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Volitional control of single cortical neurons in a brain–machine interface

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Abstract
Volitional control of cortical activity is relevant for optimizing control signals for neuroprosthetic devices. We explored the control of firing rates of single cortical cells in two *Macaca nemestrina* monkeys by providing visual feedback of neural activity and rewarding changes in cell rates. During 'brain-control' sessions, the monkeys modulated the activity of each of 246 cells to acquire targets requiring high or low discharge rates. Cell control improved more than two-fold from the beginning of practice to peak performance. Cell activity was modulated substantially more during brain control than during wrist movements. When recording stability permitted, the monkeys practiced controlling activity of the same cells across multiple days. The performance improved substantially for 27 of 36 cells when practicing brain control across days. The monkeys maintained discharge rates within each target for 1 s, but could maintain rates for up to 3 s for some cells, and performed the brain-control task equally well using cells recorded from the pre-central cortex compared to cells in the post-central cortex, and independently of any directional tuning. These findings demonstrate that arbitrary single cortical neurons, regardless of the strength of directional tuning, are capable of controlling cursor movements in a one-dimensional brain–machine interface. It is possible that direct conversion of activity from single cortical cells to control signals for neuroprosthetic devices may be a useful complementary strategy to population decoding of the intended movement direction.

(Some figures in this article are in colour only in the electronic version)

Introduction

Brain–machine interfaces (BMIs) have the potential to dramatically improve the quality of life for individuals with motor paralysis (Donoghue 2002, Hatsopoulos and Donoghue 2009, Nicolelis 2003, Schwartz 2004). The activity of neurons in motor and sensory areas of the brain have been used to control the movement of computer cursors and robotic arms (Carmena *et al* 2003, Hochberg *et al* 2006, Kennedy *et al* 2004, Musallam *et al* 2004, Santhanam *et al* 2006, Taylor *et al* 2002, Velliste *et al* 2008). There is an ongoing debate, however, about the best sources for these control signals (Daly and Wolpaw 2008), and the best method for transforming cortical activity into control signals for BMIs (Andersen *et al* 2004, Fetz 2007).

Single neuron activity recorded from within the cortex is one promising control signal. The activity of these cells can be volitionally modulated when monkeys or humans are provided with the visual feedback of the discharge rate (Fetz 1969, Fetz and Baker 1973, Fetz and Finocchio 1971, Hochberg *et al* 2006). We have recently demonstrated that single neurons can be used to control functional electrical stimulation (FES) delivered to paralyzed muscles (Moritz *et al* 2008). Monkeys learned to modulate cell activity to control FES and restore simple movements to an otherwise paralyzed wrist. After brief practice periods, the monkeys controlled the activity of each cell regardless of the strength of directional tuning; this

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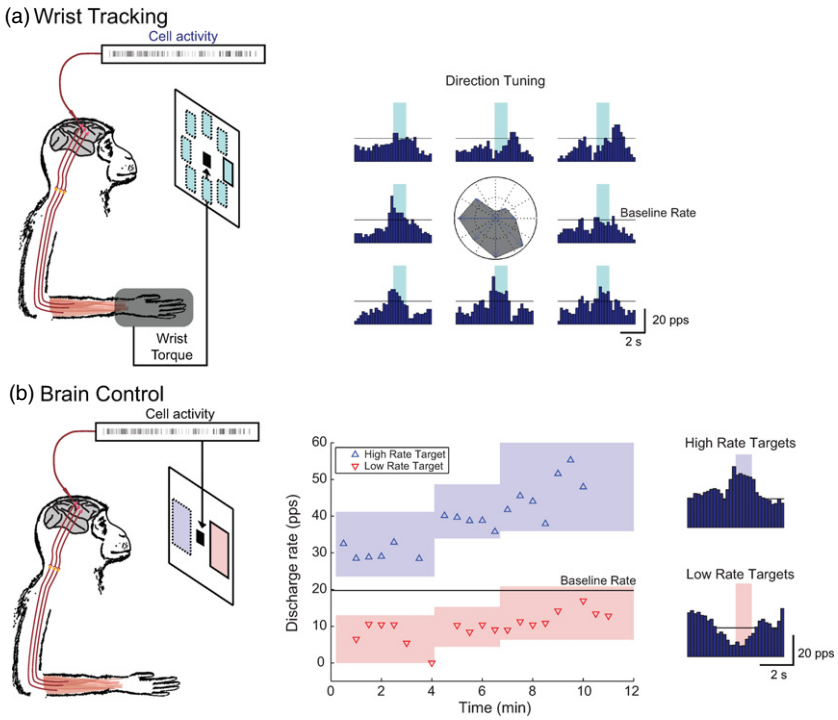

