Motor cortex single-neuron and population contributions to compensation for multiple dynamic force fields

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Addou T, Krouchev NI, Kalaska JF. Motor cortex single-neuron and population contributions to compensation for multiple dynamic force fields. J Neurophysiol 113: 487–508, 2015. First published October 22, 2014; doi:10.1152/jn.00094.2014.—To elucidate how primary motor cortex (M1) neurons contribute to the performance of a broad range of different and even incompatible motor skills, we trained two monkeys to perform single-degree-of-freedom elbow flexion/extension movements that could be perturbed by a variety of externally generated force fields. Fields were presented in a pseudorandom sequence of trial blocks. Different computer monitor background colors signaled the nature of the force field throughout each block. There were five different force fields: null field without perturbing torque, assistive and resistive viscous fields proportional to velocity, a resistive elastic force field proportional to position and a resistive viscoelastic field that was the linear combination of the resistive viscous and elastic force fields. After the monkeys were extensively trained in the five field conditions, neural recordings were subsequently made in M1 contralateral to the trained arm. Many caudal M1 neurons altered their activity systematically across most or all of the force fields in a manner that was appropriate to contribute to the compensation for each of the fields. The net activity of the entire sample population likewise provided a predictive signal about the compensation for each of the fields. The neurons showed a broad range of sensitivities to the different fields, and there was little evidence of a modular structure by which subsets of M1 neurons were preferentially activated during movements in specific fields or combinations of fields.

motor cortex; elbow movements; force fields; neural activity; monkey


Despite all of this experimental evidence, what specific attributes of movement are encoded in the discharge of M1 neurons remains controversial (Graziano and Aflalo 2007; Kalaska 2009; Reimer and Hatsopoulos 2009; Scott 2008). Resolution of this issue has been made all the more imperative with the advent of chronic multielectrode implants and brain-machine interface (BMI) technology that holds the promise of greatly enhancing the quality of life of many neurological patients by allowing them to covertly control the actions of computer cursors, remote robotic tools and other devices via their own brain activity (Collinger et al. 2013; Green and Kalaska 2010; Hatsopoulos and Donoghue 2009; Hochberg et al. 2006; Velliste et al. 2008). BMI studies have likewise demonstrated that signals can be extracted from M1 activity about multiple movement attributes ranging from spatiotemporal trajectories to specific muscle activity patterns (Bansal et al. 2011, 2012; Carmena et al. 2003; Cherian et al. 2011; Fagg et al. 2009; Lebedev et al. 2005; Rivera-Alvidrez et al. 2010; Saleh et al. 2012; Santucci et al. 2005; Suminski et al. 2011; Taylor et al. 2002; Truccolo et al. 2008; Vargas-Irwn et al. 2010; Yu et al. 2007).

M1 is also implicated in the acquisition, retention and recall of motor skills. M1 neuron discharge patterns appear to change during and after learning new movement sequences and skills (Kargo and Nitz 2003, 2004; Karmi et al. 1998), arbitrary visuomotor associations that alter the mapping between visual input and the direction of motor output (Paz et al. 2003; Paz and Vaadia 2004; Zach et al. 2008, 2012), and while adapting to novel mechanical environments that alter the mapping between the direction of causal output forces and resulting movements (Arce et al. 2010a, 2010b; Gandolfo et al. 2000; Li et al. 2001; Mandelblat-Cerf et al. 2011; Padoa-Schioppa et al. 2002, 2004; Xiao et al. 2006). In particular, during adaptation to a viscous-curl force field applied perpendicular to the direction of arm movements and subsequent readaptation to the baseline conditions (“washout”), some M1 neurons showed apparent rotations in the directionality of their motor output tuning curves that resembled the corresponding rotations in the activation patterns of muscles required to compensate for the force fields (Arce et al. 2010a, 2010b; Cherian et al. 2013; Gandolfo et al. 2000; Li et al. 2001; Mandelblat-Cerf et al. 2011; Padoa-Schioppa et al. 2002, 2004; Thoroughman and Shadmehr 1999; Xiao et al. 2006).

Changes in M1 neural activity have also been reported as subjects acquire covert control of remote effectors, such as...

Most of the studies of adaptation to external force fields only looked at changes in the mean activity level averaged over extended behavioral epochs, such as an instructed-delay period or from the appearance of the target to the end of the movement (Arce et al. 2010a, 2010b; Gandolfo et al. 2000; Li et al. 2001; Xiao et al. 2006). In contrast, Sergio et al. (2005) recorded neurons in the caudal M1 of two monkeys while they either generated isometric forces against a rigid handle or made arm movements with a heavy movable handle, in the same eight directions in a horizontal plane. This was not a learning study per se, because the animals were extensively trained before neural recordings and performed both tasks skillfully during the recordings. The time-varying discharge pattern of many single neurons and of the averaged population response in the caudal part of M1 provided signals that clearly reflected the differences in the time course of motor output dynamics between the two tasks (Sergio et al. 2005). In contrast, the activity of posterior parietal area 5 neurons was strongly related to the direction of arm movements, but provided far less information about motor output forces and EMG activity in the same tasks (Hamel-Pâquet et al. 2006).

All of these experiments demonstrated a significant diversity of response changes in single M1 neurons that could reflect different aspects of skilled performance in the different dynamical environments. However, it is unclear whether this diversity indicates the existence of separate neural subpopulations with distinct functional roles in the control of motor output kinematics vs. kinetics or simply reflects local ranges of empirically-shaped response changes at the single-neuron level within a larger continuum of activation patterns distributed across the entire M1 neural population (Green and Kalaska 2010; Li et al. 2001; Rokni et al. 2007).

Furthermore, human subjects are capable of learning, retaining and recalling a wide range of motor skills. However, all of the studies of force-field adaptation have been limited to one or two different external force fields. It is not clear how M1 contributes to skilled motor performance over a wide range of task conditions, nor how it ultimately minimizes the problems of anterograde and retrograde interference that arise during attempts to acquire different motor skills in rapid succession in the classic A-B-A task design (Addou et al. 2011; Brashers-Krug et al. 1996; Caithness et al. 2004; Davidson et al. 2005; Miall et al. 2004; Overduin et al. 2006; Shadmehr and Brashers-Krug 1997; Shadmehr and Mussa-Ivaldi 1994).

One hypothesis proposes a system architecture that can adapt to multiple dynamic environmental contexts: the Modular Selection and Identification for Control (MOSAIC) model (Haruno et al. 2001; Imamizu et al. 2007b). This model proposes the existence of multiple pairs of predictor-controller modules. The predictors provide the probability of each task context, and these probabilities are used to weight the outputs of a set of corresponding controllers tuned to each context. This system can simultaneously train the multiple predictors and controllers and learn how to select the appropriate controller(s) for a given context. Evidence from neural recording studies of oculomotor pursuit tracking (Shidara et al. 1993) and more recently from imaging studies during tool use (Higushi et al. 2007; Imamizu et al. 2000, 2003, 2004, 2007a) and a single-neuron study with elbow movements (Yamamoto et al. 2007) support the prediction of the MOSAIC model that the neural structure that acquires and houses the multiple dynamic models is the cerebellar cortex. According to this architecture, M1 functions primarily as a feedback controller for task dynamics, while any M1 feed-forward activity mainly reflects the output from the adaptive inverse-dynamics modules in the cerebellum (Schweighofer et al. 1998a, 1998b). The MOSAIC model does not make strong explicit predictions about the responses of single M1 neurons. However, in its usual configuration, the outputs of the multiple inverse-dynamics modules converge on M1 (Haruno et al. 2001; Imamizu et al. 2007b), allowing for single M1 neurons to show appropriate dynamics-related response changes over a much larger range of task conditions than expected of cerebellar neurons.

The principal goal of this study was to elucidate to what degree M1 cells change their activity as a function of task dynamics while monkeys make single-joint elbow movements against a range of velocity-dependent and position-dependent force fields. The second goal was to assess how closely any task-related changes in M1 activity paralleled the time course of the changes in output forces required to compensate for the different external force fields (Sergio et al. 2005). A third goal was to elucidate whether M1 has a modular structure or not, that is, whether single M1 neurons tended to vary their activity across most or all field conditions, or alternatively whether subsets of M1 neurons tended to show changes in activity preferentially associated with a more limited range of task conditions.

