

Perturbation-evoked responses in primary motor cortex are modulated by behavioral context

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¹Center for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada; ²Department of Biomedical and Molecular Sciences, Kingston, Ontario, Canada; ³Department of Medicine Queen's University, Kingston, Ontario, Canada; and ⁴Department of Integrative Medical Biology, Physiology Section, Umeå University, Umeå, Sweden

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Omrani M, Pruszynski JA, Murnaghan CD, Scott SH. Perturbation-evoked responses in primary motor cortex are modulated by behavioral context. *J Neurophysiol* 112: 2985–3000, 2014. First published September 10, 2014; doi:10.1152/jn.00270.2014.—Corrective responses to external perturbations are sensitive to the behavioral task being performed. It is believed that primary motor cortex (M1) forms part of a transcortical pathway that contributes to this sensitivity. Previous work has identified two distinct phases in the perturbation response of M1 neurons, an initial response starting ~20 ms after perturbation onset that does not depend on the intended motor action and a task-dependent response that begins ~40 ms after perturbation onset. However, this invariant initial response may reflect ongoing postural control or a task-independent response to the perturbation. The present study tested these two possibilities by examining if being engaged in an ongoing postural task before perturbation onset modulated the initial perturbation response in M1. Specifically, mechanical perturbations were applied to the shoulder and/or elbow while the monkey maintained its hand at a central target or when it was watching a movie and not required to respond to the perturbation. As expected, corrective movements, muscle stretch responses, and M1 population activity in the late perturbation epoch were all significantly diminished in the movie task. Strikingly, initial perturbation responses (<40 ms postperturbation) remained the same across tasks, suggesting that the initial phase of M1 activity constitutes a task-independent response that is sensitive to the properties of the mechanical perturbation but not the goal of the ongoing motor task.

feedback control; task dependency; transcortical feedback pathway; reflex; task-independent response; neural activity; primary motor cortex

A CORRECTIVE RESPONSE TO SOMEONE bumping our arm can vary from a minimal reaction if our arm is just resting on a table to a rapid and precise correction if we are holding a cup of coffee. The influence of behavioral context on such corrective responses has been studied extensively in human subjects (for recent reviews, see Shemmell et al. 2010; Pruszynski and Scott 2012). Briefly, the earliest muscle activity called the short-latency stretch response (R1: ~20–50 ms) is generated via a spinal circuit and is generally not influenced by behavioral context. In contrast, the long-latency stretch response (R2/R3: ~50–100 ms), which includes supraspinal contributions, is highly sensitive to a wide range of behavioral contexts.

Despite the wealth of knowledge on how behavioral context can influence long-latency responses, far less is known regarding the neural substrates underlying such task-dependent

changes. Phillips (1969) suggested that the primary motor cortex (M1) forms part of a transcortical pathway that contributes to the long-latency responses and that its gain can be altered based on the behavioral task. Indeed, several studies have demonstrated that neural activity in monkey M1 quickly responds to mechanical perturbations and that the timing of this response is consistent with it contributing to the long-latency stretch response of the muscles (Cheney and Fetz 1984; Evarts and Tanji 1976; Herter et al. 2009; Picard and Smith 1992; Pruszynski et al. 2011). It has also been shown that perturbation-related activity in M1 can be altered by behavioral context before concomitant changes in the long-latency stretch response (Conrad et al. 1974; Evarts and Tanji 1976; Wolpaw 1980a,b; Pruszynski et al. 2014).

Of particular note is the seminal work of Evarts and Tanji (1976) in which monkeys were trained to rapidly push or pull a handle following a mechanical perturbation that either pushed or pulled the limb and thus assisted or resisted the instructed action. They found that the initial response (20–40 ms following perturbation onset) was tightly coupled to the applied perturbation but that the later response at ~50 ms clearly reflected the instructed motor action. Pruszynski et al. (2014) recently found a similar pattern of responses in M1 when monkeys responded to mechanical perturbations by quickly placing their hand into visually defined spatial targets: a relatively invariant initial response followed by a modulated (i.e., task-dependent) later response (see also, Conrad et al. 1974; Wolpaw 1980a,b).

This invariant initial response may reflect a task-independent somatosensory signal transmitted to M1 neurons. It is well known that M1 responds to a range of different sensory stimuli including passive limb motion (Cheney and Fetz 1980; Fromm et al. 1984; Hummelsheim et al. 1988; Scott and Kalaska 1997; Suminski et al. 2009), tactile or cutaneous stimuli (Lemon 1981; Picard and Smith 1992; Murray and Keller 2011), and electrical stimulation of peripheral nerves (Herman et al. 1985; Marple-Horvat and Armstrong 1999). Direct transmission of the sensory response to a perturbation into motor regions of the brain may assist in the appropriate selection of the motor response as it depends on both the motor instruction and the properties of the perturbation itself. Alternatively, the presence of an invariant initial response may reflect the use of sensory feedback for ongoing postural control of the limb. That is, the initial perturbation response may reflect a corrective response used to maintain the hand at the initial posture. In this case, the nervous system needs to disengage this postural control before specifying a motor response for the instructed action.

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Previous studies were not able to test between these two possibilities because the monkeys were always engaged in the same ongoing motor task before perturbation onset. In this study we explicitly changed the ongoing motor behavior and tested how this change altered the initial and late perturbation responses in M1. Specifically, we recorded behavioral, muscular, and neural responses to a mechanical perturbation applied randomly 1) when the monkey was maintaining its hand at a spatial target and the monkey was rewarded for returning its hand to the spatial goal following the perturbation (posture task), and 2) when the monkey was quietly watching a movie and not required to maintain its hand at a spatial target nor to respond to the perturbation to be rewarded (movie task). If the initial M1 response reflects a task-independent somatosensory response to the mechanical perturbation, then it should remain relatively similar across posture and movie tasks. In contrast, if the initial response reflects the use of sensory feedback for ongoing postural control, then the initial M1 response should be substantially diminished in the movie task compared with the posture task, as there is no ongoing postural control in the movie task, before the perturbation.

As expected, behavioral, muscular, and late M1 responses were generally reduced but not eliminated in the movie task compared with the postural task, indicating that the monkeys modulated their motor responses across these behavioral contexts. Despite these changes, initial M1 responses were strikingly similar. Taken together, our results suggest that the initial perturbation response in M1 is not sensitive to the ongoing motor task but reflects a relatively task-independent sensory signal transmitted from the periphery.

METHODS

Subjects and Apparatus

Three male rhesus monkeys (*Macaca mulatta*, 10–17 kg) were trained for 4–6 mo to perform whole limb visuomotor tasks wearing an exoskeleton robot (KINARM; BKIN Technologies, Kingston, ON, Canada). The robot permitted combined flexion and extension movements of the shoulder and elbow in the horizontal plane and applied loads to the shoulder and/or the elbow (Scott 1999; Herter et al. 2009). Two monkeys (*monkeys X* and *A*) used a right arm robot, and one monkey (*monkey P*) used a left arm robot. Targets and hand feedback

were presented to the monkeys in the horizontal plane via a display composed of an overhead projector and semitransparent mirror. The position of the hand was represented by a white circle (5-mm diameter) positioned at the tip of the index finger. All procedures were approved by the Queen's University Animal Care Committee.

Behavioral Tasks

The experiment was composed of two different tasks: a posture task and a movie task (Fig. 1). The monkeys' goal in the posture task was to maintain their hand at a visual target (12-mm diameter). The target was displayed near the center of the arm's workspace (angles of 30 and 90° at the shoulder and elbow, respectively), where passive viscoelastic forces of the limbs are relatively small (Graham et al. 2003). The monkey started each trial by placing the white circle (representing hand position) into the visual target and maintaining it within the target's acceptance window (16-mm diameter). Following a random time (between 1,000 and 1,500 ms), the limb was perturbed with one of nine mechanical loads applied to the shoulder and/or elbow (Fig. 1A) including one unloaded "catch" trial in which no perturbation was applied. Each perturbation lasted 300 ms, and the size of the load was varied to consider the size of each monkey (*monkey P* and *monkey X*, 0.24 Nm and *monkey A*, 0.32 Nm). Equal perturbation magnitudes in all directions cause different magnitudes of hand motion, with the biggest joint motions for shoulder flexor + elbow extensor and shoulder extensor + elbow flexor torque pairs (Herter et al. 2009). Therefore, we lowered the perturbation magnitude for these two pairs to compensate for this effect (0.04 Nm less than other load conditions). The monkeys were trained to bring their hands back to the target window within 750 ms and maintain it there for 1,000 ms to be rewarded with water (Fig. 1B). The 9 load conditions were presented randomly in each block, and the monkeys were required to complete 10 blocks in each set.

In the movie task, monkeys were not required to do anything in response to the perturbation. All task-related visual feedback (i.e., target position and hand position) was replaced by a movie, and the monkeys were trained to quietly watch the movie. At the beginning of each trial, the robot moved the hand to the central target. Following a random time (between 1,000 and 1,500 ms), the hand was perturbed using the same nine load combinations as in the posture task (Fig. 1C). The monkeys were rewarded regardless of their response to the perturbation.

Our standard approach was to use a fixed order of tasks: first the posture task and then the movie task, followed by a repeat of the posture task. For cells isolated near the end of the recording session,

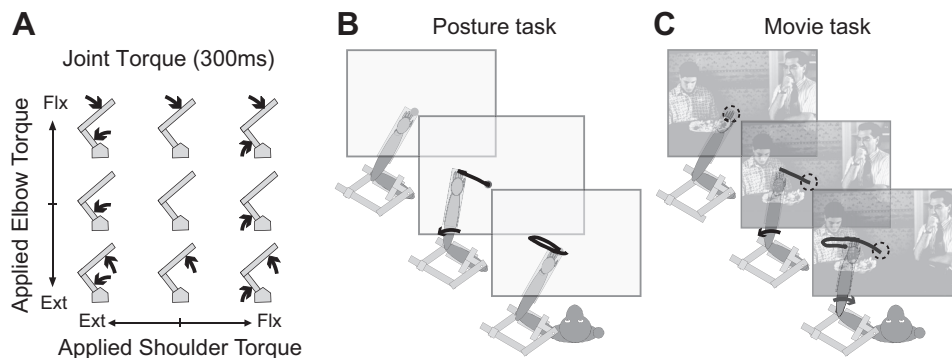


Fig. 1. Task apparatus and experimental paradigm. *A*: different combinations of shoulder and/or elbow loads applied to the arm in each trial. *B*: in the posture task, the monkey started each trial by placing the hand cursor and maintaining it within the target's acceptable window (light grey circle). Following a random time interval (1–1.5 s), the limb was perturbed with 1 of the 9 mechanical loads depicted in *A*. The monkeys were trained to bring their hands back to the target window within 750 ms and maintain it there for 1,000 ms (solid black line illustrates a sample hand path in response to the perturbation). *C*: in the movie task, all task-related visual feedback (i.e., target position and hand position) was replaced by a movie. At the beginning of each trial, the robot moved the hand to the central position. Following a random time interval (1–1.5 s), the hand was perturbed using the same 9 load combinations as in the posture task. The "American Pie" picture is reproduced with permission from Universal Studios.

a reduced version of the experiment was performed. In this case, the posture and movie tasks were performed once, in a random order.