Figure 1. Experiment overview. (a) Monkeys first performed wrist tracking, while activity from each cell was recorded, to document directional tuning. (b) Cell activity was then displayed as the movement of a cursor in one dimension, with targets presented to elicit high or low discharge rates. This pre-central cell increased discharge rate with practice at brain control as the high-rate target (blue shading) was gradually moved further from the baseline. The center figure shows the average discharge rate while holding each randomly presented target for 1 s. Histograms show average cell activity around acquisition of each target. The shaded bars on all histograms denote the target hold period (target appears before shading), and the horizontal lines are the baseline discharge rate.

potentially expands the population of cells useful for BMI control.

Here our goal was to determine the degree of volitional control over arbitrary neurons recorded from primary motor and sensory cortices. In contrast to previous work, we also explored the monkeys' ability to sustain discharge rates within high- and low-rate targets, and quantified improvements across days when recording stability permitted. We found that monkeys can learn to control nearly all neurons tested, with success largely independent of the strength of directional tuning observed during movement. Thus, relatively direct connections between cortical neurons and BMI controls or muscle stimulation may be a useful complementary strategy to decoding of movement intention, especially after paralysis.

Methods

Two male *Macaca nemestrina* monkeys participated in the experiments (4–5 years old, weight 4.5–6.5 kg). All procedures were approved by the University of Washington Institutional Animal Care and Use Committee.

The activity of a single motor cortex cell was recorded using either acute (monkeys I and L) or chronically implanted (monkey L) electrodes. Sterile surgeries were performed with isoflurane anesthesia (1–1.5% in 50:50 O_2:N_2O). All surgeries were followed by a program of analgesics (buprenorphine 0.15 mg kg^{-1} IM and ketoprofen 5 mg kg^{-1} PO) and antibiotics (cephalexin 25 mg kg^{-1} PO). Each animal was implanted with a cranial recording chamber centered over the left hand and wrist area of the motor cortex at stereotaxic coordinates A: 13 mm, L: 18 mm (Evarts 1968, Woolsey *et al* 1952). Postmortem examinations confirmed that recording sites were in primary motor or somatosensory (S1) cortices, in areas related to the hand and wrist. For S1 recordings, electrode penetrations were made on the convexity of the postcentral gyrus, targeting area one. Receptive fields on the hand and forearm were identified for some S1 neurons included here, and all recording sites were within several millimeters of these neurons.

To obtain longer duration cell recordings, monkey L was re-implanted with a chronic electrode array over the left motor cortex. The array of 12 independently movable microwires is fully described elsewhere (Jackson and Fetz 2007). This array provided stable recordings from the same isolated cell for the duration of an experimental session for all cells, and across multiple days for 36 cells (Jackson and Fetz 2007, Jackson *et al* 2007, Mavoori *et al* 2005).

Each session began by quantifying the cell's responses during an isometric, eight-target wrist torque-tracking task in the flexion-extension and radial-ulnar plane (figure 1). Isolated cell activity was discriminated on-line using template-matching software (Alpha Omega MSD). In subsequent brain-control trials, cell activity drove cursor movement in one dimension. Inter-spike intervals were averaged over a 0.5 s sliding window to create a continuous signal for cursor position. If the cell was directionally tuned, the rate targets

were aligned with its preferred direction. For untuned cells, either the left or right screen position was arbitrarily chosen to represent high discharge rates for visual feedback.

Targets were randomly presented to evoke either high- or low-discharge rates of the cell. Targets remained on the screen until the monkey maintained the discharge rate within each target for at least 1 s (longer in some experiments—see the Results section). After a brief (1.5 s) reward period, the next target was presented. Visual feedback of the cell discharge rate was initially normalized to the maximum discharge rate observed during the wrist tracking task. This was subsequently increased to examine higher cell discharge rates. Discharge rate targets spanned 30% of the screen area, which encompassed discharge rates of 0 pps through the maximum rate observed.

