Shared internal models for feedforward and feedback control of arm dynamics in non-human primates

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Abstract

Previous work has shown that humans account for and learn novel properties or the arm's dynamics, and that such learning causes changes in both the predictive (i.e., feedforward) control of reaching and reflex (i.e., feedback) responses to mechanical perturbations. Here we show that similar observations hold in old-world monkeys (macaca fascicularis). Two monkeys were trained to use an exoskeleton to perform a single-joint elbow reaching and to respond to mechanical perturbations that created pure elbow motion. Both of these tasks engaged robust shoulder muscle activity as required to account for the torques that typically arise at the shoulder when the forearm rotates around the elbow joint (i.e., intersegmental dynamics). We altered these intersegmental arm dynamics by having the monkeys generate the same elbow movements with the shoulder joint either free to rotate, as normal, or fixed by the robotic manipulandum, which eliminates the shoulder torques caused by forearm rotation. After fixing the shoulder joint, we found a systematic reduction in shoulder muscle activity. In addition, after releasing the shoulder joint again, we found evidence of kinematic aftereffects (i.e., reach errors) in the direction predicted if failing to compensate for normal arm dynamics. We also tested whether such learning transfers to feedback responses evoked by mechanical perturbations and found a reduction in shoulder feedback responses, as appropriate for these altered arm intersegmental dynamics. Demonstrating this learning and transfer in non-human primates will allow the investigation of the neural mechanisms involved in feedforward and feedback control of the arm's dynamics.

Introduction

Monkeys, like humans, perform arm movements that require coordinating multiple joints. One complexity of such movements are the mechanical interactions that arise across moving limb segments, as movements around one joint cause rotational forces at other joints (Hollerbach and Flash, 1982; Graham et al., 2003). Many previous studies have demonstrated that the nervous system develops an internal representation of such arm dynamics that can be used to generate predictive (i.e., feedforward) muscle activity during self-initiated reaching (Gribble and Ostry, 1999; Debicki and Gribble, 2005; Gritsenko et al., 2011; Maeda et al., 2017, 2018, 2020a, 2020b, 2020c) and also reflex (i.e., feedback) responses to mechanical perturbations, in a way that accounts for the arm dynamics (Lacquaniti and Soechting, 1984, 1986a, 1986b; Soechting and Lacquaniti, 1988; Kurtzer et al., 2006b, 2008, 2009, 2014, 2016; Pruszynski et al., 2011; Crevecoeur et al., 2012; Maeda et al., 2017, 2018, 2020a; Kurtzer, 2019). For instance, when generating single-joint elbow movements and when responding to mechanical perturbations that create pure elbow motion, the nervous system generates predictive shoulder muscle activity and robust shoulder feedback responses to counter the underlying torques that arise at the shoulder joint because of forearm rotation about the elbow joint (Gribble and Ostry, 1999; Kurtzer et al., 2008; Maeda et al., 2017, 2018, 2020a). This similarity between feedforward and feedback control reflects, in part, the shared neural circuits between feedforward and feedback control at the level of the spinal cord, brainstem and cerebral cortex (Pruszynski and Scott, 2012; Kurtzer, 2014; Scott, 2016).

One way of determining how the nervous system represents arm dynamics is by altering the normal mapping between joint torques and joint motion. For example, we have recently shown in humans that generating pure elbow movements with the shoulder joint fixed, causes people to reduce shoulder muscle contraction during self-initiated reaching and that such learning transfers to feedback responses (Maeda et al., 2018, 2020b). Such learning and transfer is appropriate and efficient because mechanically fixing the shoulder joint eliminates the interaction torques that arise at the shoulder when the forearm rotates and thus removes the need to recruit shoulder muscles.

Here we address the same question in old-world monkeys (macaca fascicularis). Multi-joint arm movements in monkeys account for arm intersegmental dynamics (Graham et al., 2003) and monkeys generate predictive underlying muscle activity (Scott, 1997; Gribble and Scott, 2002; Kurtzer et al., 2006a) but it is unknown whether and how they learn new muscle activity patterns to adapt to novel arm dynamics. It is also unknown whether such learning transfers to feedback responses in monkeys. It is important to emphasize that neither the learning or transfer phenomena need to exist because, in our paradigm, the pre-fixation pattern of muscle activity would continue to yield successful outcomes with the shoulder fixed for both self-initiated reaching and when responding to mechanical perturbations. Therefore, establishing these phenomena in monkeys at the level of muscle activity is a critical starting point for detailing the underlying neuronal circuits and mechanisms that make this type of learning and transfer possible.

We trained two monkeys to sit and use a robotic exoskeleton to generate self-initiated elbow reaching rotations and to compensate for mechanical perturbations that created pure elbow motion. As in our human experiments, we altered the normal mapping between joint torque to joint motion by fixing the shoulder joint of the robot. First, we tested whether monkeys adapt to this altered arm dynamics during reaching, and we found that, like humans, monkeys show a reduction in shoulder muscle activity over trials. Second, we tested whether this new feedforward coordination pattern is expressed in feedback responses. As in humans, we found a reduction in shoulder reflex responses when a mechanical perturbation is occasionally introduced

after learning. Taken together, these results suggest that, like in humans, feedforward and feedback control in macaque monkeys share an internal model of the arm's dynamics.

Materials and Methods

Animals and apparatus

The Institutional Animal Care and Use Committee at Western University approved all the procedures described below. Two male cynomolgus monkeys (macaca fascicularis, Monkeys A and O, ~9 and 13 kgs, respectively) were trained to perform a range of upper-limb tasks while seated in a robotic exoskeleton (NHP KINARM, Kingston, Ontario).

As described previously (Scott, 1999; Pruszynski et al., 2011, 2014), this robotic device permits flexion and extension movements of the shoulder and elbow joints in the horizontal plane, and can independently apply torque at both of these joints. Target and hand feedback were projected from an LCD monitor onto a semi-silvered mirror, in the horizontal plane of the task. Direct vision of the monkey's arm was blocked with a physical barrier, and the ambient lights in the experimental room were turned off for the duration of data collection.

The two segments of the exoskeleton robot (upper arm and forearm) were adjusted to fit each monkey's arm. Monkey A used their left arm while monkey O used their right arm (Figure 1 A-B). The robot was then calibrated so that the projected hand cursor was aligned with the tip of each monkey's index finger. Calibration was saved and used across training and testing sessions. At the beginning of each session, an experimenter gently strapped each monkey's arm to the two links of the robot, to ensure a tight coupling, and certified that the calibrated hand cursor matched the actual index finger for each animal.

Reaching and posture perturbation tasks

Monkeys performed a version of the reaching and posture perturbation tasks described and performed by human participants in Maeda et al. (2018). Briefly, each monkey was trained to perform 20° of elbow flexion and extension movements or to counter mechanical perturbations applied by the robot that caused pure elbow motion. Animals did so with the shoulder joint either free to move or with the shoulder joint fixed. Shoulder fixation was achieved by inserting a physical pin into the robot linkage that permits shoulder motion.

At the beginning of a trial, a home target was displayed (blue circle, 0.5 cm diameter). The home target position corresponded to each monkey's hand cursor position (white circle, 0.4 cm diameter), when their shoulder and elbow joint was positioned at 35° and 60°, respectively (external angles; Figure 1 A-B). Monkeys were trained to move their hand cursor into this home target, and when they did so the home target turned green. After maintaining their hand cursor at this home location for a random period (500 –1000 ms, uniform distribution), a goal target (red circle: 0.8 cm diameter) was presented in a location that could be reached with a 20° of pure elbow flexion movement. The monkey received water reward and visual feedback (the goal target turned green) if it transported its hand to the goal target within 550 ms and remained in it for an additional 500 ms. After an interval period of 1000 ms, the goal target became a new

home target (blue circle, 0.5 cm diameter) and the same procedure was repeated for an extension movement.