We trained two monkeys to perform elbow flexion-extension movements in five different external force-field conditions. In behavioral studies, we reported that monkeys (Krouchev and Kalaska 2003) and human subjects (Addou et al. 2011) are able to use an arbitrary cue (the color of a computer monitor background) to recall the motor skill necessary to compensate for different external force fields associated with each cue, even before encountering the field physically in that trial. Here we show that single M1 cells and the pooled activity of the sampled neural populations alter their activity in a manner appropriate to contribute to the compensation of several different fields and show changes in activity prior to movement onset and during movement that anticipate the changes in motor output necessary to compensate for the different force conditions. Data collection focused on neurons in the caudal part of M1 located in the rostral bank of the central sulcus, where the neurons most sensitive to external loads and motor output dynamics are concentrated (Kalaska et al. 1989; Sergio et al. 2005; Sergio and Kalaska 1998, 2003).

METHODS

Task Apparatus

Two young adult male rhesus monkeys (A and B) were trained to perform single-degree-of-freedom elbow flexion and extension movements that could be perturbed by externally generated force fields (Fig. 1). The monkeys’ arm was placed in a single-joint torquable manipulandum positioned beside a primate chair. The height of the primate chair was adjusted so that the upper arm of the monkey was abducted into the horizontal plane at shoulder height (~90° with
dependent viscoelastic (VE) field, magenta. dependent resistive elastic (E) field, blue; resistive velocity- and position-field was associated with a different monitor background color. The

Behavioral Task

The primate chair could be placed on either side of the manipulandum so that the monkey could perform the task with either arm. However, during the recording periods, the monkeys performed the task with only the arm contralateral to the recording site. The other, nonperforming, arm was placed on an arm rest and loosely constrained.

The manipulandum and its associated control hardware and software were developed by the Kawato Dynamic Brain Project (ERATO, JST). The same manipulandum was used by Krouchev and Kalaska (2003) and Addou et al. (2011) for behavioral studies in monkeys and humans, respectively, and a similar manipulandum was used by Wada et al. (2003) and by Yamamoto et al. (2007) for human behavioral and monkey cerebellar neural recording studies, respectively.

Behavioral Control

During each trial, the monkey viewed a horizontal 150° arc of 17 cm radius presented on the computer monitor, and a cursor that swept along the arc as a function of the angular position of the monkey’s elbow. This plotting scale permitted a 1:1 representation of the displacement of the monkeys’ forearm. At the beginning of each trial, the arc and cursor appeared superimposed on the field-dependent monitor background color, and a circle of 1.7-cm radius (corresponding to an angular precision range of ±5.74°) was displayed centrally at the top of the arc (designated arbitrarily as 0°) as a start center-hold window. This corresponded to a starting elbow angle of 90° of the forearm with respect to the trunk. The animals performed elbow flexion/extension movements in the horizontal plane at shoulder level with their forearm positioned on the handle of a torquable robotic manipulandum. They made flexion or extension movements of their elbow from an initial posture of 90° to displace a cursor on a monitor screen between a central starting target window and a target at either 45° to the left or right of the central starting position on the arc displayed on the screen, whose position was arbitrarily designated as 0°. The background color of the monitor changed to signal different task conditions: null (N) field, black; velocity-dependent resistive viscous (V+ field, red; velocity-dependent assistive viscous (V−) field, pink (monkey A) or green (monkey B); position-dependent resistive elastic (E+) field, blue; resistive velocity- and position-dependent viscoelastic (VE) field, magenta.

Movement duration was controlled to ensure that monkeys encountered velocity-dependent “viscous” force fields of similar magnitude, and

Fig. 1. Task apparatus. Monkeys made single-joint movements in the horizontal plane at shoulder level with their forearm positioned on the handle of a torquable robotic manipulandum. They made flexion or extension movements of their elbow from an initial posture of 90° to displace a cursor on a monitor screen between a central starting target window and a target at either 45° to the left or right of the central starting position on the arc displayed on the screen, whose position was arbitrarily designated as 0°. The background color of the monitor changed to signal different task conditions: null (N) field, black; velocity-dependent resistive viscous (V+) field, red; velocity-dependent assistive viscous (V−) field, pink (monkey A) or green (monkey B); position-dependent resistive elastic (E+) field, blue; resistive velocity- and position-dependent viscoelastic (VE) field, magenta.
to avoid a strategy whereby the monkeys could “compensate” for the viscous fields by making slower movements to reduce their magnitude. To that end, movement duration was calculated at the end of each trial as the time interval between the exit of the start target window and entrance into the movement target window. At the end of each trial, monkeys were given knowledge of results about movement duration, as follows:

1) If the cursor entered the target window within 300–400 ms after exiting the start target, and monkeys successfully held the cursor in the target window until the end of the THT, the target circle appeared to “explode” on the monitor, accompanied by a chime sound to signal a successful trial.

2) If the cursor entered the target more than 400 ms after exiting the start target, the color of the target changed from white to blue and a 0.5-s low tone (150 Hz) was played to signal that the movement was too slow.

3) If the cursor entered the target in less than 300 ms, the color of the target changed from white to yellow and a 0.5-s high tone (1000 Hz) was played to signal that their movement was too fast.

If the monkeys failed to perform a movement within these behavioral constraints, the trial was repeated until completed successfully.

There were some differences between the task performed by monkeys A and B. Monkey A performed behaviorally controlled trials from the central start target to the peripheral targets (i.e., left arm and right arm movements) just as described. It then performed controlled return movements from the peripheral targets back to the central target under the same task conditions, including the force fields [i.e., right to center (RC) and left to center (LC) movements]. Furthermore, the gains of the force fields remained constant throughout all phases of each trial, including the center-hold time (CHT) and THT epochs. It performed the task in 5 successive blocks of 48 successful trials (12 successful trials each of the CR, CL, and LC movements) during which it encountered one of the 5 different force fields. The data from trials in which the monkey moved only from the center to the peripheral targets (CR, CL) will be presented here.

In contrast, monkey B performed behaviorally controlled task trials only during the movements to the peripheral targets (CR, CL). The return movements to the central target (RC, LC) were uncontrolled, self-paced and made in the N field. Furthermore, the gain of the force field gradually increased from zero to reach its nominal value (full gain) over the last 500 ms of the center-hold period preceding the appearance of the peripheral target, while monkey B held its arm in the central start target. As a result, monkey B could not use proprioceptive cues during the center-hold period to determine the nature of the field and appropriate forward control strategies. At the end of each fielded trial, the gain of the field was gradually reduced over the 500-ms time period after the monkey entered the target window, and monkey B then returned its arm to the start position in the N-field condition. The field gain was then gradually restored to its full value at the beginning of the following trial. These gradual changes in the gain of field strength at the beginning and end of each trial were intended to eliminate abrupt, uncomfortable perturbations of the monkey’s arm that could result from instantaneous field application and inactivation, especially of the position-dependent E+ and VE fields.

Moreover, monkey B encountered the five different fields in a pseudorandom sequence of short eight-trial blocks during which only one of the fields was presented. A complete data file of the task for monkey B included four pseudorandomly ordered sequences of the eight-trial blocks in the five force fields, plus one final replication of the first force-field block presented at the start of the file, for a total of 108 successful trials.

The multipin connector was secured to the skull with titanium neurosurgical screws and neurosurgical acrylic. During the implantation surgery, pairs of the wire electrodes were soldered to a multipin connector, and the solder joints were insulated with epoxy. During the implantation surgery, pairs of the wire electrodes were threaded subcutaneously to each muscle and then inserted into and secured to the belly of each muscle using standard procedures. The multipin connector was secured to the skull with titanium neurosurgical screws and neurosurgical acrylic.

Acute EMG recordings were also made in the left arm of monkey B. Pairs of hooked wire electrodes were made from Teflon-insulated single-stranded stainless steel wire (Cooner no. AS633) were soldered to a multipin connector, and the solder joints were insulated with epoxy. During the implantation surgery, pairs of the wire electrodes were threaded subcutaneously to each muscle and then inserted into and secured to the belly of each muscle using standard procedures. The multipin connector was secured to the skull with titanium neurosurgical screws and neurosurgical acrylic.

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One force-field effect that is not evident in the mean velocity profiles is that the inherently unstable V– field often resulted in small oscillations of the arm within the peripheral targets at the end of movements, which was not observed for any of the other force-field conditions. This was more prominent in monkey A than in monkey B because the V– field strength was maintained during the target-hold periods of the task for monkey A, whereas it was reduced to zero over the 500 ms after monkey B entered the target window. However, the main focus of this study was on how the monkeys initiated and executed movements with relatively constant kinematics across the wide range of force fields, whereas identical end-point stability across all conditions was less of a priority.