The monkey's hand remained in the isometric wrist torque transducer throughout the experiment, permitting wrist torque to be measured during brain-control sessions. The monkeys produced much less wrist torque on average during brain control compared to wrist tracking (see the Results section and figure 3(c))

We studied all well-isolated active neurons encountered by the recording electrodes, without any selection bias for cells related to wrist movement. Cells included here were considered well-isolated single units if an average of only $1.1 \pm 1.3\%$ of spikes occurred with an ISI of less than 2 ms. Data are reported for 246 cells recorded on 251 separate days. The total practice duration with each cell averaged 28 ± 27 min (range: 4–206 min). Practice durations were similar for cells in the pre- and post-central cortex ($p = 0.41$).

Strength of directional tuning was calculated for cells during the initial torque-tracking task using the vector method (Batschelet 1981). Vectors (V_i) were constructed in each of the eight peripheral target directions (θ_i) with magnitudes proportional to the average cell rate (r_i) during the target hold period (Batschelet 1981, Gribble and Scott 2002, Scott and Kalaska 1997). These vectors were then summed and normalized to produce a resultant vector (V) with magnitude between 0 and 1. Note that if normalizing to the average or baseline firing rate, the discharge rate during each target must be individually divided by the baseline firing rate before calculating the vector in each target direction. If the *vectors* in each target direction are later normalized to an average firing rate the result will vary depending on the average firing rate. Nearly identical results to those reported below were obtained when the maximum Z-score between targets was calculated as an estimate of directional tuning.

Larger resultant magnitudes indicate more sharply tuned cells. A bootstrap test was used to determine significant ($p < 0.05$) directional tuning by assigning measured spike rates to random target positions 4000 times (Scott and Kalaska 1997). Based on this test, cells were considered tuned ($n = 82$) or untuned ($n = 164$). Linear regression determined the correlation between directional tuning and the peak performance during brain control.

Baseline cell rates were obtained during 1 min periods in which the monkey viewed a blank screen immediately following the first 10 min period of cell control of the cursor. Baseline rates were computed from average cell activity only over periods when the monkey produced no wrist torque.

The peak performance was quantified by the maximum number of targets acquired during a 2 min period. The peak performance was compared among conditions and to the performance during the initial 2 min of practice. The performance was quantified as the number of targets acquired in a 2 min period for several reasons related to the experimental design. First, targets remained on the screen until satisfied. Therefore, no metrics about the number of correct trials could be calculated. Second, the task difficulty was incremented at 5–10 min intervals to extend the range of cell control. Thus, 2 min struck the balance between permitting time for learning of the new task constraint (e.g. higher discharge rate or longer hold time), and assessment of stable performance. The 2 min period was chosen to provide a conservative estimate of sustained performance, and reduce the effect of random fluctuations in cell rate.

To rule out the possibility that the monkey learned a strategy of generally increasing cortical activity in order to control the isolated neuron, the activity of cells recorded simultaneously with the neuron participating in brain control were examined. For the 55 cell pairs recorded, the firing rates of the two recorded cells were generally uncorrelated. The average cross-correlation between the firing rates of the two recorded cells was only 0.04 ± 0.08 (range: -0.12 to 0.29). Monkeys were also carefully observed for general body movements (such as leg movements) known to broadly increase cortical activity.

The non-parametric rank sum test was used for all comparisons because at least one data set for each comparison failed the Lilliefors test for normality. Unless otherwise noted, all reported values are means $\pm$ standard deviation (SD).

Results

Monkeys readily learned to control the activity of 246 cells recorded from the pre- and post-central cortex when provided with visual feedback of the discharge rate. Rapid learning was evident in that performance improved more than two-fold from the beginning of practice to peak performance ($p < 0.001$). At the beginning of practice with each cell, the monkeys acquired 6.4 ± 4.5 targets min^{-1} using brain control. After an average of 24 ± 17 min of practice with each cell, the monkeys reached the peak performance and acquired 13.3 ± 5.6 targets min^{-1} using brain control.

The monkeys performed the brain-control task equally well using cells recorded from the pre-central cortex ($n = 240$) compared to cells in the post-central cortex ($n = 16$). At the beginning of practice, they matched discharge rate targets at a similar pace using each group of cells ($p = 0.21$), acquiring 6.4 ± 4.6 and 7.2 ± 3.3 targets min^{-1} using pre- and post-central cells, respectively (figure 2). Control improved substantially with practice for cells in both brain areas ($p < 0.001$), reaching a similar level of performance (13.3 ± 5.6 versus 13.8 ± 4.7 targets min^{-1} pre- versus post-central cells, $p = 0.52$).

