochip Brain–Computer Interface has been published previously[17]. The battery-powered circuit allows continuous long-term recording and stimulation during unrestrained behaviour through an array of 12 chronically implanted moveable tungsten microwire electrodes in M1 (diameter 50 μm; impedance 0.5 MΩ; interelectrode spacing 500 μm). A microprocessor identified isolated action potentials from Nrec and instructed a stimulator circuit to deliver biphasic, constant-current pulses (0.2 ms per phase) to Nstim after a specified delay. Short sections of raw recording (sampled at 11.7 kHz) and stimulation rate in 1-s bins over the duration of conditioning were stored to on-board memory.

ICMS protocol. ICMS effects were documented with a current that was just above the threshold for eliciting a torque response before conditioning, and the same current was used throughout. The monkey sat with elbow and hand immobilized by padded restraints. A force transducer measured the two-dimensional isometric torque produced at the wrist in the flexion–extension and radial–ulnar directions. During some sessions, the EMG was recorded with pairs of stainless steel wires inserted transcutaneously into the wrist muscles. Torque and EMG were recorded at 5 kHz. Offline the torque trace was smoothed and downsampled to 100 Hz. Trains of 13 biphasic ICMS pulses (0.2 ms per phase) at 300 Hz were delivered at 2-s intervals. Peristimulus averages of torque and rectified EMG profiles were compiled from 100 ms before each stimulus to 500 ms after it. Traces in which the torque level before the stimulus exceeded 0.02 N m in any direction were excluded from the average. The trajectories in Fig. 2 connect the vector average of two-dimensional torque across stimulus trains for consecutive sample points up to 200 ms after stimulation. The vector average of this trajectory was used to determine the direction and magnitude of the mean torque response to ICMS at each site.

Received 1 May 2006; accepted 29 August 2006.
Published online 22 October 2006.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements We thank C. Kirby for technical help, F. Miles for development of the Neurochip stimulator, L. Shupe for programming, and S. Perlmutter for advice. This work was supported by grants from the National Institutes of Health, the Office of Naval Research and the University of Washington Royalty Research Fund.

Author Contributions A.J. and E.E.F. conceived and designed the experiment. J.M. designed the Neurochip electronics. A.J. and J.M. performed the experiments. A.J. and E.E.F. wrote the paper.

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