Once the monkeys’ performance suggested adequate compensation for the different fields (Fig. 2), they were then prepared for neural recording in M1 using standard aseptic surgical techniques (Kalaska et al. 1989). During each recording session, a microelectrode was advanced through the cortex while the animal performed the task. When a neuron was isolated, its task-related responses were tested initially by performing a few trials in the two movement directions. Its passive responses were tested by manipulating the arm joints, touching the skin, and palpating muscles. A neuron was selected for further study if this evidence indicated that it was related to movements of the contralateral elbow and/or shoulder but not to more distal joints, and it displayed directional tuning.

The monkeys learned the task first using the right arm. After neural data were collected from the left motor cortex, the monkeys were retrained with the left arm, and recordings were then made in the right hemisphere.

While recording neural data in the left hemisphere of each monkey, we also simultaneously recorded the EMG activity of eight muscles of the right arm: six elbow muscles (three heads of triceps, two heads of biceps, brachoradialis), and two shoulder muscles (pectoralis and posterior deltoid). Prior to the surgery, pairs of Teflon-insulated multistranded stainless steel wires (Cooner no. AS633) were soldered to a multipin connector, and the solder joints were insulated with epoxy. During the implantation surgery, pairs of the wire electrodes were threaded subcutaneously to each muscle and then inserted into and secured to the belly of each muscle using standard procedures. The multipin connector was secured to the skull with titanium neurosurgical screws and neurosurgical acrylic.

Acute EMG recordings were also made in the left arm of monkey B. Pairs of hooked wire electrodes were made from Teflon-insulated single-stranded stainless steel wire (Cooner no. AS765-40) and were inserted percutaneously into the target muscles using fine 30-gauge syringe needles. The implantations were verified by electrical stimulation through the wires with short trains of stimuli (0.2-ms pulses, 20 Hz, 0.1–15 mA) to evoke muscles contractions. For both chronic and acute recordings, EMG activity was amplified, filtered (100–3000
Hz), rectified and integrated in 5-ms bins to retain a record of the area under the EMG signal envelope in each trial.

Data Analyses

Manipulandum angle was measured by a rotary position encoder. Position data were sampled at 1 kHz for manipulandum control and at 200 Hz for behavioral performance analysis. Typical movement velocity profiles peaked well below 3 rad/s and had frequency contents well below the 1-Hz range. Hence the position signals were low-pass filtered at 25 Hz (third-order Butterworth filter) to increase the signal-to-noise ratio. The velocity and acceleration signals were then estimated by finite approximations.

For analysis of the neural data, we defined four trial epochs based on the timing of task events and the kinematics of the monkeys’ movements. CHT started from the moment the monkey entered the

Fig. 2. Average angular velocity profiles (A) and perturbation torques (B) recorded during one data set for extension and flexion movements of monkey B. Extension velocities were arbitrarily plotted as positive, and flexion velocities as negative. Torques that oppose the direction of movement (V+, E+, VE) were plotted inverted relative to the corresponding velocity curve, whereas the assistive V−torque curves were plotted in the same orientation as the corresponding velocity curves. Plot colors correspond to monitor backgrounds for each of the force field conditions: N, black; V+, red; V−, green; E+, blue; VE, magenta. Note that, for convenience, the V−field data are illustrated in green in this figure and all subsequent figures, even though the actual monitor color for that field was pink for monkey A.
center-hold target to the moment of movement target presentation on the computer screen (GO). RT was the interval from the moment of movement target presentation (GO) to the moment of movement initiation by the monkey [estimated movement start (MS)]. Movement time (MT) was the time interval from the estimated MS, to the moment of movement completion and attainment of a static posture by the monkey [estimated movement end (ME)]. THT started from the estimated ME, to the end of the peripheral THT.

Estimated movement onset (MS). The mean velocity and SD were calculated during the last 500 ms of the CHT, before the GO signal appeared. The area under the velocity profile was then calculated from the first time it exceeded the criterion value, the mean CHT velocity + 2 SD, to the peak of the velocity profile. The estimated movement onset, MS, was determined as the time at which the area under the velocity profile exceeded 5% of the total integrated area up to the peak velocity.

Estimated ME. The same approach was used to determine the time of the start of the last 5% of the area of the velocity profile after the peak of velocity (ME).

For all analyses, data were aligned to the estimated MS. For each trial, unless otherwise noted, the recorded spike train was converted into an instantaneous discharge rate by dividing the trial into 5-ms bins and calculating the discharge rate in each bin based on the number of whole and partial interspike intervals in each bin (Georgopoulos et al. 1982; Kalaska et al. 1989). The 5-ms bins corresponded to the 200-Hz sampling rate for the EMG recordings. The EMG records, stored as the area under the EMG envelope every 5 ms after amplification, rectification and integration, were likewise aligned to MS and processed in the same manner as the neural data.

The elbow flexor and extensor muscles behaved in the expected manner in the task. They were typically more active during one or more of the behavioral epochs (RT, MT, THT) in the movement direction in which they were agonists and showed strong increases in their contractile activity when the V+, E+ and VE fields resisted those movements (See Figs. 5 and 6). As a result, we called those movement directions the task-related preferred direction (PD) of those muscles. We used the same criteria to define the task-related PD of the pectoralis and posterior deltoid muscles, even though they do not exert direct forces across the elbow joint.

We used the same criteria to assign a PD to each M1 neuron. The neuron’s PD was defined either as the movement direction in which the neural discharge rate was higher during one or more behavioral epochs in N-field movements, or in which the resistive external force fields caused an increase in neural activity over that recorded in N-field trials, or both.

Statistical Data Analysis of Individual Cell Properties

We applied repeated-measures ANOVA (P < 0.05; Matlab Statistics Toolbox, The Math Works) for each of the three epochs of interest (RT, MT, THT) to assess the effect of force-field and movement direction on neural and EMG activity.

We also used a Kolmogorov-Smirnov (KS) two-sample test (KSTEST2; P < 0.05; Matlab Statistics Toolbox, The Math Works) to compare the activity of each neuron during movements in their PD under different combinations of force fields. We aligned the activity of all trials in a given neuron’s PD in each force field separately to the onset of movement, divided the single-trial data into 100 consecutive 20-ms bins from −1,000 ms to +1,000 ms relative to movement onset, and calculated the single-trial discharge rate during each bin, including partial spike intervals (Kalaska et al. 1989). We then tested whether the resulting cumulative frequency distributions of single-trial discharge rates in a given 20-ms bin were significantly different for a particular pair of fields (KS two-sample test, P < 0.05), and repeated this test for all 100 sequential bins in the trial. This yielded a 100-element vector of 1’s (significant difference in a given bin) and 0’s (nonsignificant difference) for the activity of the neuron between the two fields. This was repeated for all neurons collected in each monkey for that pair of fields. We then generated a histogram of the time-varying probability that neurons in the population would show a significant difference in activity between the pair of fields throughout the trial by counting all the 1’s in each bin. This process was repeated for all 10 unique combinations of the 5 force fields.

The KS test was also used to determine whether the M1 sample populations could be divided into subpopulations that showed distinctly different patterns of responses to the different force fields. To this end, the mean single-trial activity of each neuron at its PD and opposite to the PD (oPD) was calculated during a 200-ms perimovement time window from −100 ms to +100 ms relative to movement onset. These single-trial spike rates were then normalized to the mean spike rate of each neuron recorded at its PD in the N field. This allowed us to compare how the activity of different neurons changed relative to their N-field PD activity under different field conditions without being confounded by differences in absolute spike rates. We then generated the cumulative distribution functions of the normalized single-trial spike rates of each neuron for the 10 combinations of movement direction and force field. Next, a KS two-sample test (P < 0.05) was used to determine whether the normalized cell activity of a given pair of neurons was the same or different for each combination of movement direction and force field. If the result was significant, a 1 was placed in the corresponding spot in a 10-element vector; if not, a 0 was placed into that spot. This yielded a 10-element vector of significant (1) or nonsignificant (0) KS test outcomes for the normalized perimovement activity at the PD and oPD for all five force-field conditions for that pair of neurons. This was repeated for all nonredundant combinations of pairs of neurons in each monkey, separately. The similarity or difference between the 10-element vectors from any two neurons could then be calculated using their Hamming distance. Repeating this analysis across all possible cell pairs yielded a neighborhood matrix (adjacency table). This matrix was then used by a general-purpose algorithm (Krouchev et al. 2006; Krouchev and Drew 2013) to determine which cells group together to form associative clusters of neurons with similar patterns of significant and nonsignificant changes in activity across force fields in the two movement directions.