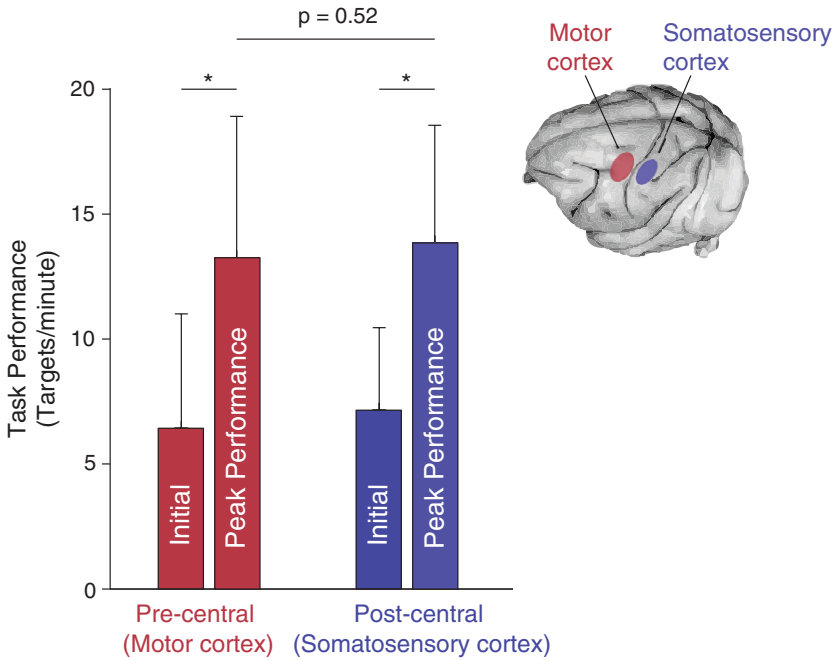

Figure 2. Monkeys performed the brain-control task equally well using cells recorded from the pre-central cortex ($n = 240$) compared to cells in the post-central cortex ($n = 16$). At the beginning of practice, they matched discharge rate targets at a similar pace using each group of cells ($p = 0.21$). Control improved substantially with practice for cells in both brain areas ($^*p < 0.001$), reaching a similar level of performance ($p = 0.52$). Mean + SD.

Cell rates increased with continued practice at brain control. Figure 1(b) shows an example in which monkey L modulated cell activity to acquire high- and low-rate targets under brain control. The monkey learned to nearly double the cell activity over the 10 min shown in order to acquire targets requiring progressively higher discharge rates. For all cells combined, 1 s averages of cell activity during matching of the high-rate targets increased from 29.4 ± 14.5 to 39.2 ± 25.3 pps ($p < 0.001$) over the course of practice with brain control. Increased discharge rates were similar for pre- and post-central cells ($p = 0.11$).

Cell activity was modulated to a greater extent during brain control than during wrist tracking. Average cell modulation was 12.7 ± 8.1 pps during wrist tracking, compared to 21.1 ± 12.7 pps during brain control ($p < 0.001$; figure 3(a)). For each cell the amount of modulation was correlated during brain control and wrist tracking (figure 3(b), $R^2 = 0.41$, $p < 0.001$). For 213 of 246 cells, activity was modulated to a greater extent during brain control than during wrist tracking.

Greater modulation of cell activity occurred during brain control despite the production of smaller wrist torque. For all cells during brain control, monkeys produced an average of only 36% of the torque used during wrist tracking (figure 3(c)). Increases in cell rate were not correlated with changes in wrist torque during brain control ($p > 0.30$). Wrist torque during brain control of post-central cells was similar to pre-central cells ($p > 0.20$), and much less than during wrist tracking ($p < 0.001$). During brain control, the monkeys produced marginally more wrist torque when controlling cells with significant directional tuning during the wrist-tracking task (0.056 ± 0.066 N m), compared to cells with no directional tuning (0.042 ± 0.050 N m; $p = 0.043$).

Directionally tuned cells performed only slightly better than untuned cells. Figure 4 shows that the strength of cell directional tuning during the tracking task was a poor predictor of brain-control performance ($R^2 = 0.12$).

Two-thirds (164/246) of the cells were not directionally tuned, and the monkeys acquired targets only slightly more slowly with these unturned cells (12.0 ± 5.2 targets min^{-1}) compared to the 82 cells with significant preferred directions (15.8 ± 5.5 targets min^{-1}; $p < 0.001$). Brain control did not lead to the emergence or change in directional tuning during the wrist-tracking task. The presence or absence of directional tuning remained similar ($p > 0.20$) for the 199 cells that were tested both before and after each brain-control session.