Hand motion following the perturbation was used to determine how much the monkeys changed their behavior between the posture and movie tasks. However, this hand motion reflects both active (e.g., voluntary response to perturbation) and passive (e.g., viscoelastic forces of the limb and inertia) mechanisms opposing limb motion. To estimate the contribution of the passive mechanical properties of the arm, we compared hand motion in each task with a task in which the monkey was anesthetized. For this control, *monkey P* was anesthetized using ketamine (2 mg/kg) and medetomidine (0.05 mg/kg) and identical perturbations as in the main tasks were applied to the limb. Electromyographic (EMG) recordings of shoulder and elbow muscles were monitored for any reflexive or voluntary muscle activity. Anesthesia was performed on *monkey A* as well. However, due to its size, we were not able to maintain its posture upright in the chair, so the arm motion was skewed and therefore the data were not usable. Such measures were not performed on *monkey X* due to complications.

Data Collection

After training, we recorded neural data from shoulder/elbow regions of M1 using standard extracellular recording techniques (Herter et al. 2007). The recording area included the bank of M1 to ~3 mm rostral to the bank. Microelectrodes were advanced through M1 until neural activity was observed in response to active or passive movements of the shoulder and/or elbow (but not the wrist and/or fingers). Single neurons were then isolated, and neural activity was recorded in the behavioral tasks. In some sessions, the recording location was verified using microstimulation, eliciting movement or muscle twitches in shoulder and/or elbow muscles (<30 μ A; Stoney et al. 1968).

EMG activity of shoulder and elbow flexor and extensor muscles was recorded using standard percutaneous EMG techniques (Kurtzer et al. 2006). EMG was obtained from pairs of single-strand wires that were percutaneously inserted within the muscle belly ~5 mm apart (see Table 1 for a list of recorded muscles). Electrode placement was verified using microstimulation (stimulations <2 mA), ensuring that a contraction was isolated within the target muscle. We aimed to record from three to six muscles in each EMG session. Given the time-consuming nature of electrode placement, EMG and neural recordings were performed in separate sessions. There were a few differences between the EMG and neural recording sessions. First, a variant of the posture task (normalization task) was added in the EMG session, in which the perturbation lasted for 3,000 ms instead of 300 ms. In addition, each task was repeated at least twice (i.e., 20 trials for each load combination) to have a better estimate of the muscle responses to the perturbations.

All the neural, EMG, and kinematic data were recorded using a Plexon data acquisition system (Plexon, Dallas, TX). The neural data were sampled at 40 kHz, and the kinematic and EMG data were sampled at 1 kHz. The neural data were sorted online for single units and further examined using the Plexon offline sorter. Kinematic data (joint angles, velocities, and torques applied by the robot) were down sampled at 200 Hz to reduce the size of each session's data file. Cartesian hand positions and tangential hand velocity were calculated using joint angles, limb length, and velocities.

Data Analysis

M1 neurons. Spike times were extracted from the Plexon files into Matlab (Mathworks, Natick, MA). Spike density functions were then generated by convolving each spike time stamp with an asymmetric double-exponential kernel that roughly mimicked a postsynaptic potential (1-ms rise and 20-ms fall time; Thompson et al. 1996). Using such asymmetric spike density functions to smooth the data, rather than a Gaussian filter for instance, yields onset times without backward biasing. Each trial was aligned based on the perturbation onset, and each neuron's rapid response to the transient load was evaluated (mean cell activity 50–100 ms following the perturbation).

The load combination with the largest response was selected as the neuron's preferred-torque combination (PTC). If the response was only inhibited by the perturbation, then the largest negative response was selected as the neuron's PTC. The neuron's activity in its PTC (mean cell activity 50–100 ms following the perturbation) was compared with cell activity in the catch trial (no perturbation) using an independent sample *t*-test. The cell was classified as "perturbation responsive" if the comparison was significant ($P < 0.05$). The cell's response to its preferred combination of shoulder and elbow perturbations was then compared across tasks (independent sample *t*-test) to determine how many cells showed a significant change in activity across tasks. We also determined if baseline activity (mean cell activity 100 ms before the perturbation across all load conditions) was comparable across tasks for each cell (independent sample *t*-test). Mean population activity for each task was calculated by averaging the activity across cells. All cells with a significant perturbation response were included in the population signal.

The PTC selected in the posture task might not necessarily be identical to that of the movie task, as changing the task could also change the cell's sensitivity to the load combinations. In that case, modulation of the cell's response across tasks in the preferred load combination extracted in the posture task would simply be an epiphenomenon of a rotating PTC. To address this possibility, we correlated the cell response in all different load combinations and magnitudes (using planar regression fit; see Kurtzer et al. 2006 for details) to devise a more quantified measure of the cell's sensitivity to load. For this analysis, changes in neural activity in response to the perturbation

Table 1. List of muscles recorded across tasks, number of samples with subjective quality of 3 or higher for each muscle, number of samples with a significant perturbation response, and number of samples with significant bigger perturbation response in each task

Muscle name	No. Quality ≥ 3	No. Significant Perturbation Response	Significant Bigger Posture	Significant Bigger Movie
Brachioradialis	5	5	5	0
Brachialis	3	2	1	0
Biceps (short and long heads)	8	5	2	1
Triceps (lateral head)	7	6	4	1
Triceps (long head)	5	5	5	0
Deltoid posterior	6	5	4	0
Deltoid middle	5	3	2	0
Deltoid anterior	1	0	0	0
Pectoralis major	4	2	1	0
Supraspinatus	2	2	1	0
Sum	46	35	25	2

Significant perturbation response is at 45–100 ms postperturbation.

(spikes/s) were correlated with the applied joint torques (Nm). Flexor torques were assigned positive values, and extensor torques were assigned negative values. For visualization purposes, joint torques were organized in a Cartesian format with shoulder torques on the x axis and elbow torques on the y axis (i.e., ShoFlx = 0°, ElbFlx = 90°, ShoExt = 180°, and ElbExt = 270°). For each neuron with a significant planar fit (F -test, $P < 0.05$), coefficients related to each variable [i.e., the shoulder (Sho) and elbow (Elb)] were used to calculate the preferred-torque direction (PTD). A cell that does not respond to the perturbation or has an equal response in all directions would not have a significant planar fit.

The PTD was defined by the orientation of the plane in joint-torque space that denoted the angle associated with the greatest increase in activity (see Fig. 5B; see Herter et al. 2009 for details). We then compared the PTDs extracted in each task to test whether different tasks changed the cell's sensitivity to load combinations. We only used the cells with significant planar fits in both posture and movie tasks for this comparison.

Given the order the two tasks were presented, many cells had more than one set of each task (e.g., 2 repeats of posture task). In these cells, one set was randomly chosen for analysis. Nevertheless, to make sure presentation order did not affect the perturbation response across tasks, we compared the neural activity across repeat sets of the same task. These repeated blocks provide an important control to investigate the significance of the changes observed across tasks (e.g., influence of change in the monkey's motivation through time). We investigated whether the baseline activity and the perturbation responses changed across the repeated sets and compared the magnitude of these changes to that across tasks.

We also examined the relationship between the cell's initial evoked response (cell's mean response 20–35 ms minus baseline) and its baseline activity across tasks. This was done to investigate whether a change in a cell's baseline activity can change its response to the perturbation as well. For this analysis, we only used those cells that had significant perturbation responses between 15 and 40 ms postperturbation (to avoid missing cells, the range was 5-ms longer on each side of the epoch of interest). We then correlated the change in baseline activity to the change in the cell's evoked response.

Behavior and kinematics. Joint and hand positions and velocities were used to compare perturbation-induced motion of the limb. We used receiver-operator characteristic (ROC) analysis to determine at what time point the joint/hand motion deviated between the two tasks (Omran et al. 2013). Briefly, at each 5-ms time point, we determined the proportion of trials that exceeded a range of thresholds spanning the two distributions. The number of hits and false alarms were then plotted against each other for every threshold setting. In this analysis, the area under the curve provides a measure of how well the two distributions could be distinguished from each other (Metz 1978). Values of 0 and 1 indicate perfect discrimination (and thus complete separation between the two distributions), whereas a value of 0.5 indicates chance discrimination. Across all time points, we then found the time point ($T_{\text{criterion}}$) where the ROC passes a criterion level (set at 0.25 or 0.75). We calculated the time at which the ROC starts deviating from baseline levels by fitting a line (using linear regression) to a 30-ms period of the ROC curve, centered on the $T_{\text{criterion}}$. In our results, we report the interception point of the regression line with the baseline ROC value ("Knee" extraction technique; Pruszynski et al. 2008). Note that changing the ROC criterion level does not qualitatively change the result of this analysis.

Muscle activity. Throughout the recording session, each muscle was qualitatively scored from 1 to 5 (based on recording quality, gain of the signal, signal-to-noise ratio, and whether the muscle looked active in the task). Muscles that scored 3 and higher were included in our analysis. EMG signals were band-pass filtered (10–150 Hz, two-pass, third-order Butterworth) and full-wave rectified. Each trial was aligned based on the perturbation onset. Just like neurons, the

load combination with the largest response was selected as the muscle's PTC.

The EMG in each trial was then normalized to the mean muscle activity in the last 2 s of response in its PTC in the normalization task. This period was chosen as the monkeys resisted the load at the central target (i.e., isometric response), hence providing a steady-state assay of muscle tone against a defined load magnitude (see Pruszynski et al. 2008 for how we normalize EMG data in human subjects). Thus units for muscle activity reflect a muscle's response ratio compared with its steady-state activity opposing the same load. Hence, a value of 1 means the muscle's response was equal to this steady-state activity.

We then verified if each muscle's PTC matched its expected functional torque direction (Kurtzer et al. 2006) to confirm proper electrode placement (e.g., whether the posterior deltoid muscle responded to flexor or extensor loads). We removed any muscle with a PTC in the wrong quadrant of the torque space (1 muscle sample removed).

We evaluated each muscle's response to the perturbation in its PTC across tasks. We examined the EMG response in different time epochs (–300:0, 20:44, 45:74, 75:99, and 100:200; correspondingly named Base, R1, R2, R3, and Vol epochs) and compared them across tasks. These specific time periods were chosen based on functional results obtained in our previous studies (see Herter et al. 2009; Pruszynski et al. 2014, 2011), but generally these epochs are inspired by the response epochs (M1, M2, and M3 and Vol, ranging from 10 to 30, 31 to 50, 51 to 70, and 71 to 100 ms, respectively) proposed by Lee and Tatton (1975). The M1 epoch corresponds with the short-latency muscle response, and M2–M3 epochs correspond with the long-latency response, discussed earlier. The faster time epochs in Lee and Tatton (1975) likely reflect the use of larger loads (a 350-g load applied at the hand with force perpendicular to the elbow joint would generate ~0.8 Nm compared with 0.24–0.32 Nm in the present study) and faster load onset (3.2-ms rise time vs. 10-ms sigmoid in the present study).