Perturbation trials occurred in 15% of all trials. In these trials, after maintaining the cursor in the home target for a randomized duration (500 –1000 ms, uniform distribution), a torque pulse (i.e., perturbation) of 100 ms duration was applied simultaneously to the shoulder and elbow joints (0.48 and 0.35 N m, respectively), which displaced the monkey's hand outside the home target (Figure 2 A-B, top row). We chose this combination of shoulder and elbow loads to minimize shoulder motion (see Kurtzer et al., 2008, 2009, 2014; Pruszynski et al., 2011; Maeda et al., 2017, 2018, 2020a, 2020b; Kurtzer, 2019). At the same time as the perturbation, a goal target (red circle: 0.8 cm diameter) was overlaid at the home target location. The monkey received a water reward if it returned its hand to the goal target within 800 ms of perturbation onset and remained in it for an additional 500 ms. If the monkey returned to the goal target within this timing window, the target circle changed from red to green, otherwise the target circle remained red and no reward was provided. Note that perturbations could occur at either the more flexed or extended home target positions.

Monkeys performed blocks of trials, each consisting of 20 flexion and extension reaching trials and 4 perturbation trials. The order of reaching and perturbation trials was randomized within a block of trials. Recording sessions consisted of 1-2 blocks of trials with the shoulder joint free to move (baseline phase), 4-8 blocks of trials with the shoulder joint of the robot fixed (adaptation phase), and 1-2 blocks with the shoulder joint free to rotate again (post-adaptation phase). The precise number of blocks was determined by the experimenter based on animal behavior on that day (see Table 1).

Five to ten additional sessions were recorded from each animal using the same version of this protocol but without locking the shoulder joint. This served as a control to rule out changes caused by extensive movement repetitions within a session rather than the shoulder fixation manipulation (see Table 1).

Experimental sessions lasted approximately 2-2.5 hours. Rest breaks were given between blocks of trials. Before data collection, monkey A completed ~1 year and monkey O completed ~2 years of positive reinforcement training in this task. Each animal completed these training sessions with all the joints free to rotate and never experienced shoulder fixation over the course of training until the experimental sessions being reported here.

Table 1. Number of extension trials and % of correct trials in each session for monkeys A and O.

Monkey A Session	Base # Trials	Adapt # Trials	Post # Trials	% Correct Trials	Monkey O Session	Base # Trials	Adapt # Trials	Post # Trials	% Correct Trials
20181102 - Main	17	87	13	84%	20181017 - Main	14	97	14	70%
20181123 - Main	13	107	48	87%	20181101 - Main	18	88	18	70%
20181129 - Main	50	96	12	83%	20181114 - Main	27	77	28	91%
20181213 - Main	50	92	13	85%	20181123 - Main	13	94	13	93%
20190125 - Main	13	109	12	93%	20181129 - Main	12	91	16	77%
20190129 - Main	12	78	13	90%	20181212 - Main	13	95	36	70%
20190201 - Main	24	92	12	92%	20190125 - Main	14	97	14	70%
20180718 - Control	144	-	-	77%	20171220 - Control	96	-	-	80%
20180801 - Control	96	-	-	82%	20180607 - Control	48	-	-	60%
20180809 - Control	96	-	-	86%	20180621 - Control	192	-	-	83%
20180814 - Control	96	-	-	85%	20180628 - Control	144	-	-	85%
20180824 - Control	144	-	-	87%	20180727 - Control	144	-	-	90%
20180906 - Control	96	-	-	81%	20180823 - Control	120	-	-	85%
20180928 - Control	96	-	-	83%					
20181114 - Control	144	-	-	93%					

Muscle and kinematic recordings

We acquired bipoloar electromyographic (EMG) activity, using intramuscular fine-wire electrodes. EMG electrodes were made in-house and consisted of Teflon-coated 3 or 7 -strand stainless steel wire with 50 to

100 mm length (A-M Systems, Sequim, WA), threaded into a 30-mm, 27- gauge cannula (Kendall Monoject, Mansfield, MA), and hooked to anchor to the muscle tissue. Electrodes were spaced ~8-10mm apart and aligned to the muscle fibers.

We focused on five upper limb muscles [pectoralis major clavicular head (PEC), shoulder flexor; posterior deltoid (PD), shoulder extensor; biceps brachii long head (BB), shoulder and elbow flexor, brachioradialis (BR), elbow flexor; triceps brachii lateral head (TR), elbow extensor]. These muscles were chosen because they are easily accessible and active during flexion and extension movements at the shoulder and elbow joints (Kurtzer et al., 2006a, 2006b). A reference electrode was inserted subcutaneously on the animal's back. To decrease stress, animals were sometimes given a mild sedative prior to the EMG placement. The sedation used was a combination of medetomidine (0.01-0.02mg/kg) and midazolam (0.04-0.05mg/kg). The medications were given by intramuscular injection in the home cage. Immediately following the injection animals were moved into the KINARM chair and taken to the procedure room where the lights were dimmed to reduce stimulation. Once the animals were relaxed (usually 10-15min post injection) insertion of the EMG wires into the above mentioned muscle locations started. Once all of the wires were placed, the Medetomidine portion of the sedation was reversed using Atipamezole intramuscularly (volume same as medetomidine administered in that session).

Muscle activity was recorded at 2,000 Hz, bandpass filtered (25–500 Hz, sixth order Butterworth) and full-wave rectified before analysis (Pruszynski et al., 2014). Kinematic data and applied torques were sampled at 1,000 Hz, directly from the KINARM device, and then low-pass filtered before analysis (12 Hz, 2-pass, fourth-order Butterworth).

Data and statistical analysis

Data from reaching trials were aligned on movement onset and data from perturbation trials were aligned on perturbation onset. Movement onset was defined as 10% of peak angular velocity of the elbow joint. Only rewarded trials were selected for analysis. Only those muscle recordings sessions that yielded clear phasic responses to either movement or mechanical perturbation, and minimal motion artifact, were analyzed. Specifically, we focused our key analyses on PD and TR muscle activity because it provided the most reliable and highest quality signal across sessions and across feedforward and feedback experimental conditions. EMG during reaching was normalized to the average activity in a fixed time window (-100 to +100 ms, relative to movement onset, capturing the agonist burst of EMG activity) in baseline trials, such that a value of 1 represents a given mean activity when a given muscle is acting as agonist. EMG during perturbation was normalized to the average activity in the voluntary epoch (+100 to +150 ms, relative to perturbation onset, known to capture the agonist burst of EMG activity) in baseline trials, such that a value of 1 represents a given mean activity in the voluntary epoch when a given muscle is acting as agonist.

Our main interest here was to investigate whether monkey's shoulder (specifically, PD) muscle activity during self-initiated reaching is reduced following shoulder fixation. To answer this question, we calculated the mean amplitude of phasic PD muscle activity in reaching trials across a fixed time window (-100 to +100 ms, relative to movement onset and chosen to capture the agonist burst of EMG activity). We then tracked whether and how this measurement of muscle activity changed over time and across different phases of the protocol with the shoulder joint free and fixed (Debicki and Gribble, 2005; Maeda et al., 2018, 2020a, 2020b, 2020c).

We also quantified kinematic aftereffects of reaching movements after adapting reaching with shoulder fixation. To do so, we calculated the hand path errors relative to the center of the target at 80% of the movement between movement onset and offset (also defined at 10% of peak angular velocity of the elbow

joint). This window was chosen to select the kinematic traces before any feedback corrections (Maeda et al., 2018, 2020a, 2020b).

Our second goal was to investigate whether feedback responses in shoulder (specifically, PD) muscle activity also adapt to the novel arm dynamics learned during self-initiated reaching with shoulder fixation. To answer this question, we binned the PD EMG of perturbation trials into previously defined epochs (Pruszynski et al., 2008; Maeda et al., 2018). This included a pre-perturbation epoch (PRE; 50 – 0 ms relative to perturbation onset), the short-latency stretch response (20–50 ms), the long-latency stretch response (50 – 100 ms), and the voluntary response (100 –150 ms).

All data processing and analyses were performed using MATLAB (r2019a, MathWorks). We performed different statistical tests (e.g., repeated-measures ANOVA with Tukey tests for multiple comparisons, t test), when appropriate for each experimental question. Statistical analyses were performed using R (v3.2.1, R Foundation for Statistical Computing). Details of these procedures are provided in Results. Experimental results were considered statistically reliable if the corrected p-value was <0.05.