The SD of cursor position (measured in percent of the full screen display) averaged about three-fold higher for brain control compared to hand control, but dropped significantly with practice at brain control. The SD of cursor position during the first 2 min of brain-control practice was $8.8\% \pm 6.4\%$ of the full range of screen display, but improved to an average of $5.5\% \pm 4.6\%$ during practice ($p < 0.0001$). An example cell is shown in figure 5. This was still higher than the $2.2 \pm 0.9\%$ deviation seen during hand control. This difference is explained partly by the fact that hand-control targets were much smaller (15% of visual display) than brain-control targets (30% of display).

When recording stability permitted, the monkeys practiced controlling the same cell across multiple days. Figure 6(a) shows an example pre-central cell with nearly four-fold improvement in brain-control performance with practice over eight days. Other cells are shown in figures 6(b)–(e).

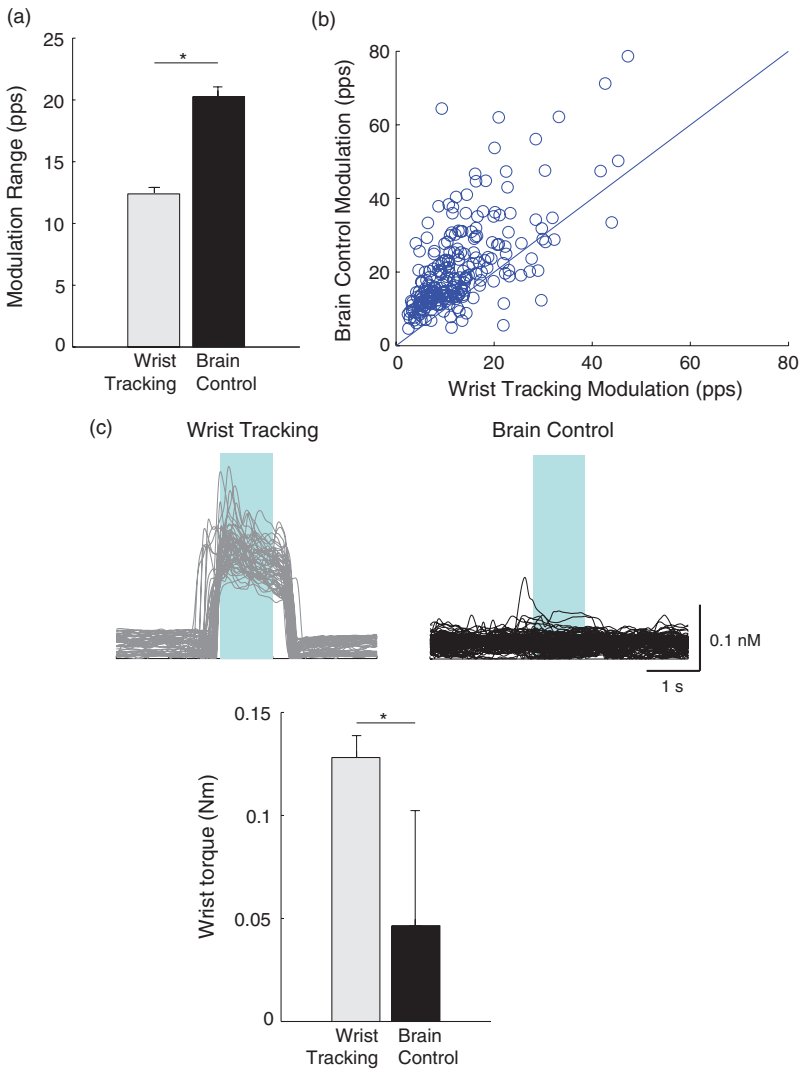

Figure 3. Cells modulated to a greater extent during brain control compared to wrist tracking, despite smaller wrist torque during brain control. (a) Average modulation range during wrist tracking and brain control (mean + SEM). (b) Scatter of modulation during wrist tracking versus modulation during brain control. Most cells fall above the unity line. (c) Example (top) and average (bottom) wrist torque during the target time for wrist tracking and brain control (mean + SD). For example traces, the shaded region defines the target hold period. $*p < 0.001$.