Activity onset. We were interested in determining the onset time of each cell/muscle's response to the perturbation and the time their activity differentiated across the posture and movie tasks. For this purpose we found the first point when the activity passed a threshold that was three times larger than the standard deviation of cell/muscle's baseline activity. Alternatively, we determined the first point in time population responses across the two tasks became significant ($P < 0.05$, running paired sample t -test performed at 1-ms intervals), and remained significant for 20 ms.

Neurons in M1 display a range of onset times following a perturbation (Herter et al. 2007). We were interested in identifying whether neurons recruited at different times showed consistent timing differences from perturbation onset to task-dependent modulation. We, therefore, separated our cells into four groups based on their perturbation onset times (response initiation between 15 and 30, 31 and 40, 41 and 50, and 51 and 100 ms) and quantified population signals for each group. We then used a similar onset calculation technique for the average activity of each group and compared the perturbation onset and task-dependent modulation for each group.

To estimate the variance in perturbation onset and task modulation for each group of cells, we used a bootstrap technique (Altman and Goodman 1994). For this analysis, we resampled cells in each group 10,000 times (with replacement) and calculated each measure for every sampled group.

RESULTS

Comparison of Kinematics and Muscle Responses Across Tasks

Kinematics. In the posture task, mechanical perturbations applied to the upper limb generated 2 to 4 cm of hand motion, with larger motions generated following multijoint loads (Fig.

2A). In response to the ShoExt + ElbFlx perturbation (Fig. 2C), shoulder and elbow motion peaked at ~ 300 ms just before the load was removed and returned to the target at ~ 500 ms [hand distance from target 500 ms postperturbation: 0.9 ± 0.3 cm (means \pm SD) for *monkey P*, 0.4 ± 0.1 cm for *monkey X*, and 0.8 ± 0.4 cm for *monkey A*]. In the movie task, perturbations generated patterns of hand motion that were initially similar to those observed in the posture task (Fig. 2, B and C). However, the hand did not return to the spatial target when the load was removed (hand distance from the target center 500 ms after perturbation: 2.8 ± 1.3 cm for *monkey P*, 2.2 ± 1.1 cm for *monkey X*, and 3.0 ± 1.6 cm for *monkey A*). Before the next trial, the hand was successfully moved back in close proximity of the target center by the robot (hand distance from the center of target before the next perturbation: 0.23 ± 0.51 cm for *monkey P*, 0.36 ± 0.65 cm for *monkey X*, and 0.38 ± 0.33 cm for *monkey A*).

Hand distance from the target (at 500 ms postperturbation) was significantly smaller in the posture task compared with the movie task in all load combinations and for all monkeys (Fig. 3; paired *t*-test, $P < 0.001$ and $t > 6$ in all conditions, $df = 84$ for *monkey P*; $P < 0.001$ and $t > 5.6$ in all conditions, $df = 40$ for *monkey X*; and $P < 0.001$ and $t > 4$ in all conditions except for elbow extensor load $P = 0.2$ and $t = 1.2$, $df = 32$ for *monkey A*). On average, the hand distance from the target was 75% smaller in the posture task compared with the movie task (72% in *monkey P*, 82% in *monkey X*, and 74% in *monkey A*).

Using ROC analysis, we identified that shoulder and elbow angles were similar across the two tasks for the first 200 ms and began to deviate around 225 and 245 ms following the perturbation, respectively (Fig. 2C). Across all load conditions, we identified differences in hand motion only after 100 ms [ROC deviating from the baseline levels at 231 ± 93 ms (means \pm SD) in *monkey P*, 123 ± 53 ms in *monkey X*, and 129 ± 62 ms in *monkey A*]. Changes in the kinematics of the limb can also be observed in the 95% confidence interval ellipses of hand positions through time (Fig. 2E, red and blue for movie and posture tasks, respectively). Note that the ellipses completely overlap throughout the first 200 ms and then begin to separate. However, there is still considerable overlap in hand positions 500 ms postperturbation across recording sessions. This could mean that there were sessions where the hand position in the movie task was closer to the target than in the posture task. However, within a given session, there was a consistent reduction in the behavioral response in the movie task compared with the posture task (Fig. 2E, dashed lines connect corresponding average hand positions in each task for 5 random sessions). In fact, in only six (of 129) sessions, the hand distance from the target (500 ms postperturbation) was bigger in the posture task than the movie task.

When *monkey P* was anaesthetized, virtually no perturbation-related activity was observed in the two limb muscles recorded during this procedure (data not shown). Hand motion during the perturbation was greater than that observed during

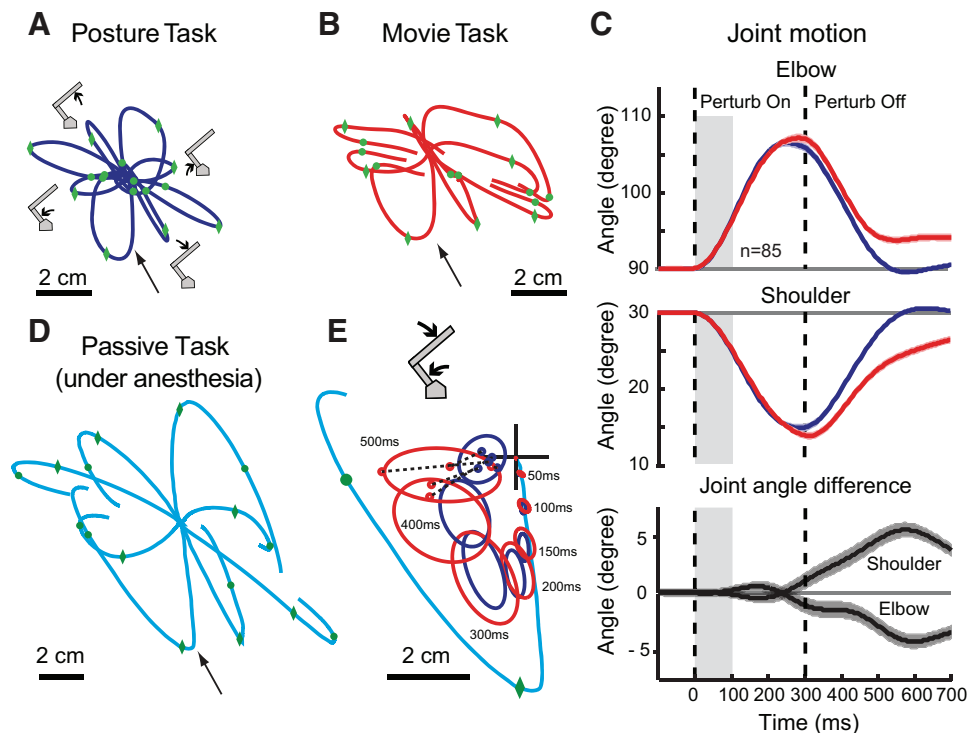


Fig. 2. Hand motion across tasks. Hand motion in response to different combinations of perturbations in the posture (A) and movie (B) tasks. Green diamonds and circles denote the time the perturbation turned off (300 ms) and hand position 500 ms following the perturbation, respectively. C: elbow (top) and shoulder (middle) joint angles for each task in the load condition shown by the arrow in A and B and the differential joint motion (bottom) across tasks. Solid lines represent average joint positions (blue: posture; red: movie; and black: differential motion) and the shaded areas denote 2 SE (largely blocked by solid lines) of joint position across sessions (85 sessions in *monkey P*). Vertical dashed lines denote the time the perturbation turned on and off. The grey rectangles show the time period for analysis of neural activity. D: hand motion in response to perturbation when the monkey was under anesthesia. Note that the scale is smaller than for A and B. E: comparison of hand positions through time in response to the condition marked with the arrow in A, B, and D (shoulder extension/elbow flexion). Each ellipse represents the 95% confidence interval of hand positions across sessions at 50-ms intervals following the perturbation (blue and red ellipses for posture and movie task, respectively; cyan: passive task). Dashed lines connect average hand positions in the posture and movie tasks for 5 random sessions.

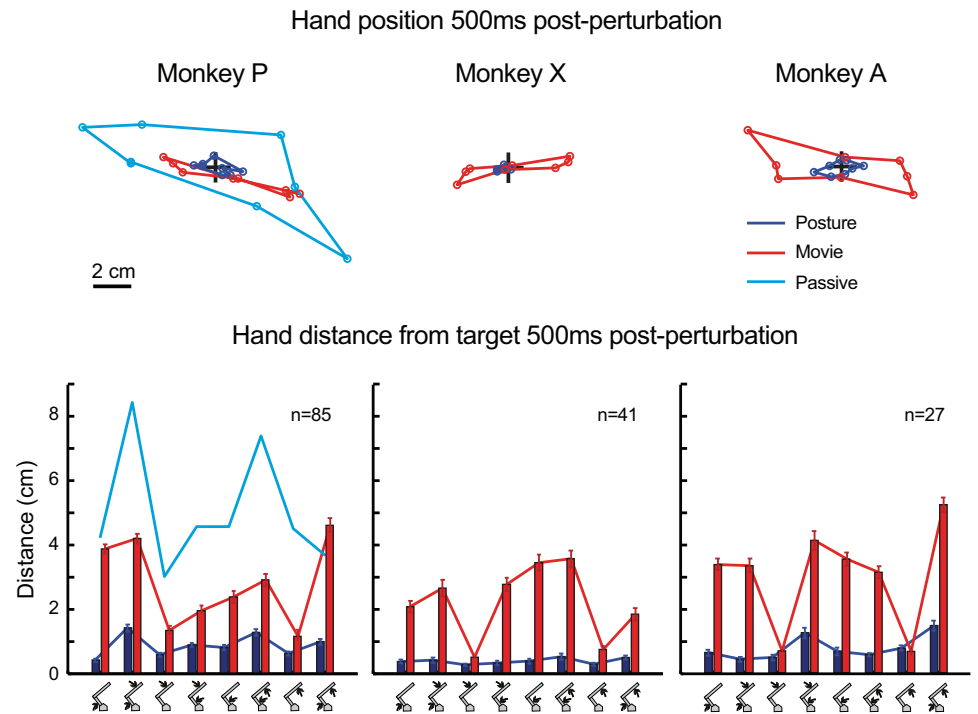


Fig. 3. Kinematics of perturbation response. Hand position and distance from target center in each monkey across tasks. *Top*: average hand position relative to the target (black cross indicates target and its acceptable spatial limits) 500 ms following the perturbation for each of the 8 load combinations (blue: posture; red: movie; and cyan: passive). *Bottom*: corresponding distance from target in each load condition. *Inset*: number of recording sessions in each monkey. Error bars indicate 2 SE across sessions. The passive data were obtained while the animal was under anesthesia.

the posture or movie tasks (Fig. 2D). Hand distance from the central target 500 ms following the perturbation was 5 ± 1.8 cm across load conditions (Fig. 3). We quantified the distance between hand positions 500 ms postperturbation for the posture and movie tasks relative to the position observed in the anaesthetized state, which measured passive limb properties when there were no active corrective responses. For the load combination displayed in Fig. 2E, the distance of the hand at 500 ms postperturbation between the movie task and anaesthetized state was 30% smaller than the distance between the posture task and the anaesthetized state. Across all eight load conditions, the average drop in this distance was $42 \pm 24\%$ (means \pm SD) for the movie task compared with the posture task.