RESULTS

Task Performance

The monkeys performed elbow movements with similar velocity profiles in all five field conditions (Fig. 2A), despite the presence of different externally applied torques in the different conditions (Fig. 2B). The torque profiles (Fig. 2B) illustrate the time course of the torques generated by the torque motor and applied to the elbow joint of the monkey via the manipulandum. The monkeys had to apply equal and opposite torques to the handle to maintain the required elbow movement kinematics (Fig. 2A). They accomplished this by generating large field-dependent changes in muscle contractile activity (see below).

The primary objective of this study was to examine neural correlates of task performance in the different force fields. Task switching and context-dependent recall of different motor skills was not the main objective. Nevertheless, both monkeys showed a striking ability to respond to the change in the monitor color at the start of each force-field block and make appropriate predictive changes to their motor output, starting with the first trial after the monitor color changed.

The data files collected from monkey A for this report contained only four transitions between the five successive 48-trial force-field blocks, and so do not provide extensive
evidence for this ability. Elsewhere, however, this monkey showed compelling evidence of predictive changes in response to the monitor color changes when it performed a modified task that involved multiple transitions between short eight-trial blocks of V− and V+ force fields (Krouchev and Kalaska 2003).

In contrast, the task performed by monkey B used short 8-trial force-field blocks and presented 1 occurrence of each of the 20 possible nonredundant transitions between the 5 force fields in each complete run of the task. Analysis of monkey B’s performance showed very consistent levels of performance throughout each eight-trial block (Fig. 3). In particular, there was no evidence that monkey B made systematically more errors at the start of each eight-trial block after a field transition than in the remainder of the block. The only exceptions were in transitions from the resistive V+, E+ and VE fields to the N field (Fig. 3), for which the frequency with which the monkey incorrectly performed a trial before successfully performing the first trial in the eight-trial N-field block was 5–10% higher than for the remaining N-field trials in the block. For the other force-field transitions, error rates were fairly constant throughout each eight-trial block.

It is also evident that the error rates in the N-field blocks were not substantially lower than in any of the other force-field blocks. This showed that movements in the N field also required considerable skill in control of muscle activity to produce elbow movements that respected the constraints in precision of elbow angle and timing imposed by the task paradigm, even if the level of muscle activity was much less in the N field than in the resistive fields (see below).

Analysis of the velocity profiles of monkey B’s movements further reinforced the degree of motor skill recall at each field transition (Fig. 4). That figure shows the mean velocity of the first movement made in each force-field block after a transition from a different force field, irrespective of its outcome (success or error) (Fig. 4, solid lines) and the last trial in the same force-field block, which by task design would always be a successful trial (Fig. 4, dotted lines). The most salient feature of the first-trial velocity profiles is how similar they are to the trials performed several trials later at the end of the same force-field blocks. They show relatively little carry-over effect of the nature of the field encountered during the immediately preceding trial block. The most consistent transition was from any of the other fields into the unstable V− field. If the monkey had continued to produce the same level of force output in the first V− trial as it had in the immediately preceding trial in the V+, E+ or VE fields, the movements would have been extremely rapid because of the assisting effect of the V− field, compounded by the resistive nature of the other fields (c.f., Addou et al. 2011). Instead, they were essentially identical to the movements performed at the end of the same V− block, indicating a very effective transition from the motor output appropriate for the resistive fields to that required by the V− field. Similarly, transitions from all other fields into the V+ field.
and VE fields also evoked very clear recall of the appropriate output. Interestingly, transitions into the N field after all the other fields were not quite as ideal, with a modest underestimation of required motor output after performing a block of V/H trials and a slight overestimation after the preceding resistive fields. Again, however, these deviations from ideal are substantially smaller than would have resulted if the monkey had not adjusted its output in the appropriate way, but has instead continued to produce the same output as in the immediately preceding trials in the other fields (c.f., Addou et al. 2011). This also further reinforced how movements in the N field were not just a "default" response but required as much skill to perform as any of the other movements. Monkey B showed the greatest effect of the preceding field when transitioning into the E/H field, but still showed adjustments to their motor output from the previous field that were appropriate for the E/H field. In parallel, monkey B made more errors in the E/H field than in any other field, but they occurred uniformly throughout the entire E/H field block, not just at the transition from a different preceding force field (Fig. 3). The only exception was when monkey B encountered the E/H field in the very first eight-trial block of a file (Fig. 3, top row).

These behavioral data demonstrated that these highly practiced monkeys were well adapted to the different force fields and rapidly adjusted their motor output in anticipation of a change in force fields at the start of each block of trials, in a manner that was appropriate to the nature of the force field that was signaled by the change in monitor color. The recall in the first trial in a block was not necessarily perfect, but required only minor adjustments in subsequent trials in the force-field block for most combinations of field transitions.

**Neural Data Set**

Neural data were collected over several months in the M1 of both hemispheres of each monkey. Cells were only included in the data sample if they showed either a significant difference in neural activity during flexion and extension movements in the N field or significant changes in activity between force fields or both, and remained well isolated while recording at least eight trials in each of the five field conditions. Adequate data sets were collected from 59 cells in monkey A (39 from the right and 20 from the left hemisphere) and 104 cells from monkey B (8 from the right and 96 from the left hemisphere). No significant difference was noted for neural data collected from the left and right hemispheres of either monkey, so the data were pooled across hemispheres.

All of the neurons described in this study were located in caudal M1 within the rostral bank of the central sulcus or the crown of the sulcus. A small number of neurons were recorded in the more rostral part of M1 more than 3 mm from the sulcus, but are not included in this report. Any neurons related to wrist or hand movements, as determined by evidence of responses during active or passive wrist, hand or finger movements during testing outside
of the task, were not retained, even though they were also often active and directionally tuned in the task.

**Task-related Responses of Arm Muscles and Single M1 Neurons**

Figures 5 and 6 illustrate the task-related activity of two M1 neurons that preferred elbow extension or flexion, respectively, as well as the contractile activity of an elbow extensor muscle (lateral head of triceps, Fig. 5B) and an elbow flexor (short head of biceps, Fig. 6B).

The activity of the elbow extensor muscle (Fig. 5B) and the flexor muscle (Fig. 6B) showed large differences in their activity across all field conditions that clearly reflected the time courses of differences in the external force fields (Fig. 2B). These changes in EMG activity provided compelling evidence that the monkeys adapted their motor output to compensate for the external perturbing forces on a moment-to-moment basis rather than using a default strategy of extensive co-contraction of arm muscles independent of the nature of the fields.

Both muscles showed relatively modest levels of contractile activity in the N field (black; Figs. 5 and 6). This level of activity is an indirect measure of the small elbow-centered torques that the monkeys had to generate to rotate the forearm and the light-weight manipulandum between the targets in the N field. Compared with their weak activation in the N field when the muscles acted as agonists (Fig. 5B, top row; Fig. 6B, bottom row), there was a many-fold phasic increase in contractile activity of both muscles during the movement in the resistive V+ field (red) and a clear late ramp-like increase in activity as the elbow angle changed in the E+ field (blue). In the VE field (magenta), the activity of the muscles was approximately the linear sum of their activity in V+ and E+. When the muscles acted as antagonists (Fig. 5B, bottom, and Fig. 6B, top), they showed a small delayed phasic activation near the peak of movement velocity in the N field that presumably served to slow the movement as the handle approached the target circle (note that the size of this braking pulse was sufficiently large for the biceps that it was visible in Fig. 6B but was too small to be visible for the triceps muscle in the plotting scale of Fig. 5B). This braking burst was strikingly enhanced in V− field (green) when the monkeys had to apply a strong force in the direction opposite to the direction of movement to slow the movement down against the assistive effect of the V− field. As a result, the late-braking contractions of both muscles were several times larger than their agonist activation in the N field. Note as well that both muscles showed some sustained contractile activity late in each trial in the V− field in both directions. This reflected a modestly elevated degree of co-contraction required to stabilize the elbow in the targets at the end of the movements in the unstable V− field. In contrast, the size of the braking pulse was generally reduced when the monkeys made the movements against the resistive V+, E+ and VE fields (see in particular Fig. 6B, top row).