Results

Compensating for arm dynamics during reaching and perturbation trials

Both monkeys were successful at achieving the imposed speed and accuracy constraints of the tasks in the testing sessions (average success rate 85% for monkey A and 78% for monkey O, see Table 1).

Even with the shoulder free to move (i.e., baseline trials), monkeys moved from the home target to the goal target with minimal motion at the shoulder joint and with substantial motion at the elbow joint (Figure 1 C-D), similar to what humans do when presented with similar targets and without instruction about how to move (Maeda et al., 2017, 2018). Despite minimal shoulder rotation, we found substantial shoulder extensor muscle activity before movement onset (10% of peak elbow velocity; see Materials and Methods), as required to compensate for the torques that arise at the shoulder when the forearm rotates (Gribble and Ostry, 1999; Maeda et al., 2017, 2018, 2020a, 2020b; Figure 1 E-F).

In selected trials, we occasionally applied mechanical perturbations to the arm while the monkeys maintained their hand in the home target. The mechanical perturbations consisted of 100ms torque pulses applied simultaneously to the shoulder and elbow joints with magnitudes chosen to elicit minimal shoulder motion but different amounts of elbow motion (Figure 2 A-B and inset). Consistent with previous work, we found that these mechanical perturbations elicited substantial shoulder muscle activity in the long-latency epoch (50-100 ms post-perturbation; Figure 2 C-D), as appropriate for countering the imposed joint torques (Kurtzer et al., 2008, 2009, 2014; Pruszynski et al., 2011; Maeda et al., 2017, 2018, 2020a, 2020b; Kurtzer, 2019).

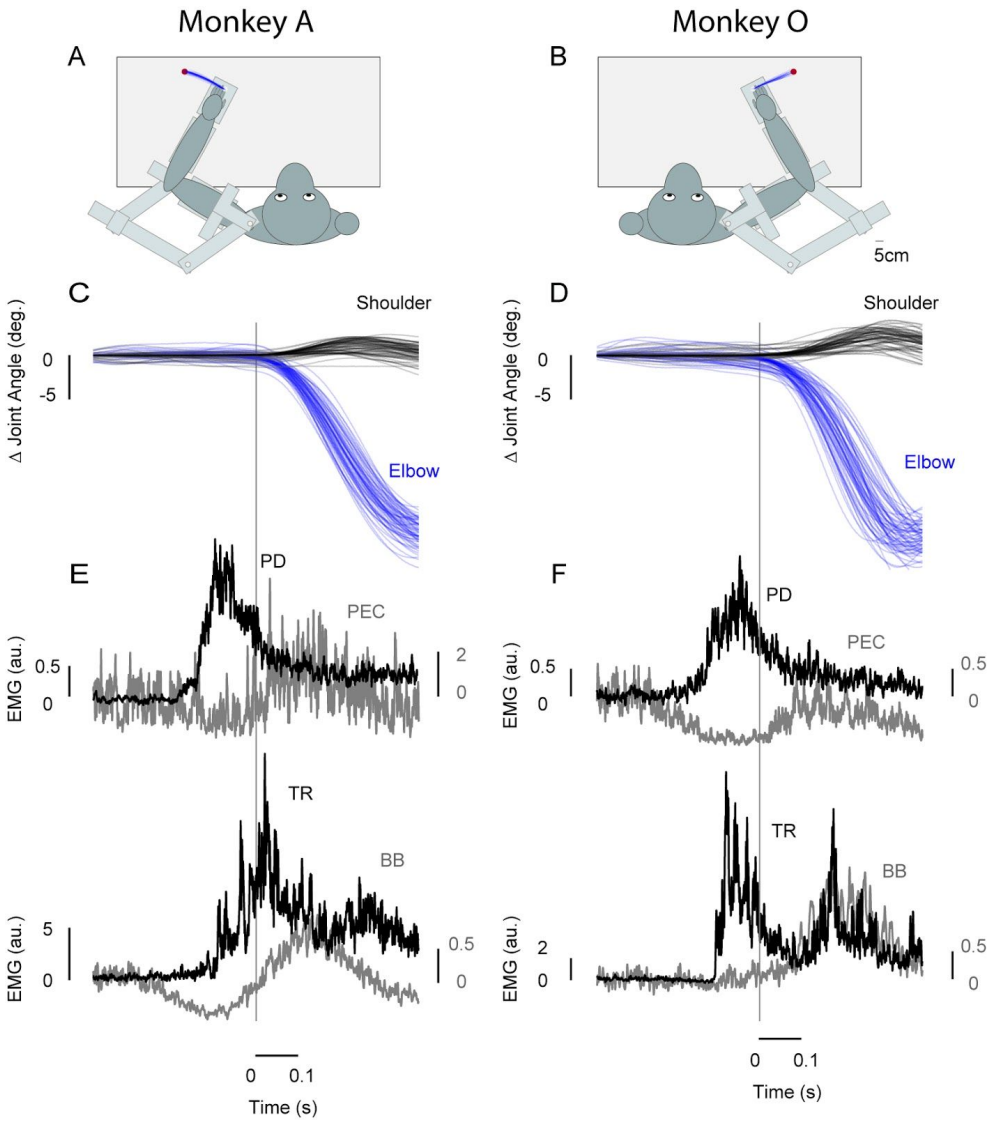

Figure 1: Compensating for arm dynamics during feedforward self-initiated elbow reaches. A-B, Reaching task set-up with hand kinematic traces of elbow extension movements from one exemplar session with the shoulder joint free to move (i.e., baseline trials) for monkeys A and O, respectively. **C-D**, Kinematics of the shoulder (black) and elbow (blue) joints for elbow extension movements for monkeys A and O, respectively. Data are aligned on movement onset. Data is shown for individual trials. Data from the same session as in A-B. **E-F**, Average agonist (black traces: PD, top row and TR, bottom row) and antagonist (gray traces: PEC, top row and BB, bottom row) muscle activity of the movements in **C-D** for monkeys A and O, respectively. EMG data are normalized as described in the Methods. Data are aligned on movement onset.