Muscle activity. We recorded EMG from 3 to 6 proximal limb muscles in 18 sessions. Thirty-five samples were identified as good quality (score 3 or higher on subjective rating scale out of 5) and had significant perturbation responses ($P < 0.05$, Table 1; 16, 15, and 4 muscles in *monkey P*, *X*, and *A*, respectively). There was variability in each muscle's response to the perturbation and how much it changed across the tasks. Some muscles displayed minimal decreases during the movie task, whereas others displayed virtually no activity following the perturbation in the movie task (Fig. 4A). In fact, the majority of recorded muscles displayed a significant decrease in perturbation-related activity (45–100 ms postperturbation) in the movie task (Fig. 4, B and C). Twenty-seven muscles showed a significant change in perturbation activity across tasks ($P < 0.05$). Of these, 25 showed a decrease and only 2 showed an increase in the movie task. On average, the perturbation-evoked response (average activity 45–100 ms postperturbation minus baseline activity) dropped 65% across the two tasks (paired t -test, $P = 0.002$, $df = 34$ and $t = 3.34$). A similar reduction in perturbation-related muscle activity was observed for all three monkeys (54% drop in *monkey P*, 72% drop in *monkey X*, and 53% drop in *monkey A*, paired t -test, $P < 0.035$ in all monkeys).

This variability in muscle response could reflect varying levels of a monkey's engagement in response to the perturbation during the movie task. However, we did not find any correlation between the reduction in EMG activity for the movie task and the magnitude of motor load required to move the hand to the target before the perturbation (Pearson correlation coefficient = 0.05, $P = 0.77$ and Pearson correlation coefficient = 0.11, $P = 0.52$ for torques applied on shoulder and elbow, respectively) nor to the hand distance from the central target following the perturbation (Pearson correlation coefficient = -0.02 , $P = 0.89$). For the two sessions in which the EMG was significantly larger in the movie task, the hand distance was on average 2.5 cm farther from the target 500 ms postperturbation in the movie task compared with the posture task.

Muscle activity across tasks was not significantly different in the baseline period (Fig. 4C; -300 – 0 ms, $P = 0.81$, $df = 34$, and $t = 0.23$) or the R1 period (20–45 ms postperturbation, $P = 0.31$, $df = 34$, and $t = -1$). The average muscle response to the perturbation only started 34 ms postperturbation (Fig. 4C, black arrow). The differentiation across tasks started 45 ms postperturbation (Fig. 4D, gray arrow), and all subsequent stretch response epochs (R2, R3, and Vol) were significantly different across the tasks (46–75 ms, $P = 0.004$, $df = 34$, and $t = 3.04$; 76–100 ms, $P = 0.003$, $df = 34$, and $t = 3.13$; and 100–200 ms, $P = 0.02$, $df = 34$, and $t = 2.35$, respectively). Response onsets in individual monkeys were 27, 38, and 60 ms and response differentiation times were 43, 46, and 80 ms in *monkey P*, *X*, and *A*, respectively. Note that later response onset and differentiation observed for the latter monkey (*A*) likely reflects that there are only four muscle samples for this animal (i.e., bigger baseline variability, therefore a higher threshold).

General Neural Findings

We recorded 161 neurons (86, 42, and 33 from *monkey P*, *monkey X*, and *monkey A*, respectively) in M1 of 3 monkeys

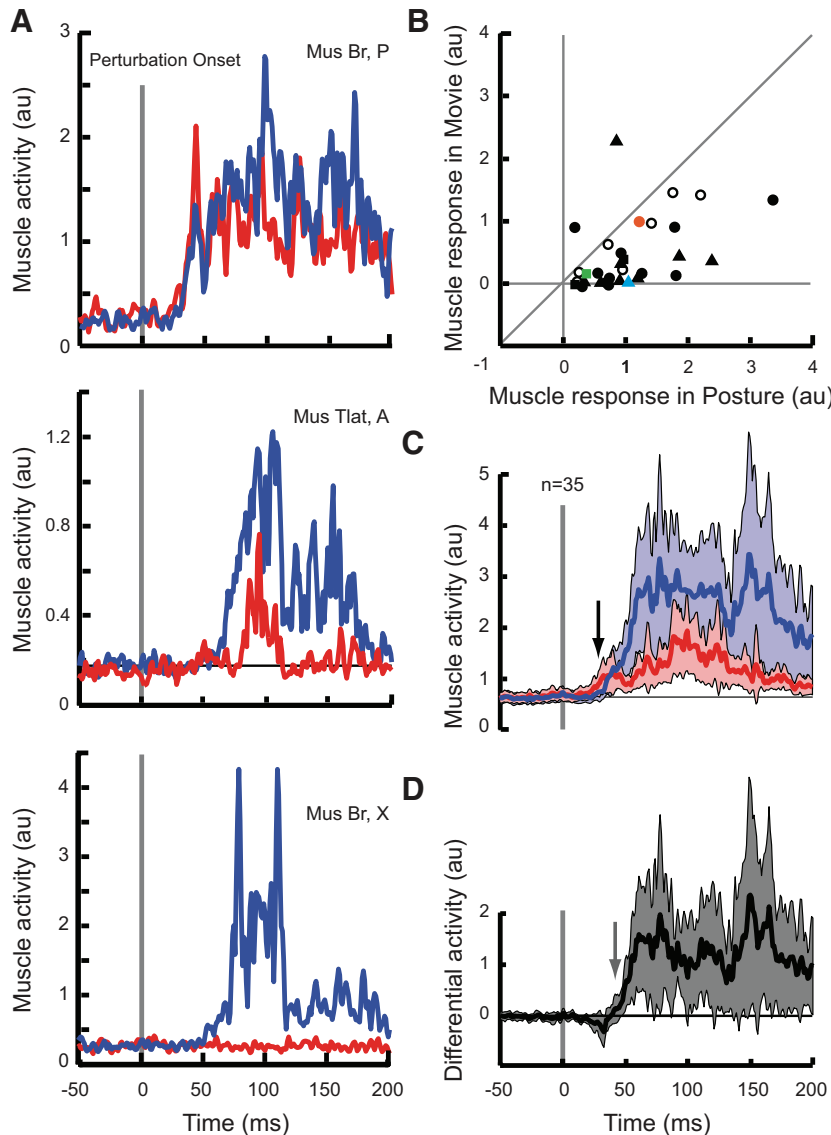


Fig. 4. Muscle response to perturbation across tasks. *A*: exemplar EMG activities in response to the preferred torque combination in the posture (blue) vs. the movie (red) task. Grey lines denote the onset of the perturbation. These exemplar muscles (Mus) highlight the range of responses from substantive to no change between tasks (Tlat: triceps, lateral head; Br: brachioradialis). *B*: average EMG response (45–100 ms following the perturbation) in the posture (horizontal axis) vs. movie (vertical axis) task. Filled shapes denote muscle responses with a significant change across tasks. Each symbol represents a different monkey (circle, triangle, and square, represent *monkey P*, *X*, and *A*, respectively). The 3 exemplar muscles in *A* are represented by the colored symbols (orange: *top*; green: *middle*; and cyan: *bottom*). For visualization purposes, 4 data points are not plotted (response values for data points not shown are: posture task = 5.75, 6.32, 13.85, and 5.22; and movie task = 3.5, 2.78, 2.4, and 0.46, respectively). *C* and *D*: mean EMG response across all recorded muscles ($n = 35$) in the posture and movie tasks (*C*) and their differential activity (*D*) across the 2 tasks (posture-movie). Solid lines represent average EMG response (blue: posture; red: movie; and black: differential motion) and the shaded areas denote 2 SE (blue and red shaded areas denote between muscle variability of perturbation response and the black represents within muscle variability of differential response). The black and the grey arrows represent the onset and the differential time of muscle activities, respectively.

while performing the posture and movie tasks. Of these, 129 had a significant perturbation response in the posture task (50–100 ms postperturbation, independent sample t -test, $P < 0.05$). Figure 5*A* illustrates one exemplar neuron that displayed perturbation-related activity for all load conditions in both the movie and the posture tasks (except for ShoFlx in posture and movie and ShoFlx + ElbFlx in movie, $P < 0.01$ for all other loads). The response was largest in the ShoExt + ElbFlx condition ($P < 0.001$), and thus, this load response was selected as its PTC for further analysis.

Figure 5*B* displays similar preferred torque directions of the exemplar cell for each task (arrows in Fig. 5*B*, 134 and 158° in joint-torque space for posture and movie, respectively, $P < 0.001$ for both). One-hundred and nineteen neurons were identified as directionally tuned in joint-torque space during the posture task. Of these, 94 neurons were directionally tuned in the movie task as well. As shown previously (Cabel et al. 2001; Herter et al. 2009; Pruszyński et al. 2014), neurons tended to have preferred directions skewed towards shoulder flexor and elbow extensor loads or towards shoulder extensor or elbow flexor loads (Fig. 6*A*

displays the PTDs associated with the posture task). Figure 6*B* illustrates the difference in the PTD across tasks. The average absolute change in PTD was 24.9°. However, we found no systematic change in PTDs for the posture and the movie tasks (average PTD rotation = -4.9° , Rayleigh test = 0.86, $P < 0.001$).

The majority of neurons (75/129) displayed a significant change in baseline activity between posture and movie tasks (Fig. 7*A*; $P < 0.05$, 39 and 36 higher in posture and movie tasks, respectively). In the exemplar neuron in Fig. 5*A*, baseline activity 100 ms before the perturbation was slightly lower in the movie compared with the posture task (18.1 vs. 14.6 spikes/s for posture and movie tasks, respectively, independent sample t -test, $P = 0.03$, $df = 178$, $t = 2.1$). The average absolute change in baseline activity was 5 spikes/s between tasks, but there was no systematic shift in baseline activity across the population, (14.6 spikes/s in the posture task and 14.1 spikes/s in the movie task, paired t -test, $P = 0.38$, $df = 128$, and $t = 0.88$), reflecting that a similar number of cells increased vs. decreased their baseline activity from posture to movie task.