In summary, the muscles responded as expected, showing large changes in contractile activity level and temporal pattern across all field conditions to counteract the effects of the different external force-field profiles. The force fields evoked EMG contractile levels that were much larger than those required to produce the same movements in the N field, indicating that the elbow torques that the monkeys had to generate to counteract the external force fields were many-fold larger than the torques generated during unperturbed movements in the N field.

The activity of many caudal M1 neurons also clearly distinguished between all five force-field conditions (Figs. 5A and 6A) and showed many qualitative, if not necessarily quantitative, parallels with the activity of the arm muscles.

In the N field condition, an extension-related neuron recorded in monkey A (Fig. 5A) showed a “triphasic” response pattern: an early agonist burst before movement onset in its PD, followed by a pause and then sustained activity. In the oPD, there was a clear delayed “antagonist” burst around the time of peak movement velocity (Sergio et al. 2005; Sergio and Kalaska 1998). In the assistive V− field, the early agonist burst prior to movement onset in the PD was virtually absent, while the delayed “antagonist” burst was greatly enhanced in the oPD, compared with the N field. In the E+ condition, the neuron’s response at the PD was stronger, especially the later tonic response component toward the end of the trial, as the strength of the position-dependent resistive E+ field increased. Note that the transient pause during the movement in the PD was shortened but was still evident in the E+ field. In contrast, in the velocity-dependent V+ and VE fields, which required the monkeys to exert strong forces in the neuron’s PD throughout the duration of the PD movements, there was even stronger early activity prior to movement onset and no transient pause during the movements at the PD. In contrast, during movements in the neuron’s oPD, the delayed braking burst of activity was reduced in the E+ field and absent in the V+ and VE fields.

A flexion-related neuron recorded in monkey B (Fig. 6) showed almost no early agonist response during movements in its PD in the N field, but it became evident when the monkey made the same movements in the resistive V+, E+ and VE fields, along with an increase in the late tonic activity especially in the E+ and VE fields. In the oPD (extension), the neuron showed a particularly exaggerated delayed “braking” burst of activity during movements in the N field. This was further enhanced in the V− field, but reduced in the E+ field and completely absent in the V+ and VE fields (Fig. 6A). These responses in the neuron’s oPD showed clear parallels with the activity of the biceps muscle, although there is no direct evidence to claim that this neuron’s activity was causally implicated in the control of elbow flexor muscles.

One could argue that, since the neuron in Fig. 6 had a quantitatively larger discharge rate during extension movements in the N field (Fig. 6A, top row), that direction should have been designated as its PD. However, that extension-related activity clearly began at (V−) or after (N, E+) the onset of movement, was absent for the V+ and VE fields but was enhanced for the assistive V− field. In contrast, a small initial “agonist” burst arose prior to movement onset in the resistive V+, E+ and VE fields. Overall, because resistive fields reduced the neuron’s discharge during extension movements and increased its activity in flexion, in parallel to the behavior of flexor muscles, its PD was designated as flexion.

**ANOVA Analysis of Neural and EMG Activity**

We used ANOVA to assess the effects of the main task factors (force fields, movement directions) on the single-trial cell activity in both monkeys (Table 1). ANOVA analyses were based on the mean single-trial discharge rates per epoch.
(RT, MT, THT) in each trial in each combination of movement direction and force field for 163 cells and from chronically implanted (62 recording sessions, 8 muscles/session, 496 data sets) and acutely recorded muscles (37 recording sessions, 2 muscles/session, 74 data sets). The large majority of M1 neurons and muscle records were significantly modulated ($P < 0.05$) by both the force fields and movement direction in the MT and THT epochs, and a slightly smaller number of neurons and EMG records showed a significant interaction between the two factors, i.e., the effect of the force fields on neuron/EMG activity was different in the two movement directions. Somewhat smaller majorities of neurons and muscles showed stas-
tically significant effects in the RT epoch than in the MT and THT epochs. This confirmed the descriptive evidence (Figs. 5 and 6) that both the direction of movement and the force fields had strong effects on the activity of many caudal M1 neurons, and that the effects of the force fields depended on the direction of elbow movement. Furthermore, the effects of the force fields were evident in M1 activity during the RT epoch prior to the onset of movement, indicating predictive field-dependent response changes rather than feedback-modulated modulations.

**Neural Population Activity**

The task structure differed between the two monkeys. In *monkey A*, each of the 5 fields was presented once in a block of consecutive trials until the monkey completed 48 trials successfully in that field. In contrast, *monkey B* performed the task in a pseudorandom sequence of shorter eight trial blocks in a given force field. Despite these differences, the effects of the fields were remarkably consistent between the two monkeys. To illustrate these similarities, the results of the following analyses will be presented separately for each monkey. The single-neuron response patterns suggested that the M1 activity showed modulations that paralleled the temporal profiles of the external force fields. To examine to what degree this was evident at the population level, population histograms were generated by aligning the activity of all neurons to their PD (Fig. 7, monkeys A and B, top row) and to their oPD (Fig. 7, monkeys A and B, bottom row) from both hemispheres for each monkey. The first salient point was the striking similarity of the population response profiles between the two monkeys, which indicated robust and consistent task-related responses in the sample populations from the two monkeys, despite the differences in the field-block design of the task between the monkeys.

Second, the task-related changes of the population activity across force fields clearly paralleled the nature of the fields. For instance, in the N field, the neural populations in both monkeys showed a strong activation in the PD of each cell and a smaller, delayed “antagonist” burst during movements in the oPD. In the V− field, the strength of the population response prior to movement onset in the PD was reduced relative to that in the N field, whereas the delayed “antagonist” burst in the oPD was enhanced. The enhanced “antagonist” burst was particularly pronounced in *monkey B*, for whom the strength of the V− field was more than twice as strong as in *monkey A* (+0.75 N-m/s/рад vs. +0.35 N-m/s/рад). In contrast, the neural population showed a significant increase in activity during the movement (V+, VE) and postural phases (E+, VE) of the task in the PD of the neurons, and a nearly complete loss of the delayed “antagonist” braking pulse during movements in the oPD, compared with the N field.

To assess how closely the differences in mean population histograms in each force field reflected the differences in the time courses of the fields, we subtracted the response histogram of each cell in its PD and oPD in the N field from the corresponding response histograms in the other force fields (c.f., Figs. 5 and 6). We then averaged the single-neuron response change curves and compared them to the temporal profiles of the force fields (Fig. 8). Note that, in Fig. 8, we inverted the orientation of the imposed torques compared with that in Fig. 2, so that a resistive torque has a positive value and an assistive torque is negative. This was done to ease the comparison of the torque temporal profiles with those of the field-dependent changes in population activity.

The changes in population activity from the N field to the assistive and resistive force fields followed both the sign and temporal profile of all the fields (Fig. 8) and led the force-field torques by ~100 ms. Furthermore, the patterns of discharge changes were strikingly similar in the two monkeys.

More specifically, in the PD of each neuron, cell activity decreased phasically prior to movement onset in the V− field and increased prior to the movements in the V+ field. Cell activity changed more gradually prior to and during movements in the E+ field and showed both phasic and sustained activity increases prior to and during elbow movements in the VE fields. In the elbow movement direction opposite to the cells’ PD (oPD), the delayed phasic increase in cell activity during movements in the V− field was stronger than in the N field. This reflected the need to generate a stronger transient braking force in each cell’s PD, i.e., in the direction opposite to the elbow movement direction, to decelerate the elbow rotation against the assistive action of the V− field. Notably, this increase was significantly larger in *monkey B* than in *monkey A*, paralleling the stronger assistive V− torques encountered by *monkey B* than *monkey A*. It is also noteworthy that the neural population in both monkeys showed a slightly elevated activity level late in the trials in both movement directions in the V− field compared with the N field. This paralleled the small increase in muscle co-contraction to stabilize the arm in the targets against the unstable V− field (Figs. 5 and 6). In contrast, cell activity decreased during movements in the oPD in the resistive fields, reflecting the need to exert more output torque in the direction of the ongoing movement, that is, oPD of the neurons.

It is also notable that the correspondence between the neural activity changes and torque profiles in the resistive fields encountered in the oPD were not as good as that for the PD, especially for the sustained elastic component of the E+ and VE fields. This may result because motor outputs directed in the oPD of neurons may drive them toward a basal activation.