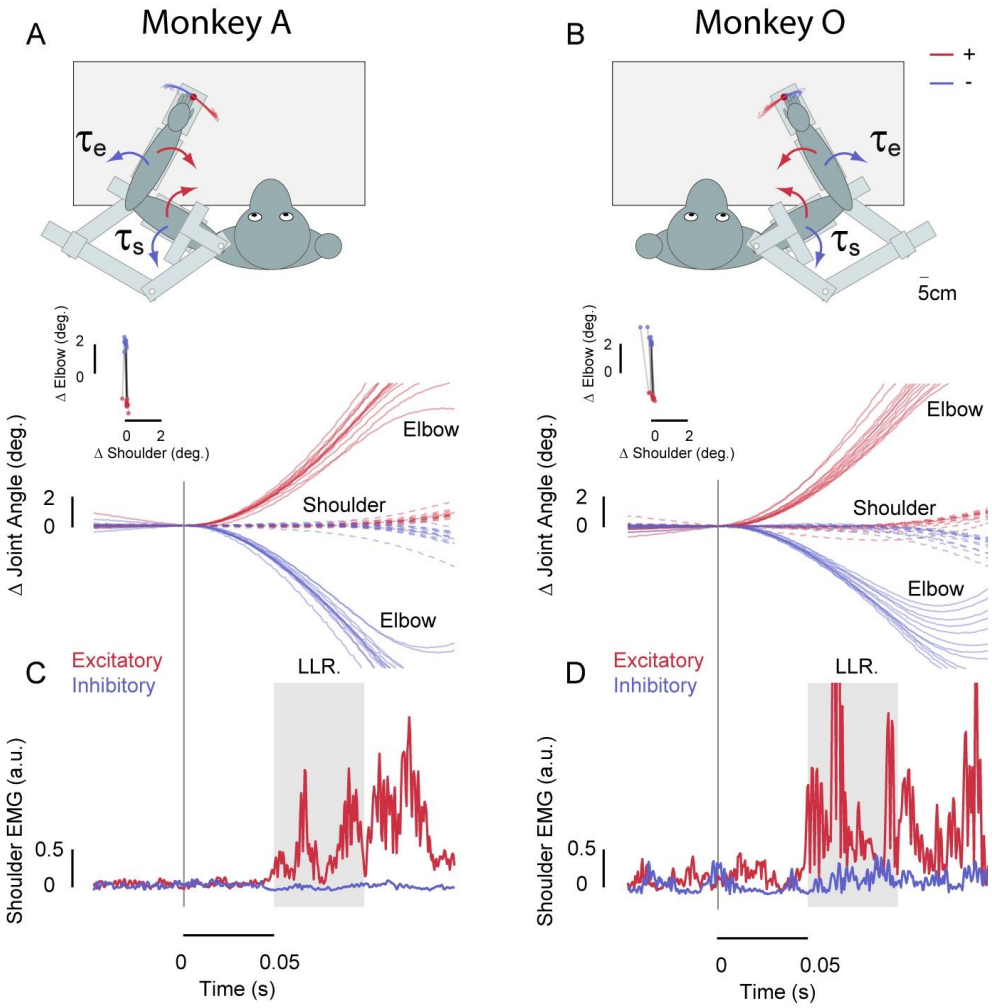

Figure 2: Accounting for arm dynamics during feedback responses to perturbation. A-B, Perturbation task set-up with hand kinematic traces (top), shoulder (dashed) and elbow (solid) joint kinematics (bottom). **C-D,** Average shoulder PD muscle activity following mechanical perturbations with the shoulder joint free to move (i.e., baseline trials). **A-D**, All data from the same exemplar session. Red and blue traces are from the shoulder/elbow flexor torque and shoulder/elbow extensor torque perturbation conditions, respectively. Data are aligned on perturbation onset. Inset shows the amount of shoulder and elbow displacement 50 ms post-perturbation (data are shown for individual trials in this session). EMG data are normalized as described in the Methods. Grey horizontal shaded area indicates the Long-Latency Reflex epoch (LLR).

Learning single-joint elbow reaching with shoulder fixation

We first asked whether monkeys adapt reaching movements to the imposed novel arm dynamics with shoulder fixation, a manipulation that eliminates the torques that arise at the shoulder and that need to be compensated by muscles at the shoulder joint with motion of the forearm. Note that monkeys were not exposed to shoulder fixation in the training sessions, but when it was introduced in the testing sessions, fixation of the shoulder joint did not alter task performance, and monkeys continued to demonstrate success rates of 85% for monkey A and 78% for monkey O (see Table 1).

Figure 3 A, E illustrates, for both monkeys, the mean shoulder extensor muscle activity in a fixed time window (-100 to +100 ms, relative to movement onset; see Materials and Methods), across elbow extension trials before (i.e., baseline phase), during (i.e., adaptation phase) and after (i.e., adaptation phase) the

shoulder was physically fixed at the robotic manipulandum. The amplitude of shoulder muscle activity was reduced over the course of adaptation trials with the shoulder joint fixed and quickly returned to baseline levels after releasing the shoulder joint again (i.e., post-adaptation phase).

A one-way ANOVA comparing shoulder extensor muscle activity late (last 20 trials) in the baseline, adaptation and post-adaptation phases indeed revealed a reliable effect of phase on shoulder muscle activity across sessions for each monkey (Monkey A: $F_{2,8} = 11.1$, $p = 0.004$; Monkey O: $F_{2,12} = 17.23$, $p = 0.0002$; Figure 3 A-B, E-F and left inset bar graphs). Tukey post-hoc tests showed a reduction of shoulder muscle activity from baseline to late adaptation phases (Monkey A: 44%, $p = 0.002$; Monkey O: 33%, $p < 0.0001$), and a quick return, becoming indistinguishable from the activity in baseline trials, when releasing the shoulder joint again in the post-adaptation phase (Monkey A: $p = 0.483$; Monkey O: $p = 0.275$). We found no corresponding changes in elbow TR muscle activity as a function of phases (one-way-ANOVA, Monkey A: $F_{2,8} = 1.49$, $p = 0.28$; Monkey O: $F_{2,12} = 0.523$, $p = 0.605$; Figure 3 C-D, G-H and insets).

Moreover, we performed a t-test on the difference in shoulder muscle activity (adapt-baseline) in sessions in which the shoulder joint was fixed and was never fixed (control), and that monkeys performed a similar number of trials. Indeed, the reduction in shoulder muscle activity in sessions with the shoulder fixed was reliably smaller than at the equivalent point in the control sessions (Monkey A: $t_{6.5} = -3.9$, $p = 0.005$; Monkey O: $t_{6.8} = -3.7$, $p = 0.007$; Figure 3 A, E and right inset bar graphs), indicating that shoulder muscle activity decay is related to shoulder fixation manipulation rather than the production of an large number of movements.