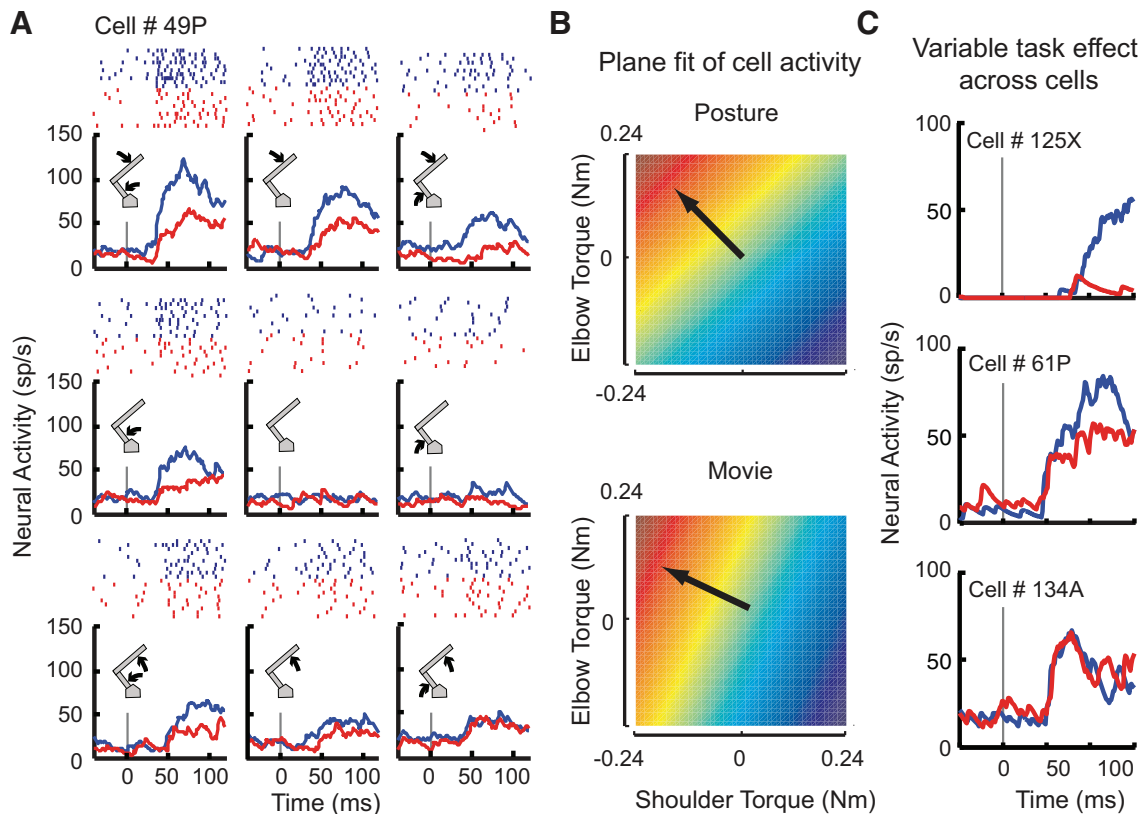


Fig. 5. Neural response to mechanical perturbation. *A*: an exemplar cell response to different mechanical loads (specified by *insets*). Each tick represents 1 action potential and each row represents 1 trial (10 trials in each condition). Spike time stamps are convolved with a double-exponential kernel (roughly mimicking postsynaptic potential) to generate a spike density function for each trial. The solid lines represent these density functions across trials. Grey vertical lines denote the onset of the perturbation. *B*: a plane was fit to the average perturbation response (50–100 ms following the perturbation) of each cell across trials and the applied torque in each condition. The heat plot (red denoting greater activity and blue denoting less activity) shows the corresponding cell activity in response to each load condition. Preferred-torque direction (PTD, solid arrows) was defined as the orientation of the plane in joint-torque space. *C*: 3 individual cells highlighting the range of responses from substantive to no change between tasks; sp/s: spikes per second.

In general, perturbation-evoked responses (average activity 50–100 ms postperturbation minus baseline activity) were smaller in the movie task compared with the posture task (Fig. 7*B*; note the points lying beneath the unity line). In the exemplar cell in Fig. 5*A*, the perturbation response was significantly bigger in the posture task compared with the movie task

(81.5 vs. 37.9 spikes/s for posture and movie tasks, respectively, independent sample *t*-test, $P < 0.01$, $df = 9$, $t = 3.1$). However, the perturbation response was not always reduced to the same magnitude across all cells. Figure 5*C* displays perturbation-related responses for three representative neurons, highlighting that some neurons display similar perturbation responses across the two tasks, whereas others lose all their response in the movie task. On average the perturbation response dropped 31% in the movie compared with the posture task (from 42.9 spikes/s in the posture task to 29.5 spikes/s in the movie task, paired *t*-test, $P < 0.001$, $df = 128$ and $t = 8.77$). Similar results were observed for all three monkeys (35% drop in *monkey P*, 23% drop in *monkey X*, and 30% drop in *monkey A*, paired *t*-test, $P < 0.03$ in all monkeys). Of the 70 neurons that displayed a significant change in perturbation response across tasks ($P < 0.05$), 63 displayed a decrease and 7 an increase in the movie compared with the posture task.

The size of the reduction in cell response across tasks was not correlated to the difference in hand distance 500 ms postperturbation (Pearson correlation coefficient = -0.02 , $P = 0.75$). In fact, even in the six sessions in which the hand was closer in the movie compared with the posture task, the neural activity decreased ~ 24 spikes/s (ranging from 1.5 to 43.6 spikes/s across these sessions).

Figure 7*C* highlights that the magnitude of response modulation across tasks was correlated with the size of the pertur-

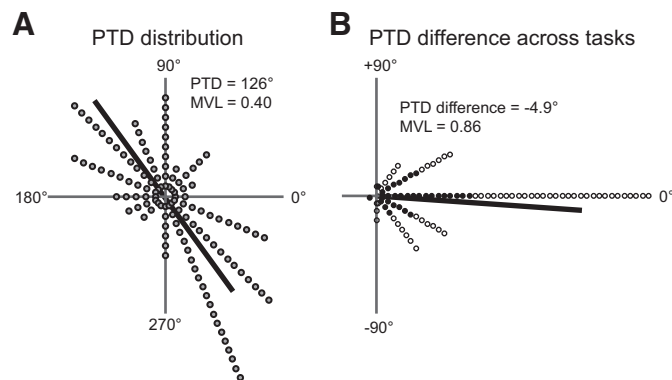


Fig. 6. Distribution of PTD across tasks. *A*: PTD of each cell in response to mechanical perturbation in the posture task. The distribution is skewed towards ShoFlx + ElbExt loads or towards ShoExt + ElbFlx loads (Sho, shoulder; Elb, elbow; Flx, flexor; Ext, extensor). The solid line shows the main axis of the distribution. *B*: change in PTD across the 2 tasks. The main axis of this distribution is close to 0, suggesting that cell's preference for torque direction does not change significantly across tasks. Filled circles denote those cells with significant activity change across tasks. MVL, mean vector length.

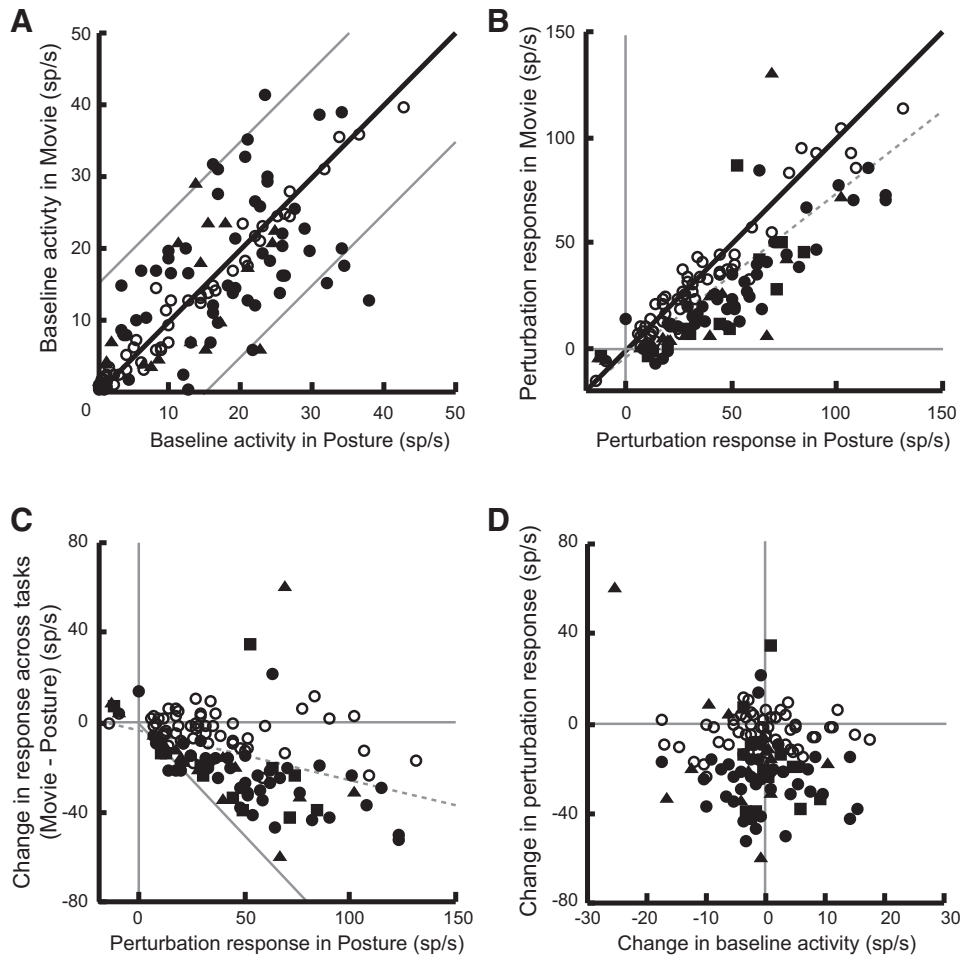


Fig. 7. Individual cell activity across tasks. **A:** average baseline activity (-100 – 0 ms before the perturbation) of individual cells in the posture (horizontal axis) vs. movie (vertical axis) task. Filled shapes indicate cells with significant difference in their baseline activity. Note that most data points lie around the unity line. The grey lines delineate ± 15 spikes/s change from unity. **B:** average perturbation response (50 – 100 ms postperturbation, with baseline activity removed) in individual cells in the posture (horizontal axis) vs. movie (vertical axis) task. Note that most data points lie beneath the unity line. Filled shapes denote cell responses with a significant change across tasks. Dashed line denotes the linear regression fit. One data point is not plotted for visualization purposes (response values for the data point not shown is posture task = 216 and movie task = 178 , respectively). **C:** average perturbation response in the posture task vs. average change in perturbation response across tasks. The grey line represents the magnitude of the cell's activity if it were reduced to its baseline level in the movie task. The dashed line represents the linear regression fit to the data. One data point is not plotted for visualization purposes (response values for the data point not shown is posture task = 216 and response change = -38 , respectively). **D:** average change in baseline activity vs. change in perturbation response across tasks. Filled shapes denote those cells with significant activity change across tasks. Each symbol represents a different monkey (circle, triangle, and square, represent *monkey P*, *X*, and *A*, respectively).

bation response observed in the posture task (Pearson correlation coefficient = -0.45 , $P < 0.001$). However, this correlation partially reflects the fact that cell discharge cannot go below 0 spikes/s, minimizing potential task changes for cells with smaller responses and low baseline activity. In some cases, cell activity decreased slightly from its baseline levels in the movie task even though it increased its activity during the posture task (data points below diagonal grey line). We found no correlation between changes in baseline activity and changes in perturbation response across tasks (Fig. 7D, Pearson correlation coefficient = -0.13 , $P = 0.14$). In addition, we found no systematic relationship between the hand distance from center before the perturbation in the movie task (as a measure of resistance against servoing of the hand) and the amount the perturbation response was reduced from the posture to the movie task (Pearson correlation coefficient = -0.1 , $P = 0.25$). In general, the load preference of individual neurons did not influence changes in their activity across tasks either (data not shown).