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*Fig. 5. Activity in raster and histogram format of an primary motor cortex (M1) neuron (A) whose preferred movement direction (PD) was elbow extension (top row), and the average contractile activity (B) of an elbow extensor muscle (lateral triceps). Clear differences in muscle activity (quantified in arbitrary units) are evident across field conditions. Note, in particular, the substantial reduction in the premovement agonist response of the muscles in its PD in the V− field (green) relative to N (black). Note also the pronounced increase in the delayed activation during movements in flexion (opposite to the PD (oPD)) in the V− field when the triceps muscle was recruited to decelerate the elbow extension movement against the assistive action of the external field. The activity of the M1 neuron (A) clearly distinguished between all 5 different force-field conditions. It showed many parallels with the activity of the recorded extensor muscle (B). In the N condition, the neuron showed a “triphasic” response pattern, including an early agonist burst, followed by a pause and then by sustained activity in its PD, as well as a delayed transient “antagonist” burst during movements in its oPD. In the E+ condition, the neuron’s response at the PD was stronger, especially the later tonic response component toward the end of the trial as the strength of the position-dependent opposing field increased. In the V+ field, there was even stronger early activity before movement onset and no transient pause during the movement at the PD. The behavior in VE was most similar to the V+ condition, with the addition of stronger tonic activity in target-hold time at the end of the trial. Finally, in the V− field, the early agonist burst was absent in the PD, whereas the delayed “antagonist” burst was greatly enhanced in oPD.*

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state below which they cannot go, which at the extreme might require negative discharge rates.

While the analyses showed a qualitative similarity between the neural activity changes and the force fields and muscle activity, there was also a clear quantitative difference. Compared with the N field, the external force fields required a many-fold change in the forces applied to the handle by the monkey and in the associated EMG activity (Fig. 2, 5, and 6). In contrast, the movements in the N field evoked strong directionally tuned neural activity, but the pooled population-level neural activity changes evoked by the force fields rarely differed by more than 40–50% from the neural activity observed during the N field trials (Fig. 7 and 8).

**Single-Neuron Pairwise Comparison of Force Field Effects**

The preceding analysis demonstrated that the time course of the field-dependent changes in the pooled activity of the
Table 1. Frequency of occurrence (and percentage) of significant main effects of force field and of movement direction, as well as of interactions between the two main factors, for neural and muscle contractile activity recorded in different behavioral epochs of the trials

<table>
<thead>
<tr>
<th>Data</th>
<th>n</th>
<th>Epoch</th>
<th>Field</th>
<th>Direction</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurons</td>
<td>163</td>
<td>RT</td>
<td>118 (72)</td>
<td>125 (76)</td>
<td>75 (46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MT</td>
<td>155 (95)</td>
<td>149 (91)</td>
<td>152 (93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>THT</td>
<td>144 (88)</td>
<td>146 (89)</td>
<td>132 (80)</td>
</tr>
<tr>
<td>Chronic EMG</td>
<td>496</td>
<td>RT</td>
<td>274 (55)</td>
<td>298 (60)</td>
<td>218 (43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MT</td>
<td>375 (76)</td>
<td>361 (72)</td>
<td>370 (74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>THT</td>
<td>372 (75)</td>
<td>324 (65)</td>
<td>358 (72)</td>
</tr>
<tr>
<td>Acute EMG</td>
<td>74</td>
<td>RT</td>
<td>47 (63)</td>
<td>66 (89)</td>
<td>42 (56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MT</td>
<td>74 (100)</td>
<td>72 (97)</td>
<td>74 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>THT</td>
<td>67 (91)</td>
<td>70 (94)</td>
<td>70 (94)</td>
</tr>
</tbody>
</table>

Values are frequency of occurrences with percentage in parentheses; n, no. of data sets. RT, reaction time; MT, movement time; THT, target-hold time. P < 0.05 (ANOVA).

The resulting time profiles of the incidence of significant differences in single-neuron activity between each pair of force fields, we separated all the trials collected at the PD of a given neuron in the five force-field conditions, aligned the single-trial data to the onset of movement, divided the single-trial data into 100 consecutive 20-ms-long bins from −1,000 ms to +1,000 ms relative to movement onset, and calculated the single-trial discharge rate during each bin, including partial spike intervals. We then tested whether the resulting cumulative frequency distributions of single-trial discharge rates in each bin were significantly different (scored as a 1) or not different (scored as a 0) for each of the 100 bins of spike data (KS two-sample test; P < 0.05), for all 10 unique combinations of pairs of fields. This yielded ten 100-element vectors that indicated when in a trial that neuron’s activity was significantly different (1) or not (0) between two pairs of force-field conditions. We repeated this analysis for all neurons in each sample population and tallied how many neurons showed a significant difference in discharge rate in each bin for each pair of fields (Fig. 9). This analysis complements the analysis in Fig. 8 by indicating the time-varying probability that neurons would have significantly different discharge rates during movements in their PD under different force-field conditions, rather than the time-varying difference in discharge rates per se.

The resulting time profiles of the incidence of significant differences in single-neuron activity between two force fields in each monkey once again paralleled the differences in the time course of the force fields and showed consistent similarities between the two monkeys. For instance, when comparing the N and V+ fields, the incidence of significant differences in activity rose abruptly prior to the onset of movement, peaked shortly after movement onset, and then declined substantially toward the end of the trial in both monkeys (Fig. 9). In contrast, when comparing the N vs. E+ field, the incidence of significant differences began to rise more slowly prior to movement onset and remained elevated for the entire duration of the trial. Comparison of the N and VE fields showed a combination of both effects. When comparing the V+ and E+ fields, the frequency of significant differences in activity increased rapidly prior to movement onset and was fairly consistent for the duration of the trial after movement onset. In contrast, when comparing the V+ and VE fields, the number of significant differences in activity gradually ramped up only after movement onset, whereas the comparison of E+ vs. VE fields showed that most of the significant differences in activity occurred primarily during the movement phase of the trial. This was particularly striking in monkey B, but was also evident in monkey A. These and other comparisons were all consistent with a clear relationship between the probability of a difference in activity and the different time courses of the force fields.

The only consistent discrepancy in this relationship was in the N/V− comparison. In principle, the probability of a difference in activity should be limited primarily to the period prior to and during the movements but not during the THT epoch at the end of the movements, similar to that seen for the N/V+ comparison. However, in both monkeys, the incidence of significant differences remained elevated to the end of the trial (Fig. 9). This likely reflected the inherently unstable nature of the V− field, whose effects continued into the target-hold period of each trial and required a modest amount of muscle co-contraction to stabilize the arm in the target zone (Figs. 3–6).

There was also one consistent difference in the results of this analysis between the two monkeys. During the center-hold period prior to the appearance of the movement target, ~10–15% of the neurons in monkey A showed a difference in activity from moment to moment between two fields, whereas in monkey B, less than 5% of the cells showed a difference at any given time before the target appeared. This may have reflected the difference in the task design between the two animals. In monkey A, the center-out movements analyzed in Fig. 9 were preceded by a controlled movement in the same force field from one of the peripheral targets back to the central target, and the field remained on during the center-hold period. The incidence of significant effects may have resulted from a carry-over from the preceding movement, the continued presence of the field, or both factors. In contrast, monkey B made controlled movements in the force field only from the central target to the peripheral targets, and the return movements were uncontrolled, self-paced, and made in the N field. Furthermore, the force field was only gradually ramped up to full strength while monkey B held its arm motionless in the central window prior to the appearance of the peripheral target and so would not perturb the arm until the monkey began to move toward the target after it appeared.

Cluster Analysis

The analyses to this point confirmed that the external force fields had a strong effect on the activity of most M1 neurons at one time or another during the trial. One final question is whether the force field-dependent response modulations were distributed relatively uniformly across the M1 sample populations, or, conversely, whether different subgroups of M1 neurons showed a preferential sensitivity to fields with particular properties (for instance, assistive vs.
resistive or viscous vs. elastic) or at particular times during the trial. We were particularly interested in response modulations that were centrally generated and predictive of the fields and less likely to reflect feedback-mediated response modulations. Therefore, we confined this analysis to the perimovement period from $-100$ ms to $+100$ ms relative to the onset of movement.