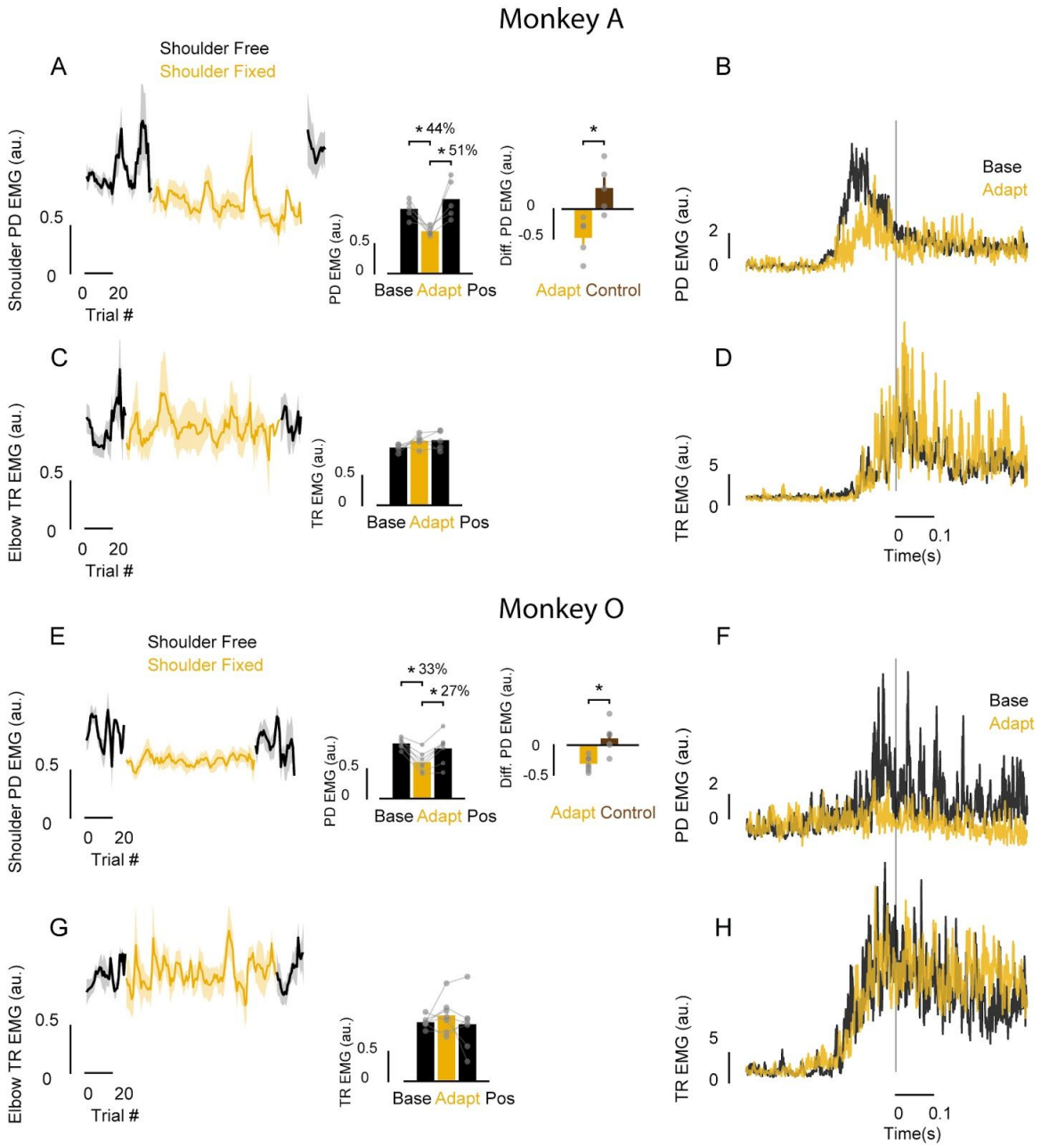

Figure 3: Learning novel arm dynamics during elbow reaching with shoulder fixation. A, Normalized PD muscle activity in a fixed time window (-100 to +100 ms relative to movement onset), averaged across sessions and smoothed over trials (i.e., moving average of 5 trials) with the shoulder free (black) and fixed (yellow). Shaded error areas represent standard error of the mean (SE). Left inset bar graph shows the average normalized PD muscle activity (-100 to +100 ms relative to movement onset) associated with these trials late in the baseline, adaptation and post-adaptation phases. Each dot represents data from a single session. Asterisks indicate reliable effects ($p < 0.05$; see main text). Right inset bar graph shows the difference in shoulder PD muscle activity (late of adaptation - baseline phases) for sessions in which the shoulder was fixed (adapt) and sessions in which the shoulder was never fixed (control). **B**, Time series of normalized PD muscle activity in one exemplar session averaged over the last 20 baseline and adaptation trials. Data are aligned on movement onset. **C-D**, Data for TR muscle are shown using the same format as **A-B**. **E-H**, Data for monkey O are shown using the same format as for monkey A in **A-D**.

Additional evidence that monkeys adapted to the imposed novel arm dynamics with shoulder fixation was the presence of robust kinematic after-effects. That is, early in the post-adaptation phase, monkeys also generated substantial kinematic reaching errors, and those errors were in the direction expected when failing to compensate for intersegmental arm dynamics during elbow extension trials (Figure 4 A-B). Note that this early release of the shoulder joint resulted in monkeys not achieving the speed and accuracy constraints imposed in our task. A one-way ANOVA comparing averaged reach errors (measured as hand distance from the center of the goal target at 80% of the movement, see Material and Methods) in trials late in the baseline (last 20 trials), early in the post-adaptation (first 3 trials) and late in the post-adaptation (last 20 trials) phases revealed a reliable effect of phase across sessions for each monkey (Monkey A: $F_{2,8} = 12.9$, $p = 0.003$; Monkey O: $F_{2,10} = 8.26$, $p = 0.007$; Figure 4 A-B, bottom row). We chose a smaller bin size early in the post-adaptation because the return to baseline after unlocking the shoulder joint happens quickly (Figure 3 A-B). Tukey post-hoc tests showed a reliable increase in kinematic errors from baseline to early-post-adaptation phases (Monkey A: 80%, $p = 0.001$; Monkey O: 81%, $p < 0.0001$), and a return to baseline accuracy levels late in the post-adaptation phase (Monkey A: $p = 0.147$; Monkey O: $p = 0.025$).

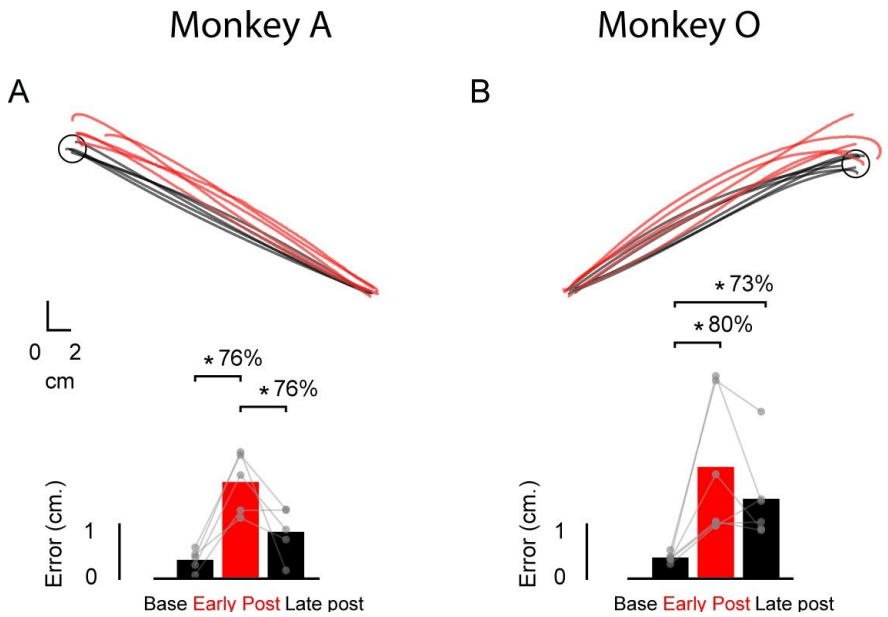

Figure 4: Hand trajectories before and after adapting elbow reaches with shoulder fixation. A, Average hand trajectories (top row) late in the baseline (20 trials) and early in the post-adaptation trials (first 3 trials) both with the shoulder joint free to rotate. Each trace represents data from a single session. Average error to the center of the target in the last 20 trials in the baseline, first 3 trials in the post-adaptation and last 20 trials in the post-adaptation. Each dot represents data from a single session. Asterisks indicate reliable effects ($p < 0.05$; see main text). **B**, Data for monkey O are shown using the same format as for monkey A in **A**.

Transfer to feedback control

Our second main question was whether learning novel arm dynamics during feedforward reaching with shoulder fixation in monkeys also modifies feedback responses to mechanical perturbations.

Figure 5 A, C left panel illustrates the average of the difference (excitatory - inhibitory conditions) of shoulder (PD) muscle activity in the long-latency epoch over trials late (last 3 trials) in the baseline, adaptation and post-adaptation phases of the protocol. Each dot represents the average EMG from a single session. A one-way ANOVA on this data revealed a reliable effect of phase on shoulder long-latency muscle responses across sessions for each monkey (Monkey A: $F_{2,8} = 37.73$, $p < 0.0001$; Monkey O: $F_{2,10} = 8.04$, $p = 0.008$).

Tukey post-hoc tests showed a reliable reduction of shoulder long-latency responses from baseline to late adaptation phases (Monkey A: 23%, p = 0.001; Monkey O: 30%, p = 0.03), and a quick return to that seen in baseline levels (Monkey A: p = 0.01; Monkey O: p = 0.28).