Task-Independent and -Dependent Neural Responses

Response timing. Perturbation responses averaged across the three monkeys were first observed at ~ 20 ms (task-independent response; Fig. 8A; black arrow) and, across tasks, were similar until 39 ms (task-dependent response; Fig. 8A; grey arrow; the time differential signal surpassed baseline activity $+3$ SD). At this point, the population signal was greater for the

posture task compared with the movie task. The same pattern could be observed in each individual monkey (Fig. 8B). For individual monkeys, population response initiation occurred at 20 , 26 , and 26 ms in *monkey P*, *monkey X*, and *monkey A*, respectively (black arrows), and population differentiation occurred at 39 , 52 , and 44 ms (grey arrows). Population signals for the opposite load from the PTC displayed similar initial increases starting at 21 ms. The population activity differentiated between the two tasks at a later time (46 ms), although the differentiation was fairly small and did not remain above threshold for significance for very long (returning back to baseline ~ 55 ms postperturbation). Using an alternative technique (running *t*-test) to determine response timings, we found a similar pattern of results both for the population (response initiation = 24 ms and response differentiation time = 45 ms) and the individual monkeys (response initiation = 25 , 42 , and 38 ms and response differentiation time = 45 , 61 , and 48 ms for *monkey P*, *X*, and *A*, respectively).

Population signals, described above, were based on simply averaging cell discharge rates. This approach means that cells with higher firing rates dominate the population signal. We therefore repeated the analysis by normalizing each cell's activity to its maximum firing rate before calculating the population signal. Effectively, the same pattern of response was observed following this normalization, with the perturbation response starting at 24 ms postperturbation and differences in the response across tasks starting at 41 ms. Similar patterns

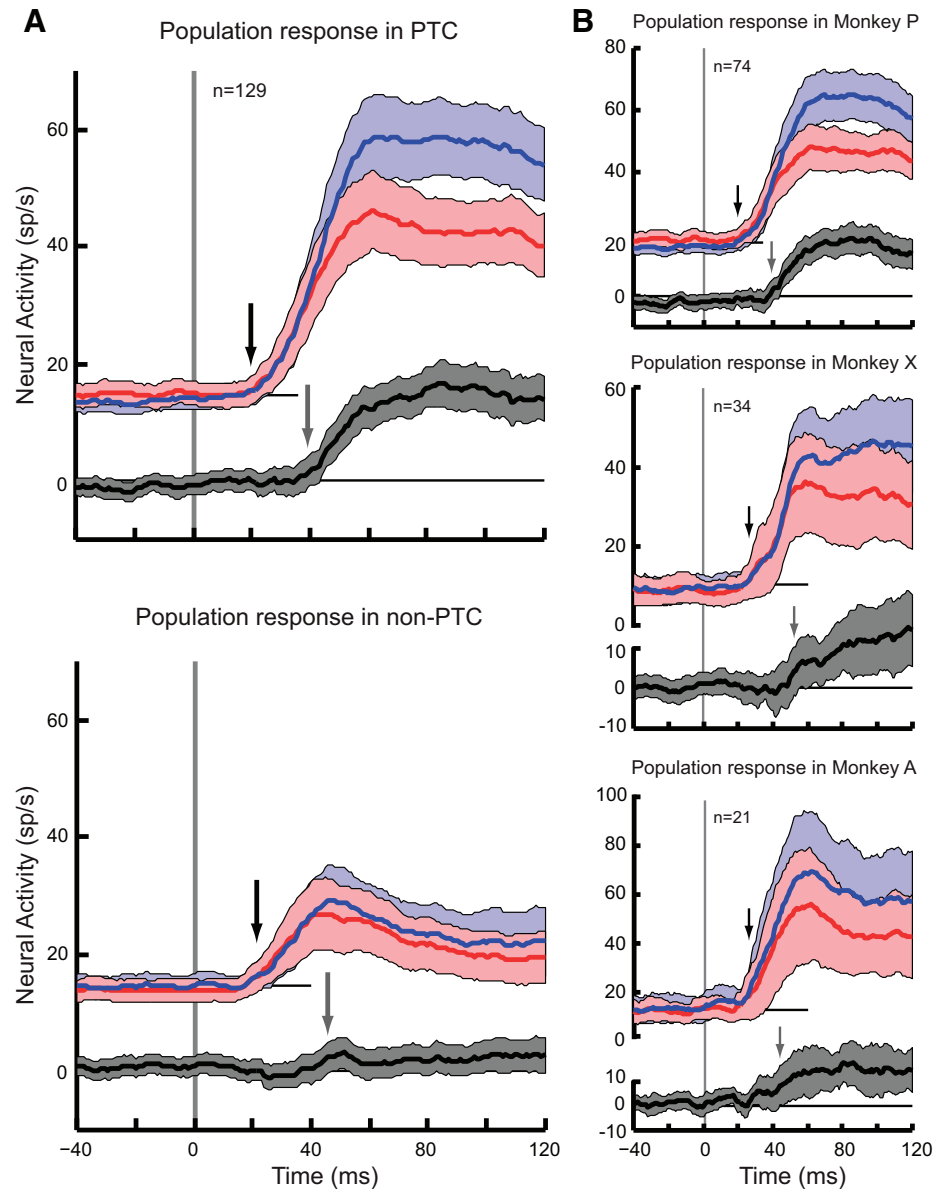


Fig. 8. Population activity across tasks. Mean population response in the posture and movie tasks (blue and red lines, respectively) across cells with a significant response to the perturbation and their differential activity (black line) across the 2 tasks. Population activity is calculated for all cells across all monkeys in their preferred torque combination and nonpreferred torque combination (*A*) and for each monkey individually (*B*). Solid lines represent the average population response and the shaded areas denote 2 SE (blue and red shaded areas denote between cell variability of perturbation response and the black represents within cell variability of differential response). Vertical grey lines represent the onset of the perturbation. The black and grey arrows represent the perturbation onset and differential response in the population signals, respectively. *Inset*: number of cells in each population.

were observed for individual monkeys as well. Population response initiation occurred at 24, 28, and 29 ms in *monkey P*, *monkey X*, and *monkey A*, respectively, and population differentiation occurred at 40, 51, and 45 ms.

We further examined the properties of the initial task-independent perturbation responses. Sixty-three cells showed a significant perturbation response within 15–40 ms postperturbation. The magnitudes of these initial perturbation evoked responses were highly correlated across the posture and movie tasks (Pearson correlation coefficient = 0.88, $P < 0.001$). There was no correlation between the difference in the initial responses across tasks (cell's mean response 20–35 ms minus baseline) and the corresponding change in baseline activity (Pearson correlation coefficient = 0.07, $P = 0.57$). We also did not find any significant correlation between the ratio of the baseline activity for movie vs. posture tasks and the corresponding ratio of the initial perturbation response across tasks (Pearson correlation coefficient = -0.2 , $P = 0.11$).

Task-dependent signal and cell onset time. Cells were divided into four groups based on their perturbation onset times (Fig. 9A; response initiation between 15 and 30, 31 and 40, 41 and 50, and 51 and 100 ms). The population signals associated with the cells with the earliest onset times (15–30 ms) displayed a phasic-tonic pattern of activity following the perturbation, whereas the response for cells recruited later did not display a strong phasic component (Cheney and Fetz 1980; Herter et al. 2007). However, it is notable that the late tonic activity in the posture task (averaged over 100–120 ms postperturbation) was not significantly different across the four groups ($P = 0.37$, $df = 3$, one-way ANOVA, mean activity 100–120 ms postperturbation was 69, 59.5, 52.7, and 57.2 spikes/s for each group, respectively) nor was the change in the late tonic activity between posture and movie tasks ($P = 0.59$, $df = 3$, one-way ANOVA, mean differential activity 100–120 ms postperturbation was 14, 15.8, 12, and 19.2 spikes/s for each group, respectively).

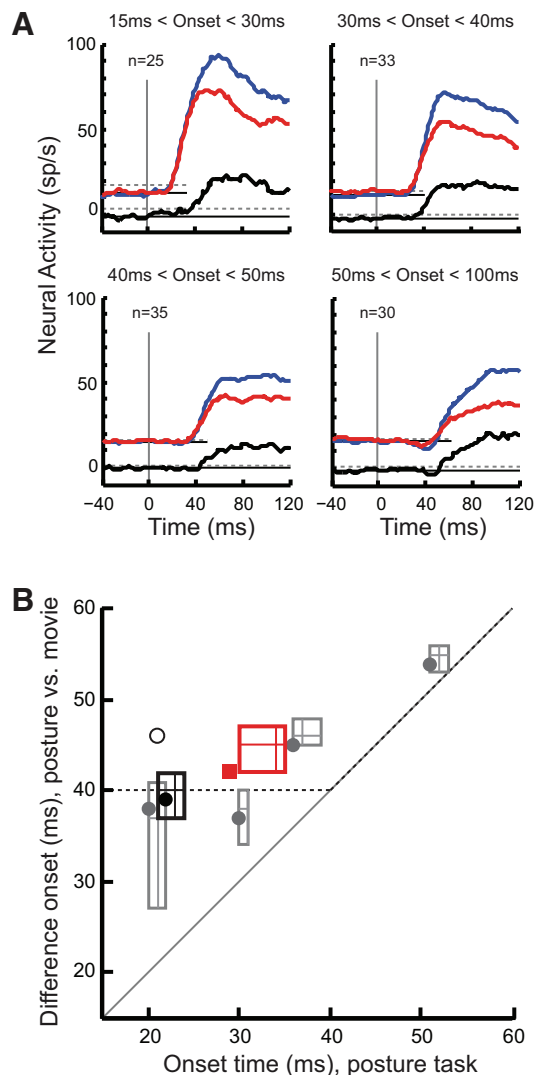


Fig. 9. Onset time clustering and the effect of differentiation time. *A*: cells are divided into 4 groups based on their perturbation response times (15–30, 31–40, 41–50, and 51–100 ms). Red and blue lines denote population signals for each group for the movie and posture tasks, respectively. Black lines represent group differential activity across tasks. Black horizontal lines represent baseline activity in the population signals and the differential signals. Dashed lines represent the thresholds for response onset and differentiation onset calculations. *B*: average onset time of perturbation response vs. time of task-dependent response differentiation for each time group (filled grey circles), for entire population of neurons (filled black circle), for population activity in non-PTC (empty black circle), and for muscles (filled red square). Thin lines within boxes represent median onset and differentiation times calculated using a bootstrap technique. Each box represents the 25th–75th percentile confidence intervals. The solid grey diagonal unity line demonstrates the hypothetical situation in which perturbation responses and task-dependent changes occurred at the same time. The dashed line represents the situation in which task-dependent changes cannot occur before a certain time (40 ms in this case), but then differentiation is immediately present.