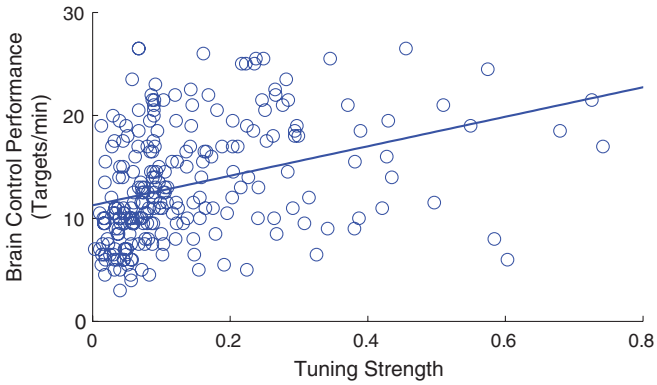

Figure 4. Regression of tuning strength measured during wrist tracking versus the number of targets/min during brain control ($R^2 = 0.12$; $p < 0.001$) for all 246 cells tested. The strength of cell directional tuning was a poor predictor of target acquisition performance during brain control.

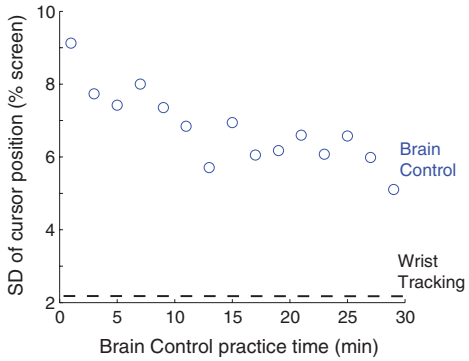

Figure 5. Improvement in cursor stability during brain-control practice for an example cell from monkey L. The standard deviation of cursor position as a percentage of the screen display during the target hold time is plotted over the course of a 30 min practice session. The dashed line shows the average cursor deviations during the wrist-tracking task matching targets half the size of those used for brain control.