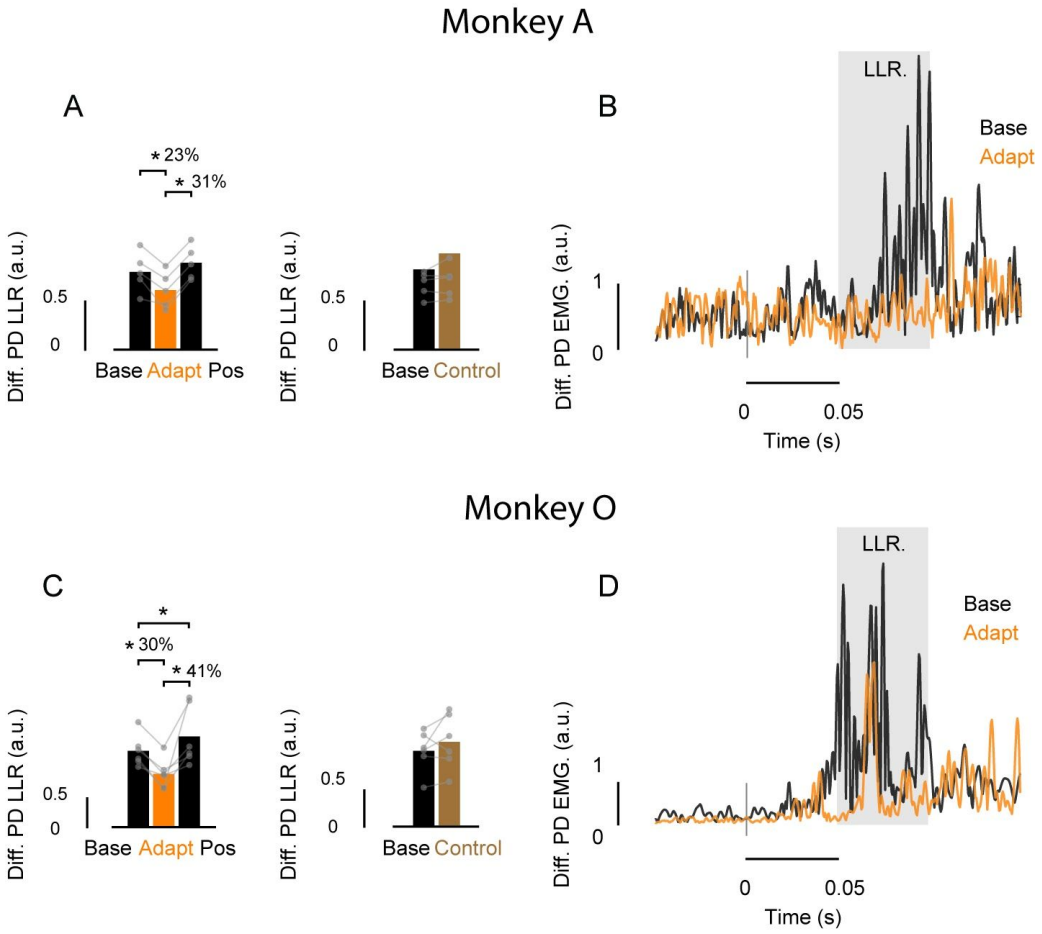

Figure 5: Rapid feedback responses before and after adapting self-initiated elbow reaching with shoulder fixation. A, Left bar graph shows the average of the difference (excitatory-inhibitory) of shoulder PD EMG (filtered, rectified and normalized) in the long latency epoch (50-100 ms) across trials late in the baseline, adaptation and post-adaptation (last 3 trials). Each dot represents data from a single session. Asterisks indicate reliable effects ($p < 0.05$; see main text). Right bar graph shows the data of the average of the difference (excitatory-inhibitory) of shoulder PD EMG in the long latency epoch across control sessions (first and last 3 trials) in which the shoulder joint was never fixed. **B**, Time series of normalized PD muscle activity in one exemplar session averaged over the last 3 baseline (black) and adaptation (orange) trials. Data are aligned on perturbation onset. Grey horizontal shaded area indicates the Long-Latency epoch (LLR). **C-D**, Data for monkey O are shown using the same format as for monkey A in **A-B**.

We found no reliable differences in EMG activity in a pre-perturbation epoch across learning phases (one-way-ANOVA, Monkey A: $F_{2,8} = 9.32$, p = 0.43; Monkey O: $F_{2,10} = 9.97$, p = 0.409, Figure 5 B, D) suggesting that changes in the long-latency epoch do not merely reflect changes in the state of the motor neuron pool (gain scaling, Marsden et al., 1976; Bedingham and Tatton, 1984; Pruszynski et al., 2009). However, as we did not ensure that the muscle was active prior to perturbation onset, we cannot rule out this possibility (see limitation section below). We also found no corresponding changes in shoulder PD muscle response in the short-latency epoch as a function of the phases of the protocol (one-way-ANOVA, Monkey A: $F_{2,8} = 2.442$, p = 0.149; Monkey O: $F_{2,10} = 0.07$, p = 0.9, Figure 5 B, D). Note that we used a combination of loads that created minimal shoulder joint motion, and thus it was expected minimal to no

activity in this epoch even in baseline trials (Kurtzer et al., 2008, 2009; Maeda et al., 2018, 2020b). Moreover, we found no corresponding changes in elbow muscle responses in long-latency epoch as a function of experimental phase (one-way-ANOVA, Monkey A: $F_{2,8} = 1.9$, $p = 0.21$; Monkey O: $F_{2,10} = 0.17$, $p = 0.84$).

Importantly, we also extracted data from control sessions, where monkeys performed similar number of trials but never with the shoulder fixed, and we found no decrease in shoulder PD activity in the long-latency epoch early and late in these control sessions (paired t-test, Monkey A: $t_{7.7} = -0.49$, $p = 0.63$; Monkey O: $t_{9.2} = -0.64$, $p = 0.536$, Figure 5 A, C, right panel).

Discussion

Motivated by our previous work in humans (Maeda et al., 2018, 2020a, 2020b, 2020c), we first tested whether macaque monkeys learn to reduce shoulder muscle activity when performing self-initiating pure elbow movements with their shoulder joint mechanically fixed. Consistent with such learning, we found a systematic reduction in this shoulder muscle activity over trials when the shoulder joint was fixed. After releasing the shoulder joint again, we found evidence of kinematic aftereffects (i.e., reach errors), in the direction predicted if the animal was failing to compensate for the arm's normal dynamics. We also tested whether such learning transfers to feedback responses to mechanical perturbation. Consistent with transfer, we found a reduction in shoulder long-latency feedback responses, as appropriate for the altered arm intersegmental dynamics. Together, our results demonstrate that macaque monkeys, like humans, learn novel intersegmental arm dynamics during self-initiated reaching with shoulder fixation, and that such learning transfers to feedback control (Maeda et al., 2018, 2020a, 2020b).

Relationship to human studies

Our monkey tasks were chosen in a way to mimic several aspects of previous human studies. First, research has demonstrated that humans generate predictive shoulder muscle activity when generating pure elbow movements (Gribble and Ostry, 1999; Debicki and Gribble, 2005; Maeda et al., 2017, 2018) and show robust shoulder long-latency reflex responses to perturbations applied to the arm that creates pure elbow motion (Kurtzer et al., 2006b, 2008, 2009, 2014, 2016; Crevecoeur et al., 2012; Maeda et al., 2017, 2018, 2020a; Kurtzer, 2019). Likewise, when monkeys generate elbow reaches or respond to perturbations that created pure elbow motion in our study, shoulder muscle activity begins before movement onset (Figure 1 E-F), and shows a quick shoulder responses within 50-100 ms post perturbation (i.e., long-latency epoch; Figure 2 C-D), respectively. These results are consistent with previous work showing that monkeys generate muscle activity in a way that mirrors the control of the arm's dynamics during multi-joint reaching (Scott, 1997; Graham et al., 2003; Kurtzer et al., 2006a) and perturbation tasks (Pruszynski et al., 2011).

Previous studies have shown that human participants learn to reduce shoulder muscle activity with shoulder fixation but such learning is slow (i.e., it unfolds over hundreds of trials) and is incomplete (i.e., activity is not eliminated) (Maeda et al., 2018, 2020b, 2020c). Although the rate of learning seems faster for monkey O than monkey A (Figure 3 E) and indeed both monkeys showed faster learning than the typical human participant, learning was still incomplete for both monkeys in our study. The main difference between the current study with respect to human studies is that the animals repeat this learning protocol for many testing sessions. Thus, there could be an effect of savings across sessions (Krakauer, 2009), which, to our knowledge, has not yet been examined in human studies (see also the Limitations section below). After adapting to the novel arm's dynamics, the monkeys show that rapid feedback responses are also adapted in a way consistent with the new underlying joint torques, also similar to humans in this task (Maeda et al.,

2018, 2020a, 2020b). Taken together, the similarities at the behavioural and muscle activity levels suggest that these animals are sufficient for investigating the shared neural mechanisms for feedforward and feedback control of reaching.