We found an interesting relationship between the onset time of the perturbation response and the time of differentiation across different groups. By definition, onset times increased progressively across the four groups (20, 30, 36, and 51 postperturbation, range = 31 ms). However, the timing of the task-dependent signal displayed smaller shifts across groups (38, 37, 45, and 54 postperturbation, range = 16 ms). It should be noted that as the individual baseline variability is higher for

a single cell, the time its activity passes the threshold is later compared with when it is included in a group. Therefore, group response onset might effectively be faster than the mean of all its individual cell onsets (e.g., response onset time in 41- to 50-ms group being 36 ms).

The black box for the entire population of cells in Fig. 9*B* highlights that perturbation responses can be observed at ~20 ms, whereas the task-dependent change occurs at ~40 ms, as shown in Fig. 8*A*. The solid diagonal unity line demonstrates the hypothetical situation in which perturbation responses and task-dependent changes occurred at the same time. The group for neurons recruited late (50–100 ms) is relatively close to this unity line denoting that task effects are observed as soon as these neurons respond to the perturbation. On the other hand, the earliest recruited group displays a ~20-ms shift between the perturbation response onset and the task-dependent response. The two intermediary cell groups show effects between these two extremes. Essentially the same results were observed if the perturbation responses were normalized (to the cell's peak activity) before generating the population signals.

Nonspecific Changes in Perturbation Response Between Repeated Postural Tasks

In total, 126 cells were examined twice in the posture task, of which 106 had a significant perturbation response. The average absolute change in discharge rate during the baseline period was 3.5 spikes/s across repeated blocks of trials (Fig. 10*A*). Of these, 44 neurons showed a significant difference in their baseline activity, but there was no systematic shift in the population baseline activity across the repeated blocks (Fig. 10*A*; average baseline activity for the 1st posture task = 14.6 spikes/s and the 2nd posture task = 15.5 spikes/s, paired *t*-test, $P = 0.09$, $df = 105$, and $t = 1.7$). We found the absolute change in baseline activity between posture and movie tasks to be bigger than the absolute change between repeated posture tasks (Fig. 10*B*; two-sided Wilcoxon rank sum test, $P = 0.001$).

Eighteen cells had significantly different perturbation responses across the repeated posture tasks (Fig. 10*C*; $P < 0.05$, mean activity 50–100 ms minus baseline, bigger in 10 and 8 cells in *set 1* and *set 2*, respectively). However, unlike comparisons between the posture and movie tasks, there was no systematic change in the perturbation response across the population in repeated posture tasks (Fig. 10, *C* and *D*; mean activity 50–100 ms minus baseline = 41.3 and = 39.3 spikes/s in the 1st and 2nd posture tasks, respectively, paired *t*-test, $P = 0.06$, $df = 105$, and $t = 1.89$).

We calculated cumulative distributions for changes in initial and late perturbation responses (20–35 ms, Fig. 11*A*, and 50–100 ms, Fig. 11*B*, respectively) between posture and movie tasks and repeated posture tasks. There were no differences in the distributions of the initial responses [Kolmogorov-Smirnov (K-S) test, $P = 0.1$]. Furthermore, the distribution of changes in the perturbation response observed in the initial epoch between posture and movie tasks was not significantly different than the distribution for differences immediately after the perturbation (K-S test, 0–15 ms postperturbation, $P = 0.51$) nor even the epoch right before the perturbation occurred (K-S test, –15–0 ms preperturbation, $P = 0.11$). In contrast, the distribution of changes in perturbation responses for the late

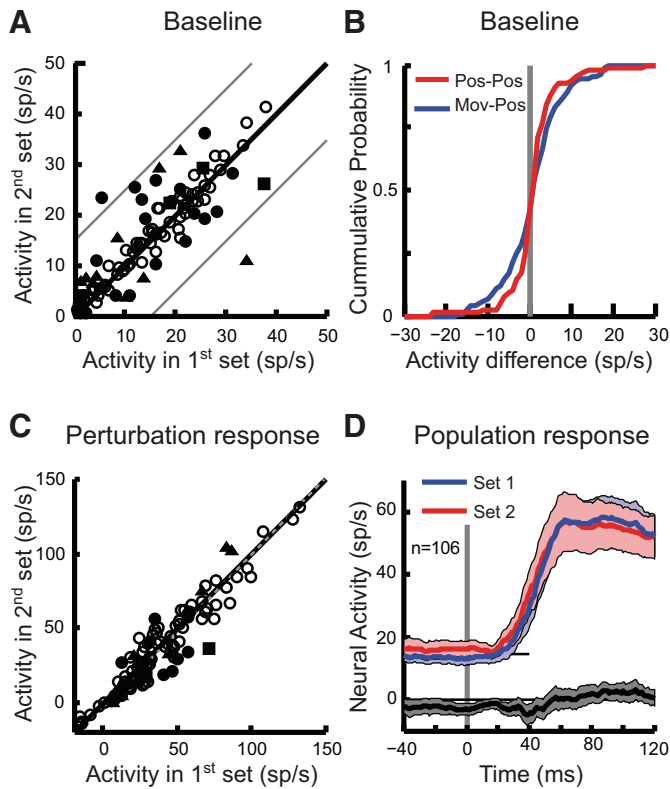


Fig. 10. Effect of set order on perturbation response. *A*: average baseline activity (-100 – 0 ms before the perturbation) of individual cells in the first vs. the second posture tasks. Each symbol represents a different monkey (circle, triangle, and square, represent *monkey P, X, and A*, respectively). Filled and open circles denote significant and nonsignificant changes in activity between sets. Grey lines delineate ± 15 spikes/s change from unity (black line). One data point is not plotted for visualization purposes (response value for the data point not shown is 1st set = 30 and 2nd set = 58 ms, respectively). *B*: cumulative probability distributions of change in baseline activity (-100 – 0 ms) across the posture-movie tasks (blue) and repeated posture tasks (red). *C*: average perturbation response in the first vs. the second sets of the posture task. Filled shapes denote cell responses with a significant change across tasks. Two data points are not plotted for visualization purposes (response values for data points not shown are 1st set = 138 and 179 and 2nd set = 153 and 213, respectively). *D*: Mean population response across all recorded cells in the first and second posture sets (red and blue lines, respectively) and their differential activity (black line) across the 2 sets. Solid lines represent average population response and the shaded areas denote SE of population activity across cells (blue and red shaded areas denote between cell variability of perturbation response and the black represents within cell variability of differential response). Vertical grey lines represent the onset of the perturbation. Pos, posture; Mov, movie.

epoch was significantly greater between the posture and movie tasks compared with repeated posture tasks (Fig. 11*B*; K-S test, $P < 0.001$).

DISCUSSION

Previous studies have illustrated perturbation responses in primary motor cortex (M1) are influenced by the behavioral context but that the initial response (20 – 40 ms) to a mechanical perturbation in M1 is relatively fixed for a given perturbation (Evarts and Tanji 1976; Pruszynski et al. 2011, 2014; see also Strick 1978 for a review). This invariant initial response to mechanical perturbations may reflect a task-independent somatosensory signal transmitted to M1 neurons that must then be converted into the appropriate motor response (in

M1 or elsewhere in motor circuits). Alternatively, the presence of an invariant initial response may simply reflect that the monkeys were using sensory feedback for ongoing postural control. The methodologies used in previous studies could not separate these two alternatives. The present study examined how neural responses in M1 depend on whether or not the monkey was engaged in a limb motor action. Mechanical perturbations were applied to the limb when the monkey was actively engaged in maintaining its hand at a central target (posture task) and when it was not engaged in a limb motor task (movie task). Corrective movements and corresponding muscle stretch responses were both diminished in the latter task. In some neurons, perturbation responses in M1 displayed no change between the two tasks, whereas other neurons entirely lost their perturbation response in the movie task. Overall, late M1 population activity in response to the mechanical perturbation (50 – 100 ms postperturbation) was reduced by $\sim 30\%$ in the movie task. However, the perturbation responses before 40 ms remained insensitive to the ongoing motor behavior, suggesting that the initial response reflects relatively task-independent somatosensory feedback into M1.

Changing Ongoing Behavior to Observe Its Influence on Perturbation Responses

Our objective was to quantify perturbation responses when the monkeys were engaged or not in an ongoing motor behavior. One option would be to examine neural responses when the monkey was anaesthetized. However, anesthetics affect sensory processing (Fontanini and Katz 2008) in a way that would

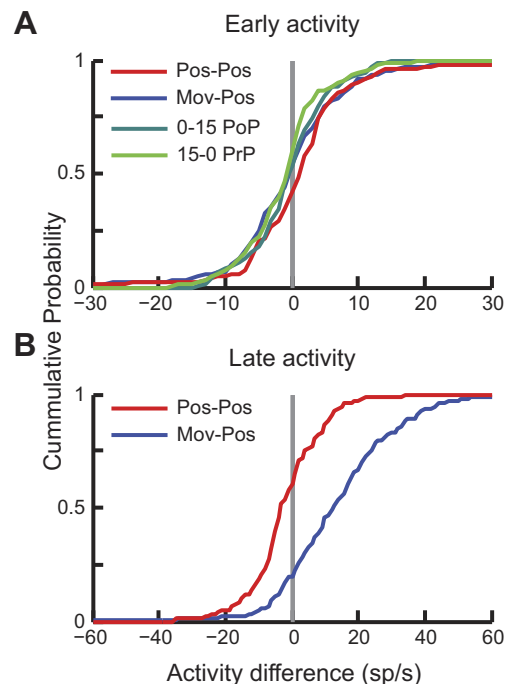


Fig. 11. Cumulative probability distributions (CPD) of activity change for different time epochs. *A*: CPD of change in activity in the late baseline (-15 – 0 ms, light green), immediately following the perturbation (0 – 15 ms, dark green), early evoked response (20 – 35 ms, blue) across posture-movie tasks, and early evoked response (20 – 35 ms, red) across repeated posture tasks. *B*: CPD of change in late perturbation response (50 – 100 ms, blue) across posture-movie tasks and late perturbation response (50 – 100 ms, red) across repeated posture tasks. Note that the horizontal axis in *A* is half the size of the horizontal axis in *B*. PoP, postperturbation; PrP, preperturbation.

limit our ability to compare neural responses when the monkey is engaged in a motor behavior vs. not. Alternatively, we could have rewarded the monkeys to not respond to the perturbation. However, direct rewarding for not responding would in itself be a behavior that could confound the results in an unknown way (i.e., the monkeys could learn to actively suppress sensory feedback).

Our approach was to compare perturbation responses when the monkeys had to maintain active postural control at a spatial target to receive a water reward (posture task) vs. responses when the monkeys were not required to maintain their hand at a spatial target nor respond to the perturbation to receive water reward (movie task). Our expectation was that the monkeys' response to the perturbation would be reduced in the latter task. A movie was presented to distract the monkeys with an oculomotor task, with the objective of minimizing the monkeys' interest to respond to the perturbation.

Although we had no direct way of evaluating the level of the monkeys' engagement in the movie task, changes in behavioral corrective responses suggest that we were at least partially successful in reducing motor responses to the perturbation. The monkeys returned their hand to the central target within 500–600 ms following the perturbation in the posture task, whereas the hand remained outside the target in the movie task. At 500 ms postperturbation, the hand was ~8 and ~30 mm away from the center of the target for the posture and movie tasks, respectively. Importantly, muscle perturbation responses between 45 and 100 ms were ~65% less, on average, in the movie task compared with those in the posture task.