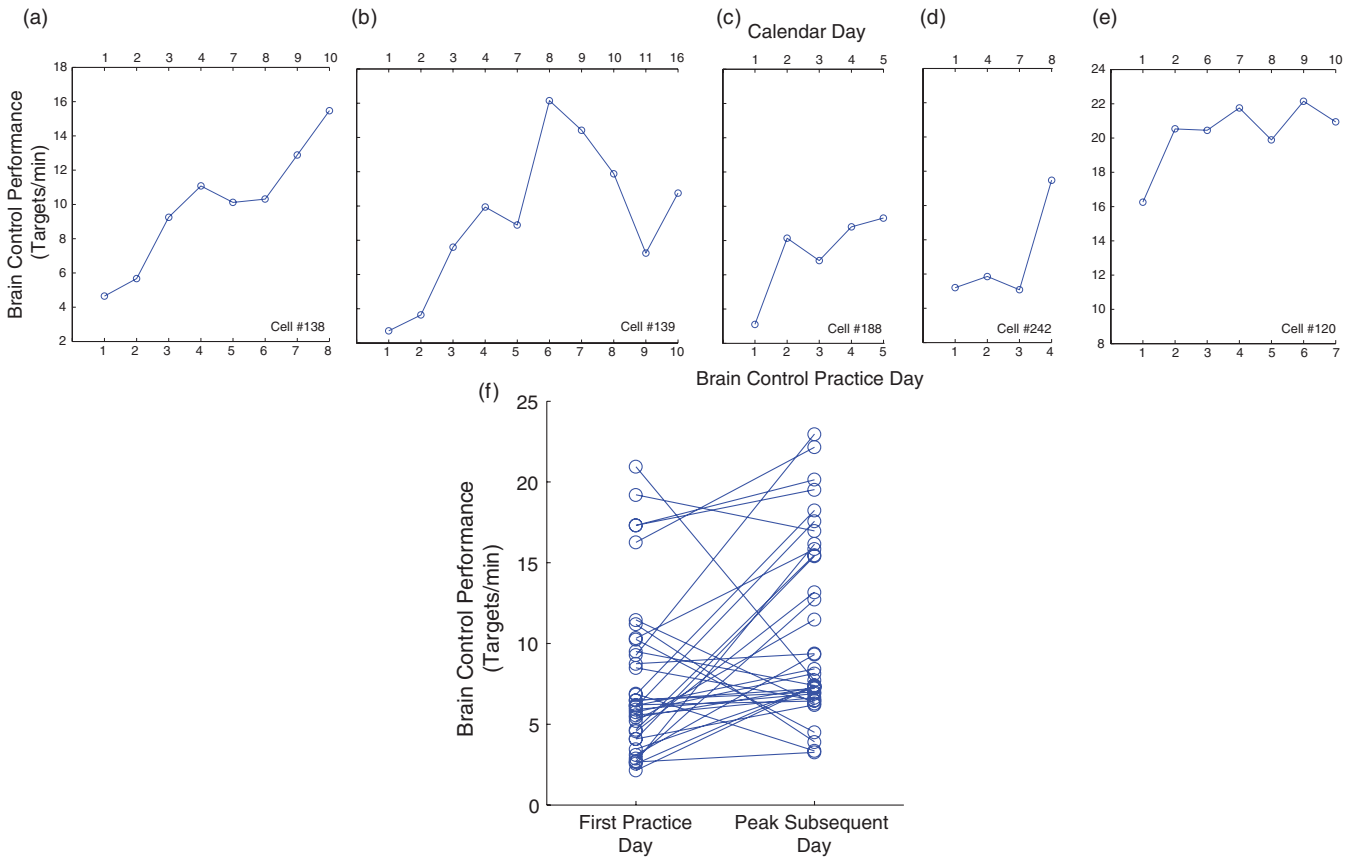

Figure 6. With practice monkey L improved controlling the same cell across days. (a)–(e) Brain-control performance during the first 10 min of each day for five pre-central cells across multiple days. Note that while the scale is consistent, the ordinate range differs for panel (e). (f) A comparison of brain-control performance on the first day and the subsequent day with peak performance for the 36 cells recorded across multiple days.

While some cells showed greater improvement when practice was provided on consecutive calendar days (e.g. figures 6(a) and (d)), no consistent advantage was found for consecutive versus non-consecutive practice days across the population ($p = 0.516$). The performance improved substantially for 27 of 36 cells recorded across multiple days (range: 2–10 days), at an average rate of 3.51 targets/min/day (figure 6(f)).

Monkeys were required to maintain discharge rate within each target for 1.0 s for all cells tested. They were able to maintain discharge rate for an average of 2.1 ± 0.7 s for 25 cells tested with longer target times. With six of these cells, monkeys were able to maintain discharge rate for 3.0 s, the longest time tested (figure 7). Cell discharge rate could be maintained well above or below baseline rates for extended periods up to 3.0 s for cells in both the pre-central cortex (figure 7(b)) and post-central cortex (figure 7(a)).

Discussion

Our major findings are that (1) monkeys can learn to use arbitrarily chosen single cells in both the pre- and post-central cortex to control the movements of a computer cursor, (2) the degree of control improves with practice within a session and across days, (3) control is only slightly related to cell directional tuning during wrist movement, and (4) rates of some cells could be maintained above or below baseline for several seconds. These findings can be compared to other BMI studies and previous studies examining volitional control of single neurons.

We observed that the firing rates of isolated neurons in the post-central primary somatosensory cortex (S1) could be controlled equally well compared to neurons in the pre-central primary motor cortex (M1). Recordings during active movements have shown that most S1 neurons have, in addition to afferent input from peripheral receptors, central input that activates them prior to the onset of muscle activity (Soso and Fetz 1980) and before active movements (Lebedev *et al* 1994, Nelson 1987). Carmena and colleagues found that an offline decoder could use S1 neurons to predict arm movement, velocity and grip force, but less effectively than from M1 neurons (figure 2 in Carmena *et al* (2003)).

In the present study monkeys maintained the discharge rate of each cell within targets for at least 1 s, and for up to 3 s for some cells. Previous studies of operant conditioning of single cell activity rewarded bursts of cell activity (Fetz 1969, Fetz and Finocchio 1971), or the transient reduction of cell activity for low-rate conditioning (Fetz and Baker 1973). While these early studies provided the first demonstration that cortical neurons could be volitionally controlled, they did not reinforce precise temporal control of cell activity. Here we demonstrate that monkeys can match rate targets both above and below baseline levels for prolonged periods (figure 7).