In both monkeys, the field-dependent perimovement activity modulations of the large majority of M1 neurons formed a single cluster, including 47/59 neurons in monkey A and 92/104...
Fig. 8. Mean change in population activity ± SE (gray) during movements in the PD and oPD in the different external force fields relative to the activity in the same movements in the N field (thick lines). The curves were calculated by subtracting the response histograms for each single neuron recorded during movements in its PD and oPD in the N field from its histograms recorded in each of the other external force fields, and then averaging the single-neuron difference curves for each field condition. Thin lines: the mean torque profiles during movements in each force field. To facilitate comparison with the time course of neural response changes, the torque curves are plotted in the opposite orientation to those in Fig. 2. The spike rate scale for the neural response curves is presented on the left-most graphs, and the torque scale is presented on the right-most graphs of the figure.
neurons in monkey B (Fig. 10). This does not mean that the patterns of response modulations were identical in all neurons, only that they were similar enough to form a cluster based on the Hamming distances between their individual response profiles (see METHODS). The average response profile of the main clusters of neurons paralleled the expected field-dependent changes in perimovement activity in both monkeys (Fig. 10). In the PD, the normalized discharge rates relative to the N field activity decreased in the V− field and increased in the resistive V+, E+ and VE fields, with the increase in the E+ field being slightly smaller than in the V+ and VE fields.

The majority (monkey A) or all (monkey B) of the remaining neurons formed a second minor cluster. In both cases, these neurons showed greater normalized increases in activity in the resistive fields during movements in their PD than the neurons in the main cluster (Fig. 10). However, this does not necessarily mean that these neurons were preferentially activated only by resistive fields, per se. For the cluster 2 neurons in monkey B, at
least, there was also a very large increase in activity during movements in the oPD in the assistive V− field (Fig. 10).

In summary, the field-predictive perimovement response modulations were relatively broadly and uniformly distributed across the large majority of the sample M1 populations in both monkeys. This cluster analysis is capable of identifying subpopulations (clusters) of neurons that are preferentially modulated, for instance, by only one specific force field, or by velocity-dependent viscous fields vs. position-dependent elastic fields, or by assistive vs. resistive fields. However, it failed to identify significant numbers of neurons with such specific dependencies in their discharge. There was relatively little evidence that the M1 neurons were organized into subpopulations that were preferentially modulated by different force fields, except for a minor group that was particularly strongly modulated by the resistive fields. These neurons may represent the extreme tail of a broader continuum of response patterns, rather than a discrete functional subpopulation.

**DISCUSSION**

In this study, two monkeys learned to perform elbow flexion/extension movements in five different task environments: a null force-field condition (N) without any externally imposed robotic-handle force perturbations, assistive (V−) and resistive (V+) velocity-dependent viscous force perturbations, resistive position-dependent elastic (E+) and combined resistive viscoelastic (VE) force perturbations. To our knowledge, no previous study has ever examined neural activity in the M1 during arm movements in such a broad a range of force-field conditions.

Behavioral data presented here and elsewhere (Krouchev and Kalaska 2003) showed that the monkeys were well adapted to the force fields and used the context cues provided by the monitor background colors to make predictive changes to their motor output at each force-field transition before physically encountering the fields in the first trial of each force-field block. Furthermore, EMG recordings showed that these extensively trained and well-practiced monkeys compensated for the force perturbations by appropriately altering the intensity and temporal pattern of contractile activity of arm muscles, rather than a default strategy such as extensive co-contraction of muscles to stiffen the elbow against the perturbing effects of the fields (c.f., Burdet et al. 2001; Franklin et al. 2003, 2007, 2012; Milner and Cloutier 1998; Osu et al. 2002). Both flexor and extensor muscles showed increased activation in the V− field when they acted as the braking antagonist during the movements, which could have resulted in a momentary increased duration of coactivation of both muscles during the movement to transiently increase the elbow’s stiffness during the movement. However, they also showed a reciprocal reduction in their activity prior to movement onset when they were the agonists for the movements in the V− field. Therefore, their contractile activity patterns were strongly dependent on movement direction, rather than being strongly and equally coactivated throughout the entire duration of the movement during both directions of movement. The only evidence of modest co-contraction in these extensively trained monkeys occurred during the target-hold phase of the movements in the unstable assistive V− field, which would have served to stiffen the elbow joint against endpoint oscillations in the targets.

**Force Field-related Modulations of M1 Activity**

The single-neuron recordings revealed that neurons in the rostral bank of the central sulcus (caudal M1) modulated their movement-related activity during movements in the different force fields. An ANOVA analysis confirmed that the fields had a significant effect on the activity of the majority of caudal M1 neurons, the population histograms revealed a systematic modi-

![Fig. 10. Profiles of the relative level of activity during the perimovement period (−100 ms to +100 ms relative to movement onset) of each neuron in cell clusters 1 and 2 from monkeys A and B, during movements in their PD (solid line) and oPD (dotted line) in each of the 5 fields, normalized to each neuron’s discharge rate in the PD of the N field. Symbols, mean normalized activity; dashed vertical lines, SD.](image-url)
ulation of the pooled M1 neural activity as a function of the temporal profile of the external forces, and the KS analysis showed that the probability of a significant difference in the activity of a neuron at a given moment in time during movements in different fields reflected the difference in the temporal profile of the fields themselves.


The findings of the present study add to the ongoing and unresolved debate about the nature of the representation of motor outputs in the M1 (Ashe 1997; Kalaska 2009; Scott 2008, 2012) by documenting how single M1 neurons and populations contribute to the compensation for a broad range of force-field conditions (e.g., assistive vs. resistive fields; position- vs. velocity-dependent fields). In particular, the present results showed neural correlates of the details of the time-dependent changes in motor output dynamics required to compensate for the movement perturbations that would arise in the different force-field environments. These findings complement the similar findings of changes in the temporal profile of M1 neural activity that parallel the differences in the motor dynamics between whole-arm isometric-force ramps vs. reaching movements (Hamel-Paquet et al. 2006; Sergio et al. 2005). The present findings also indicated that the sampled M1 cells were not generating an abstract signal about forces in an arbitrary reference frame, but rather in one that reflects the directional anisotropy of the mechanical action of muscles and the timing of their contractile activity during flexion/extension movements in the different force fields (Cherian et al. 2011, 2013; Fromm 1983; Morrow et al. 2007; Oby et al. 2013; Schieber and Rivilis 2007; Sergio et al. 2005; Sergio and Kalaska 1998, 2003).

Nevertheless, the results also suggested that the M1 activity was not just a linearly scaled reflection of causative forces and EMG activity across the full range of task conditions between the N field and the other force fields. The low level of muscle contractile activity during elbow movements in the N field and the many-fold increases in contractile activity during movements in the other fields are reliable indications of the large changes in output forces required to compensate successfully for the fields. In contrast, N-field movements evoked strong directionally tuned activity in M1, while movements in the other force fields resulted in changes in activity level that ranged from ~25–60% of the direction-related activity changes observed during the N-field movements. This suggests that the elbow movements in two opposite directions in the N field required a strong directionally tuned M1 motor output command, while the change in motor command required to signal the large changes in motor output dynamics in the other fields involved a quantitatively more modest change in M1 activity superimposed on the N-field motor output command.

One interpretation of these response trends is that the activity during N-field trials reflects primarily the desired kinematics of the movements, while the neural signal related to required dynamics is somewhat smaller and superimposed on the kinematics-related activity. Alternatively, the strong activity during the N-field trials may reflect a disproportionately strong representation of fine motor output control at low force output levels in M1 (Cheney and Fetz 1980; Evarts et al. 1983; Fetz and Cheney 1980; Fromm 1983; Muir and Lemon 1983; Werner et al. 1991). The error rates in the N field were comparable to that in the other force fields, showing that control of the elbow movements in the absence of perturbing external force fields required as much precision as the movements in the force fields. Independent of any issues about the degree to which the neural activity encoded the output kinematics vs. dynamics, the strong discharge during the N-field movements may reflect the extensive computations required to initiate and control the skilled elbow movements required even in the N field.

Whatever the explanation, the results indicate the need for an increase in the gain of the association between M1 neural discharge changes and muscle contractile force outputs across different field conditions. Part of this could likely be accomplished by the progressive recruitment of larger muscle motor units at the spinal level as force demands increased, according to the size principle. In contrast, Evarts et al. (1983) failed to find evidence of a corresponding “size principle” in the selective recruitment of some M1 neurons only at higher force levels. However, a given change in neural activity at low force levels such as the N field might recruit many small motor units, resulting in a relatively small change in total force output, whereas the same increase in neural activity at high force-output levels, such as in the resistive force fields, could recruit a small number of large motor units and result in a much larger increase in total force outputs. Further signal amplification could also occur in other neural structures and circuits, including changes in reflex pathway gains as skill progresses (Cluff and Scott 2013; Dimitriou et al. 2013; Franklin et al. 2012; Pruszynski et al. 2009, 2011; Pruszynski and Scott 2012).