The amount of hand motion and the distance returned to the target 500 ms postperturbation varied substantially across load conditions (Fig. 3). There are likely several factors that influence the size of these responses across load conditions. Most notably, the passive properties of the arm are anisotropic (including viscoelastic forces caused by the soft tissue and limb inertia, see Mussa-Ivaldi et al. 1985; McIntyre et al. 1996). This influences how far the arm is moved by the loads, how much it returns, and in some cases, generates curvatures in hand trajectories from loading to unloading. It is notable that the elbow loads had the least amount of curvature, which may explain why the arm returned rapidly to the target in both tasks.

Three factors could possibly contribute to the partial return of the hand following the perturbations during the movie task. First, the monkeys may still have voluntarily responded, to some degree, to the perturbation in the movie task. Second, the monkeys may not have responded voluntarily, but spinal and supraspinal reflexes may have remained active. Third, passive viscoelastic properties of the limb will tend to return the limb towards the central target when the load is removed (Graham et al. 2003).

To explore the contributions from the first two neural factors, we repeated the movie task in *monkey P* when it was in an anesthetized state. No perturbation-related activity was observed in the limb muscles, suggesting that voluntary movements and spinal reflexes were not present. Even in this state, there was partial return of the limb towards the central target due to passive limb properties. For comparison sake, we will assume that the response observed in the anesthetized state reflects 0% effort and the response observed in the postural perturbation response reflects 100% effort. Relative to these, the behavioral response in the movie task would represent 47% of the effort exerted during the postural perturbation task. Admittedly, hand motion in the anaesthetized state may have been

influenced by changes in the body posture in the chair (as readily observed in *monkey A*) so some caution is required in these estimates of effort. Alternatively, EMG measures displayed a 68% drop in activity from posture to movie tasks. Thus corrective responses to the perturbation appear to be reduced 50–70% during the movie task compared with the posture task.

One potential concern was that the perturbations would elicit different initial limb motions between the tasks and thus influence sensory input to the brain. However, we found hand and joint motions to be essentially identical for the first 100 ms following the perturbation. This is probably because very little EMG activity was necessary to maintain the hand at the central target (Graham et al. 2003). Even if there was some small difference that we could not measure, small changes in muscle activity have a modest effect on initial limb motion following a perturbation (Pruszynski et al. 2009).

Balanced Change in Baseline Activity Across Tasks

Several studies have found that activity in M1 during postural control before movement is influenced by factors related to ongoing control, such as limb geometry (Scott and Kalaska 1997) and load direction (Thach 1978; Fromm 1983; Herter et al. 2007), or preparing for future motor events, such as the direction of an impending movement (Evarts and Tanji 1976) or its speed (Churchland et al. 2006). In our task, we also found that baseline activity before the perturbation was commonly altered between the two behavioral contexts, with increases in baseline activity almost as prevalent as decreases in the movie compared with the postural task. Interestingly, the population activity before the perturbation was virtually the same across tasks. Thus engagement in a motor task does not necessarily generate an overall increase in motor cortex activity. Rather, engagement seems to cause a reorganization of the pattern of activity across the neural population (see Afshar et al. 2011).

Not all changes in baseline activity may reflect task-dependent changes in neural processing. Some change in baseline activity could be observed even when repeating the same posture task. Of the 106 cells with repeated posture tasks and a significant perturbation response, 36 had significant changes in baseline activity (Fig. 10A). The absolute change in baseline activity was 5 spikes/s between posture and movie tasks, whereas it was 3.5 spikes/s across repeated posture tasks. Changes in baseline activity between the two tasks (posture vs. movie) were statistically larger than that observed for repeated posture tasks. Scott and Kalaska (1997) found 14% of neurons displayed changes in activity across repeated tasks, slightly less than the proportion identified in the present study. These temporal effects may reflect altered attention to the task during the recording session. On the other hand, changes in baseline activity might indicate different equilibrium points in the network activity, all generating the same network output (i.e., redundancy in network activity, Kaufman et al. 2013, 2014).

Task-Independent Response in M1 to Mechanical Perturbations

A key observation from Evarts and Tanji (1976) was that the initial perturbation response in M1 was largely fixed and not sensitive to the instruction to push or pull a lever following the perturbation (see also Pruszynski et al. 2011, 2014). The focus

of our study was to identify whether this invariant initial response was related to the monkey being actively engaged in maintaining the hand at a location in space before the perturbation was applied. We tried to make sure the sensory feedback had no relevance for the ongoing behavior (watching a movie), and yet this invariant response was still evident between ~20 and 40 ms. We found some individual cells with significant differences in activity in this early epoch across tasks, but similar changes could also be observed in the late baseline activity (15 ms before perturbation) and right after the perturbation when virtually no response should be observed (0–15 ms; Fig. 10A). Thus the invariant initial response observed in our task appears to reflect a task-independent sensory response rather than ongoing control of behavior.

In some ways it is surprising that sensory feedback in M1 would remain similar whether the monkey was engaged or not in a motor task, given the many levels where sensory signals could be altered from the periphery to M1. First, the feedback could change at the periphery based on the behavioral task (Loeb 1985). For instance, previous work has shown spindle activity and its sensitivity are altered when a cat switches from lying down and resting, to standing still, vs. walking (Prochazka et al. 1977). Second, proprioceptive feedback could be altered centrally, notably in the cuneate nucleus or primary somatosensory cortex, the likely sources of initial sensory input to primary motor cortex. Perturbation responses arrive in M1 in just a few milliseconds after they arrive in primary somatosensory cortex (at ~20 ms; Evarts 1973; Fromm and Evarts 1982). Therefore, any peripheral or central change in this sensory pathway should be reflected in the initial perturbation response. This does not mean that changes in gamma drive (Hammond 1956) or central processing could not happen across tasks, as previously suggested. Rather, it suggests that such alterations did not occur across our posture and movie tasks.

Our observation of no interaction between changes in baseline activity of the cells and the initial perturbation response has implications for various hypotheses on integration of sensory feedback with ongoing neural processing. For instance, the evoked response could be scaled by the baseline activity; if the baseline was doubled in one task, the evoked response would double as well (Polack et al. 2013). However, we found no significant correlation between the ratio of change in baseline activities and that of the evoked responses across tasks. A second possibility is that the evoked response could remove any influence of the previous baseline activity. Thus the magnitude of the observed cell activity would always be identical, irrespective of the baseline activity (He 2013). Therefore, the absolute firing rate of the neurons would always be the same, falsely making the baseline activity and the evoked response anticorrelated; if the baseline gets bigger, the evoked response gets smaller, and vice versa. However, there was no correlation between the change in baseline activity and the change in initial perturbation response across tasks. Instead, our analysis did show that the size of the initial evoked responses was highly correlated across tasks highlighting that sensory input remains relatively constant (Azouz and Gray 1999).

The EMG activity was also not initially altered across tasks (34–45 ms postperturbation). Given the fact that the fastest transduction time between M1 activity and muscle responses is ~10 ms (Cheney and Fetz 1980, 1984; Bawa and Lemon

1993), M1 could potentially contribute to EMG responses in as little as 30–35 ms in our tasks. Such descending signals would initially contribute to the task-independent EMG response and then later contribute to task-dependent EMG response starting at 45–50 ms postperturbation.

Nevertheless, we observed initial perturbation responses for M1 neurons in the non-PTC direction (Fig. 8A, *bottom*), which is not observed for EMG responses in proximal limb muscles (for example, see Fig. 8 in Herter et al. 2009). These increases in perturbation responses in both the PTC and non-PTC are particularly common for the earliest responding neurons (Herter et al. 2009). This coactivation of M1 neurons following perturbations may minimize their net effect on spinal processing during this early time period (Kaufman et al. 2014). Therefore, further examination is required to identify whether the early task-independent responses in the EMG reflect cortical as well as spinal processing.

Task-Dependent Changes in Perturbation Responses in M1

While perturbation responses in M1 dropped by 30% in the movie task, it is possible that these responses could be reduced even further. As discussed above, our analysis of motor responses compared with the anesthetized state suggests that motor responses in the movie task were reduced ~50% relative to the posture task. The remaining 50% (i.e., the difference between the movie task vs. the anesthetized state) might indicate some degree of voluntary response even in the movie task.

However, it is unlikely that the remaining motor response was due only to voluntary control. First, early spinal stretch responses are relatively fixed and might oppose the perturbation in the movie task in the absence of any voluntary reaction (Wolpaw et al. 1986). However, the contribution from spinal reflexes may be minimal; the short-latency spinal reflex, which is expected to begin at 15–20 ms (Conrad et al. 1975; Lee and Tatton 1975), was effectively absent, probably due to the small background EMG activity before the perturbation (Pruszynski et al. 2009). While it is easy to quantify the spinal contribution to the early EMG activity, it is more complicated to estimate its contribution in later epochs when transcortical responses likely have a substantial contribution. As well, transcortical feedback may still contribute to EMG activity even if the monkey is not voluntarily responding. We found a proportion of neurons that did not change their perturbation response between the posture and movie tasks. Thus there may be an invariant transcortical response that begins at 20 ms and continues beyond 40 ms during the movie task. This invariant response may be suppressed through voluntary control when behaviorally required, although likely only after 40 ms.

Our population signal included a task-independent response starting at 20 ms followed by a task-dependent response at 40 ms. We were interested to know if this basic pattern, task-independent response followed by a delayed task-dependent response (dashed line in Fig. 9B), occurred in all neurons or just in neurons that responded early to the perturbation. Figure 9 shows that only neurons responding before 40 ms tended to show an initial task-independent response. Neurons recruited after 40 ms tend to immediately show task-dependent changes.

It remains an open question as to how the task-dependent modulation is generated in the brain. It may be generated

within M1, taking M1 20 ms to process the sensory information to generate the task-dependent signal. Alternatively, there might be different sources of feedback to M1 with different time delays and summing in M1 to form its activity; one driving the task-independent response and the other driving the task-dependent response. Most likely the initial task-independent response is produced by S1, given its rapid onset. If the task-dependent response is not generated in M1, there are a number of cortical (e.g., posterior parietal area; Kalaska 1996; Mountcastle et al. 1975) and subcortical (e.g., cerebellum; see Strick 1978 for a review) areas that may be the source of this response. The prediction is that the task-dependent signal would appear earlier than 40 ms in this other brain region, a focus for future studies.

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DISCLOSURES

S. H. Scott is associated with BKIN Technologies, which commercializes the KINARM robot used in this study.

AUTHOR CONTRIBUTIONS

Author contributions: M.O., J.A.P., and C.D.M. performed experiments; M.O. analyzed data; M.O. and S.H.S. interpreted results of experiments; M.O. prepared figures; M.O. drafted manuscript; M.O., J.A.P., C.D.M., and S.H.S. edited and revised manuscript; M.O., J.A.P., C.D.M., and S.H.S. approved final version of manuscript; J.A.P. and S.H.S. conception and design of research.

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