Learning novel for arm dynamics during self-initiated reaching

Like humans, monkeys can learn a variety of upper-limb motor tasks from reaching in the presence of force environments (Gandolfo et al., 2000; Li et al., 2001; Gribble and Scott, 2002; Arce et al., 2010; Richardson et al., 2012; Cherian et al., 2013; Perich et al., 2018) to visuomotor mapping representations (Paz et al., 2003; Mandelblat-Cerf et al., 2009; Perich et al., 2018; Vyas et al., 2018, 2020) and brain machine interface (i.e., BMI) control (Sadtler et al., 2014; Golub et al., 2015, 2018; Hennig et al., 2018; Vyas et al., 2018; Oby et al., 2019; Zhou et al., 2019). These types of learning, however, unfold as a function of errors the animals make in the task and are consistent with the monkey updating an internal model of the environment (for review on error-based learning see, Shadmehr et al., 2010). In our task, fixating the shoulder joint clamps reach trajectories to an arc rotating about the elbow joint and does not introduce large kinematic errors during learning. Reducing shoulder muscle activity in this task is efficient because fixing the shoulder joint cancels the forces that arise at the shoulder with forearm rotation, and thus removes the need to generate shoulder muscle activity. The observation that our monkeys show learning in this task in a way similar to humans expands the scope of the types of motor learning paradigms for which macaque monkeys can be a useful model (Maeda et al., 2018, 2020b, 2020c).

Transfer to feedback control

Like humans, when monkeys learn new intersegmental dynamics during self-initiated movement such learning appears to transfer to feedback control in the context of mechanical perturbations. Current theories in sensorimotor neuroscience, based on optimal feedback control, posit that voluntary motor behavior involves the sophisticated manipulation of sensory feedback (Todorov and Jordan, 2002; Scott, 2004; Pruszynski and Scott, 2012). Consistent with this idea, a number of studies in humans have shown that learning new feedforward coordination patterns (like when reaching in a novel force field) automatically transfer to transcortical feedback responses (Wang et al., 2001; Kimura et al., 2006; Wagner and Smith, 2008; Kimura and Gomi, 2009; Ahmadi-Pajouh et al., 2012; Yousif and Diedrichsen, 2012; Cluff and Scott, 2013; Maeda et al., 2018, 2020a, 2020b). For instance, when human participants learn to reach in the presence of an external force environment or learn to reduce shoulder muscle activity when generating elbow reaching movements with shoulder fixation, evoked long-latency feedback responses to mechanical perturbations mirrors such learning during reaching. Here we found that such transfer is also present in monkeys. After monkeys learn novel arm dynamics during reaching with shoulder fixation, shoulder long-latency reflex responses to perturbations were also reduced.

This transfer between feedforward and feedback control is thought to take place because of shared neural mechanisms between feedforward and feedback control. One potential node that could mediate such a transfer system is the primary motor cortex (M1). Previous work in humans and monkeys has demonstrated that M1 mediates feedforward and feedback compensation for the arm's dynamics (Gritsenko et al., 2011; Pruszynski et al., 2011), it mediates muscle coordination patterns (Morrow et al., 2009; Cherian et al., 2013; Sussillo et al., 2015; Russo et al., 2018; Naufel et al., 2019), and show single unit neural activity for both feedforward and feedback control (Evarts, 1973; Evarts and Tanji, 1976; Wolpaw, 1980; Evarts and Fromm, 1981; Picard and Smith, 1992; Herter et al., 2009; Pruszynski et al., 2011; Omrani et al., 2014; Pruszynski, 2014). M1 is likely not mediating such motor learning and transfer alone (Cherian et al., 2013; Perich et al., 2018). For example, M1 is highly connected with the cerebellum (Allen and Tsukahara, 1974; Hoover and

Strick, 1999; Holdefer et al., 2000; Wagner et al., 2019), which is also a site that has been long proposed to contain the computations for internal models that underlie feedforward motor control (Wolpert and Kawato, 1998; Wolpert et al., 1998). The cerebellum is also critical for feedforward and feedback control of the intersegmental arm dynamics, as a deficit in this region in patients has been reported to substantially impact the ability to coordinate across joints (Holmes, 1939; Goodkin et al., 1993; Bastian et al., 1996, 2000; Kurtzer et al., 2013). Demonstrating learning and transfer in monkeys, as we do here, sets the stage for further neurophysiology experiments for hunting these potential neural mechanisms of feedforward and feedback control of the arm dynamics.

Limitations

As always, there are limitations to this study that need to be explicitly noted. First, the monkeys performed the perturbation tasks without a pre-perturbation background load. Although we found no changes in the levels of muscle activity in the pre-perturbation epoch, the lack of background load means that it is not possible to rule out small changes in the state of the motor neuron pool as a function of learning (gain scaling, Marsden et al., 1976; Bedingham and Tatton, 1984; Pruszynski et al., 2009) explaining the transfer between feedforward and feedback control. The reason for not using background loads is because it reduces effort for the monkey and thus training burden. Moreover, because the monkeys were being used for cortical neural recordings, such background loads were less critical. Second, as already described above, the learning patterns appeared somewhat different across the two animals with monkey A showing slow and gradual learning similar (though still faster) to humans whereas monkey O showed a more immediate reduction in shoulder muscle activity after shoulder fixation. We do not have any definitive explanation for these differences or how they relate to the underlying neural mechanisms though the monkeys had more experience with the task than a typical human participant and, in general, individual humans also show some variability in learning rates (Krakauer et al., 2019). Third, note that similar to the human studies that investigated these same behavioural and EMG metrics (Maeda et al., 2018, 2020b), it is not possible to casually link the reduction of the feedforward motor commands with the reduction of the long-latency reflex responses without further invasive methods and neural recordings.

References

Ahmadi-Pajouh MA, Towhidkhah F, Shadmehr R (2012) Preparing to reach: selecting an adaptive long-latency feedback controller. J Neurosci 32:9537–9545.

Allen GI, Tsukahara N (1974) Cerebrocerebellar communication systems. Physiol Rev 54:957–1006.

Arce F, Novick I, Mandelblat-Cerf Y, Vaadia E (2010) Neuronal correlates of memory formation in motor cortex after adaptation to force field. J Neurosci 30:9189–9198.

Bastian AJ, Martin TA, Keating JG, Thach WT (1996) Cerebellar ataxia: abnormal control of interaction torques across multiple joints. J Neurophysiol 76:492–509.

Bastian AJ, Zackowski KM, Thach WT (2000) Cerebellar ataxia: torque deficiency or torque mismatch between joints? J Neurophysiol 83:3019–3030.

Bedingham W, Tatton WG (1984) Dependence of EMG responses evoked by imposed wrist displacements on pre-existing activity in the stretched muscles. Can J Neurol Sci 11:272–280.

Cherian A, Fernandes HL, Miller LE (2013) Primary motor cortical discharge during force field adaptation reflects muscle-like dynamics. J Neurophysiol 110:768–783.

Cluff T, Scott SH (2013) Rapid feedback responses correlate with reach adaptation and properties of novel upper limb loads. J Neurosci 33:15903–15914.

Crevecoeur F, Kurtzer I, Scott SH (2012) Fast corrective responses are evoked by perturbations approaching the natural variability of posture and movement tasks. J Neurophysiol 107:2821–2832.

Debicki DB, Gribble PL (2005) Persistence of inter-joint coupling during single-joint elbow flexions after shoulder fixation. Exp Brain Res 163:252–257.

Evarts EV (1973) Motor cortex reflexes associated with learned movement. Science 179:501–503.

Evarts EV, Fromm C (1981) Transcortical reflexes and servo control of movement. Can J Physiol Pharmacol 59:757–775.

Evarts EV, Tanji J (1976) Reflex and intended responses in motor cortex pyramidal tract neurons of monkey. J Neurophysiol 39:1069–1080.

Gandolfo F, Li C-SR, Benda BJ, Padoa Schioppa C, Bizzi E (2000) Cortical correlates of learning in monkeys adapting to a new dynamical environment. Proc Natl Acad Sci U S A 97:2259–2263.

Golub MD, Sadtler PT, Oby ER, Quick KM, Ryu SI, Tyler-Kabara EC, Batista AP, Chase SM, Yu BM (2018) Learning by neural reassociation. Nat Neurosci 21:607–616.

Golub MD, Yu BM, Chase SM (2015) Internal models for interpreting neural population activity during sensorimotor control. Elife 4:e.10015.

Goodkin HP, Keating JG, Martin TA, Thach WT (1993) Preserved simple and impaired compound movement after infarction in the territory of the superior cerebellar artery. Can J Neurol Sci 20 Suppl 3:S93–S104.