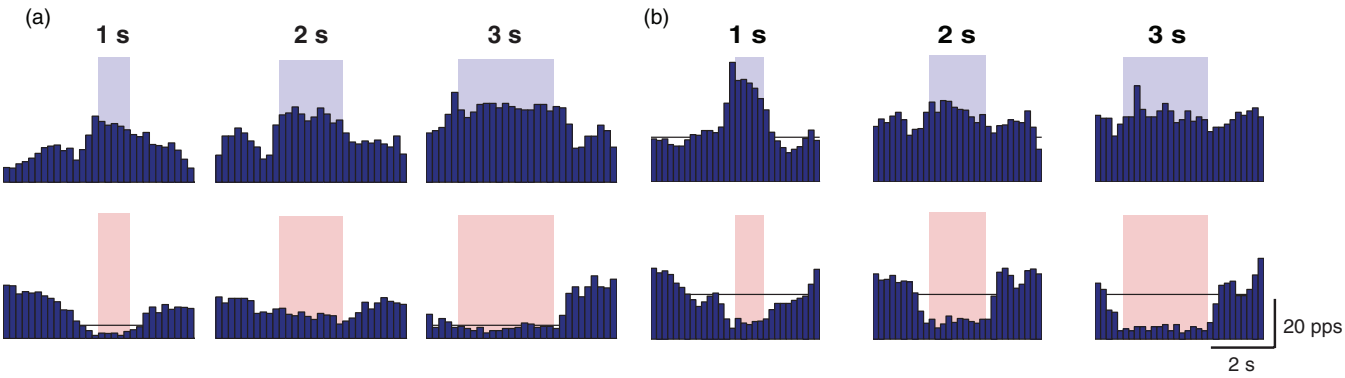

Figure 7. Monkeys maintained high or low cell rates for up to 3 s. The histograms show an example post-central (a) and pre-central (b) cell, each matching high rate (top row) and low rate (bottom row) for 1, 2 and 3 s (blue and red shaded region, respectively). With selected cells, monkeys could maintain the cell rate above (a) or below (b) baseline rates (horizontal line) for prolonged periods.

The monkeys modulated the cortical neuron discharge rate much more during the brain-control task compared to the wrist step-tracking task, despite smaller wrist torques during brain control. Increased cell modulation during initial brain-control sessions has been reported in a previous study using population decoding from large ensembles of neurons (Zacksenhouse *et al* 2007). These authors attributed increased cell rates to the learning of the new task, because cell modulation was not explained by kinematic or velocity modulation, and decreased slightly with practice. In our case, greater cell modulation was explicitly rewarded and led to increased task performance in brain control. The fact that higher cell rates could be achieved without greater wrist torque is consistent with the use of cortical activity as a control signal after paralysis (Hochberg *et al* 2006) and the dissociation of cell activity and movement observed in BCI studies (Carmena *et al* 2003, Donoghue 2002, Taylor *et al* 2002, Velliste *et al* 2008).

After brief periods of practice, monkeys could volitionally control the activity of all 246 neurons tested in the present study. There was only a slight trend for higher brain-control performance using directionally-tuned neurons. This was probably due to the fact that visual feedback was presented in the preferred direction for cells with directional tuning, whereas the visual feedback direction was randomly selected for untuned neurons. The use of untuned neurons in brain–computer interfaces could dramatically expand the useful population of randomly sampled neurons, since about two-thirds of neurons were untuned in this and previous studies (Amirikian *et al* 2000, Evarts 1968, Georgopoulos *et al* 1982, Moritz *et al* 2008).

Incorporating relatively direct connections from individual neurons to BMI controls may also be a useful complementary strategy to decoding movement parameters from large ensembles of neurons (Moritz *et al* 2008). While the majority of BMI studies decode population activity (Carmena *et al* 2003, Chapin *et al* 1999, Hochberg *et al* 2006, Musallam *et al* 2004, Pohlmeyer *et al* 2009, Taylor *et al* 2002, Velliste *et al* 2008), recent work has demonstrated that a similar performance can be achieved after decoder weights are randomized and monkeys are provided with sufficient practice time with the same decoder and cell population (Ganguly and Carmena 2009).

Prolonged practice with a fixed transform from neural or muscle activity to BMI control clearly enhances the performance (Ganguly and Carmena 2009, Radhakrishnan *et al* 2008). Here we observed substantial improvement with practice within a session and across days for neurons with stable recordings. It seems likely that longer sustained practice times than were used here would lead to even greater control than we have documented.

In summary, monkeys can readily learn to control the activity of motor and sensory cortex neurons when provided with the visual feedback of the discharge rate. The performance improves with practice, and is generally unrelated to the strength of direction tuning during movement. These findings demonstrate that arbitrary single cortical neurons, regardless of their strength of directional tuning, are capable of controlling cursor movements in one dimension. It is possible that such direct connections from cell activity to neuroprosthetic devices may be useful in controlling artificial stimulation delivered to paralyzed muscles (Moritz *et al* 2008), or for controlling robotic or prosthetic limbs.

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