This discussion is speculative and based on the assumption that the results were not an artifact of inadequate sampling of neurons whose activity was more causally related to elbow movements or elbow muscle activity and would show much larger changes in discharge rate across field conditions, or the presence in the sample of a significant number of neurons whose activity was more directly related to other aspects of the task, such as postural stabilization of the wrist or shoulder girdle, gripping the handle or other actions, and which would be coactivated while the monkeys performed the elbow movements. However, neurons were not studied in the task if their response properties outside of the task indicated that they were primarily related to movements of parts of the body other than the elbow and upper arm. It is possible that a population of elbow-related neurons whose activity would have shown a more linear relation to elbow muscle activity existed in caudal M1 but was not found. The few cells that formed the secondary cell cluster 2 in each monkey would appear to come closest to showing such properties. However, they would also appear to be a fairly small population overall in caudal M1, since the proximal-arm representation in the rostral bank of the central sulcus was extensively surveyed with microelectrode penetrations, and more such neurons were not located.
Multiskill Learning and Recall

This study showed that monkeys can learn to perform single-joint movements whose kinematics are precisely controlled in a range of dynamic environments and learn how to recall and switch between those fields in a predictive manner. Monkey A could switch predictively between V+ and V− fields (Krouchev and Kalaska 2003). Wada et al. (2003) and Addou et al. (2011) reported the same ability in human subjects, and Yamamoto et al. (2007) reported similar skillful performance in two other monkeys. Yamamoto et al. (2007) also documented predictive changes in cerebellar Purkinje cell simple-spike activity in the first trial after a switch, in anticipation of the field change between V− and V+ fields. We extended those previous findings here by showing that monkey B could use the color context cues to make predictive switches in motor output in the first trial of a field block for any combination of transitions between five different force fields, before actually encountering the field physically.

The subjects in those studies learned to compensate for the anti-correlated V+ and V− force fields over multiple practice sessions. How the motor system acquires and retains such opposing skills presents a challenge to models of motor skill acquisition, since the two skills presumably require opposite changes in the strengths of synaptic connections. This is the likely cause of the well-documented phenomena of retrograde and anterograde interference while subjects try to learn mutually incompatible motor skills (Addou et al. 2011; Brashers-Krug et al. 1996; Caithness et al. 2004; Davidson et al. 2005; Howard et al. 2013; Imamizu et al. 2007b; Miall et al. 2004; Overduin et al. 2006; Shadmehr and Brashers-Krug 1997; Shadmehr and Mussa-Ivaldi 1994; Wada et al. 2003).

The MOSAIC model (Haruno et al. 2001; Imamizu et al. 2007b) offers a solution to this problem by proposing that the acquisition of different dynamic motor skills is preferentially assigned to different parallel inverse-dynamic models in the cerebellum, whose outputs project to M1 to permit predictive adaptive changes in M1 motor output commands.

Cluster analysis indicated that most of the sampled caudal M1 neurons showed changes across most or all of the different force-field conditions tested in this study, with relatively little evidence of a modular organization in which different subpopulations of M1 neurons were preferentially activated during movements in particular sets of force fields. This indicates that, should multiple inverse-dynamic modules exist in the cerebellum, their outputs must converge extensively onto single M1 neurons, allowing them to vary their activity appropriately over a broad range of task-dynamic conditions. While consistent with the prediction of convergence of the outputs of multiple cerebellar inverse-dynamics onto M1, this finding of itself is not strong evidence supporting the MOSAIC model. Further validation of the MOSAIC model will depend on the confirmation that multiple inverse-dynamic modules exist in the cerebellum, and that responsibility for the acquisition of different dynamic motor skills is preferentially distributed to different cerebellar modules (Higushi et al. 2007; Imamizu et al. 2000, 2003, 2004, 2007a; Shidara et al. 1993; Yamamoto et al. 2007).

In the studies by Krouchev and Kalaska (2003), Wada et al. (2003), Yamamoto et al. (2007) and Addou et al. (2011), the predictive recall of the appropriate motor skill was triggered by the appearance of an arbitrary context cue, the background color of the monitor. However, in other studies, colored context cues have been largely ineffective in allowing subjects to learn multiple dynamic motor skills (Gandolfo et al. 1996; Howard et al. 2013) and visuomotor rotations (Miall et al. 2004). One possible factor was the extensive multiday practice given human subjects in the studies that showed the effectiveness of color context cues (Addou et al. 2011; Wada et al. 2003), and the many months of training of the nonhuman primates (Krouchev and Kalaska 2003; Yamamoto et al. 2007; present study), whereas the studies with negative findings typically involved single training sessions (Gandolfo et al. 1996; Howard et al. 2013; Miall et al. 2004). However, the human subjects in the Addou et al. (2011) study began to show predictive adjustments in motor output within a few encounters with the field transitions during the first training day when the monitor color provided a reliable cue about the impending force field. The major gain made during the remainder of the multiday training was in the level of skilled motor performance, not in the recognition of the significance of the colored context cues (Addou et al. 2011).

Rapid recognition of the task-related significance of the monitor colors probably did not occur with the nonhuman primates, but they did learn the predictive value of the monitor colors after extensive practice. Anecdotally, both monkeys in the present study gave occasional behavioral signs of understanding the meaning of the colors outside of the evidence for anticipatory changes in their motor performance in the task itself. They both displayed periodic brief episodes of agitated behavior whenever the monitor changed color to signal the switch to the unstable V− field, even before starting a trial in the field. Monkey B would also make similar displays or bark at starting the next trial when the monitor changed to blue to signal the imminent presentation of the E+ field. The monkey’s performance in that field showed a higher error rate than most other fields, perhaps because it could not fully distinguish its nature from that of the VE field.

Furthermore, one could argue that the tasks in which color cues were effective were relatively easy, since they all involved one-dimensional single-joint movements in two directions against one-dimensional assistive and resistive forces applied in the direction of movement (Howard et al. 2013). This simplicity could make the nature of the perturbations relatively easy to sense and define and lend itself to the development of a simple cognitive strategy or declarative stimulus-response association rule (e.g., “if the monitor is one color, push harder, if it’s the other color, push less”) to facilitate predictive adaptation to the fields. This could be the case for the studies in which the subjects only encountered anticoordinated V+ and V− fields (Addou et al. 2011; Krouchev and Kalaska 2003; Wada et al. 2003; Yamamoto et al. 2007). However, this may not be sufficient to explain how the monkey’s also succeeded in generating differential predictive signals that reflected the different temporal time courses of the three resistive fields: V+, E+ and VE.

In contrast, the studies that failed to find an effective role of colored context cues involved more complex whole-arm reaching movements to multiple targets in a two-dimensional plane and more complex anti-correlated two-dimensional viscous curl fields that displaced the arm perpendicular to the direction of motion by a force proportional to velocity (Gandolfo et al.
1996; Howard et al. 2013). This would certainly appear to be a more demanding procedural learning problem than the present task, which could also explain the greater efficacy of context cues provided by the state of the limb than by arbitrary non-state-dependent context cues during the learning of curl fields (Gandolfo et al. 1996; Howard et al. 2013; Hwang et al. 2003, 2006; Hwang and Shadmehr 2005; Shadmehr and Mussa-Ivaldi 1994). The complexity of the viscous curl field might not seem to lend itself as readily to a simple cognitive strategy or stimulus-response association rule. Nevertheless, a relatively simple declarative rule, such as “if the monitor is one color, push a bit CW during the reach, and if it’s the other color, push a bit CCW,” could provide an initial approximate solution to compensate for the curl field perturbations. Indeed, there is evidence that subjects do tend to use a simplifying solution not unlike that simplistic declarative rule, rather than attempting to learn the perfect dynamic solution, when adapting to a curl field in only one direction over a short training session (Izawa et al. 2008). The question one might then ask is why subjects do not seem to be able to recognize the anti-correlated nature of opposing curl field perturbations and their relationship to colored context cues when they are attempting to learn both fields at the same time, and develop an appropriate cognitive/declarative rule to compensate at least in part for the anti-correlated perturbations?

Why color cues work so effectively in some task environments (Addou et al. 2011; Krouchev and Kalaska 2003; Wada et al. 2003; Yamamoto et al. 2007) but not others (Gandolfo et al. 1996; Howard et al. 2013; Miäll et al. 2004) remains unresolved. The final answer to this question could provide important novel insight into the interactions between cognitive, declarative and procedural aspects of motor skill acquisition (Howard et al. 2013).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


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