Graham KM, Moore KD, Cabel DW, Gribble PL, Cisek P, Scott SH (2003) Kinematics and kinetics of multijoint reaching in nonhuman primates. J Neurophysiol 89:2667–2677.

Gribble PL, Ostry DJ (1999) Compensation for interaction torques during single- and multijoint limb movement. J Neurophysiol 82:2310–2326.

Gribble PL, Scott SH (2002) Overlap of internal models in motor cortex for mechanical loads during reaching. Nature 417:938–941.

Gritsenko V, Kalaska JF, Cisek P (2011) Descending corticospinal control of intersegmental dynamics. J Neurosci 31:11968–11979.

Hennig JA, Golub MD, Lund PJ, Sadtler PT, Oby ER, Quick KM, Ryu SI, Tyler-Kabara EC, Batista AP, Yu BM, Chase SM (2018) Constraints on neural redundancy. Elife 7:e.36774.

Herter TM, Korbel T, Scott SH (2009) Comparison of neural responses in primary motor cortex to transient and continuous loads during posture. J Neurophysiol 101:150–163.

Holdefer RN, Miller LE, Chen LL, Houk JC (2000) Functional connectivity between cerebellum and primary motor cortex in the awake monkey. J Neurophysiol 84:585–590.

Hollerbach MJ, Flash T (1982) Dynamic interactions between limb segments during planar arm movement. Biol Cybern 44:67–77.

Holmes G (1939) The Cerebellum of Man. Brain 62:1–30.

Hoover JE, Strick PL (1999) The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. J Neurosci 19:1446–1463.

Kimura T, Gomi H (2009) Temporal development of anticipatory reflex modulation to dynamical interactions during arm movement. J Neurophysiol 102:2220–2231.

Kimura T, Haggard P, Gomi H (2006) Transcranial Magnetic Stimulation over Sensorimotor Cortex Disrupts Anticipatory Reflex Gain Modulation for Skilled Action. J Neurosci 26:9272–9281.

Krakauer JW (2009) Motor learning and consolidation: the case of visuomotor rotation. Adv Exp Med Biol 629:405–421.

Krakauer JW, Hadjiosif AM, Xu J, Wong AL, Haith AM (2019) Motor Learning. Compr Physiol 9:613–663.

Kurtzer I, Crevecoeur F, Scott SH (2014) Fast feedback control involves two independent processes utilizing knowledge of limb dynamics. J Neurophysiol 111:1631–1645.

Kurtzer I, Herter TM, Scott SH (2006a) Nonuniform distribution of reach-related and torque-related activity in upper arm muscles and neurons of primary motor cortex. J Neurophysiol

96:3220–3230.

Kurtzer IL (2014) Long-latency reflexes account for limb biomechanics through several supraspinal pathways. Front Integr Neurosci 8:99.

Kurtzer IL (2019) Shoulder reflexes integrate elbow information at “long-latency” delay throughout a corrective action. J Neurophysiol 121:549–562.

Kurtzer IL, Pruszynski JA, Scott SH (2008) Long-Latency Reflexes of the Human Arm Reflect an Internal Model of Limb Dynamics. Curr Biol 18:449–453.

Kurtzer I, Meriggi J, Parikh N, Saad K (2016) Long-latency reflexes of elbow and shoulder muscles suggest reciprocal excitation of flexors, reciprocal excitation of extensors, and reciprocal inhibition between flexors and extensors. J Neurophysiol 115:2176–2190.

Kurtzer I, Pruszynski JA, Herter TM, Scott SH (2006b) Primate upper limb muscles exhibit activity patterns that differ from their anatomical action during a postural task. J Neurophysiol 95:493–504.

Kurtzer I, Pruszynski JA, Scott SH (2009) Long-latency responses during reaching account for the mechanical interaction between the shoulder and elbow joints. J Neurophysiol 102:3004–3015.

Kurtzer I, Trautman P, Rasquinha RJ, Bhanpuri NH, Scott SH, Bastian AJ (2013) Cerebellar damage diminishes long-latency responses to multijoint perturbations. J Neurophysiol 109:2228–2241.

Lacquaniti F, Soechting JF (1984) Behavior of the stretch reflex in a multi-jointed limb. Brain Res 311:161–166.

Lacquaniti F, Soechting JF (1986a) Responses of mono- and bi-articular muscles to load perturbations of the human arm. Exp Brain Res 65:135–144.

Lacquaniti F, Soechting JF (1986b) EMG responses to load perturbations of the upper limb: effect of dynamic coupling between shoulder and elbow motion. Exp Brain Res 61:482–496.

Li CS, Padoa-Schioppa C, Bizzi E (2001) Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. Neuron 30:593–607.

Maeda RS, Cluff T, Gribble PL, Pruszynski JA (2017) Compensating for intersegmental dynamics across the shoulder, elbow, and wrist joints during feedforward and feedback control. J Neurophysiol 118:1984–1997.

Maeda RS, Cluff T, Gribble PL, Pruszynski JA (2018) Feedforward and feedback control share an internal model of the arm’s dynamics. J Neurosci 38:10505–10514.

Maeda RS, Gribble PL, Pruszynski JA (2020a) Learning new feedforward motor commands based on feedback responses. Curr Biol in press.

Maeda RS, Zdybal JM, Gribble PL, Pruszynski JA (2020b) Generalizing movement patterns

following shoulder fixation. J Neurophysiol 123:1193–1205.

Maeda RS, Zdybal JM, Gribble PL, Pruszynski JA (2020c) Explicit feedback and instruction do not change shoulder muscle activity reduction after shoulder fixation. bioRxiv. Available at: https://www.biorxiv.org/content/10.1101/2020.03.25.008466v1.

Mandelblat-Cerf Y, Paz R, Vaadia E (2009) Trial-to-trial variability of single cells in motor cortices is dynamically modified during visuomotor adaptation. J Neurosci 29:15053–15062.

Marsden CD, Merton PA, Morton HB (1976) Servo action in the human thumb. J Physiol 257:1–44.

Morrow MM, Pohlmeyer EA, Miller LE (2009) Control of Muscle Synergies by Cortical Ensembles. In: Progress in Motor Control: A Multidisciplinary Perspective (Sternad D, ed), pp 179–199. Boston, MA: Springer US.

Naufel S, Glaser JI, Kording KP, Perreault EJ, Miller LE (2019) A muscle-activity-dependent gain between motor cortex and EMG. J Neurophysiol 121:61–73.

Oby ER, Golub MD, Hennig JA, Degenhart AD, Tyler-Kabara EC, Yu BM, Chase SM, Batista AP (2019) New neural activity patterns emerge with long-term learning. Proc Natl Acad Sci U S A 116:15210–15215.

Omrani M, Pruszynski JA, Murnaghan CD, Scott SH (2014) Perturbation-evoked responses in primary motor cortex are modulated by behavioral context. J Neurophysiol 112:2985–3000.

Paz R, Boraud T, Natan C, Bergman H, Vaadia E (2003) Preparatory activity in motor cortex reflects learning of local visuomotor skills. Nat Neurosci 6:882–890.

Perich MG, Gallego JA, Miller LE (2018) A Neural Population Mechanism for Rapid Learning. Neuron 100:964–976.e7.

Picard N, Smith AM (1992) Primary motor cortical responses to perturbations of prehension in the monkey. J Neurophysiol 68:1882–1894.

Pruszynski JA (2014) Primary motor cortex and fast feedback responses to mechanical perturbations: a primer on what we know now and some suggestions on what we should find out next. Front Integr Neurosci 8:72.

Pruszynski JA, Kurtzer I, Lillicrap TP, Scott SH (2009) Temporal evolution of “automatic gain-scaling.” J Neurophysiol 102:992–1003.

Pruszynski JA, Kurtzer I, Nashed JY, Omrani M, Brouwer B, Scott SH (2011) Primary motor cortex underlies multi-joint integration for fast feedback control. Nature 478:387–390.

Pruszynski JA, Kurtzer I, Scott SH (2008) Rapid motor responses are appropriately tuned to the metrics of a visuospatial task. J Neurophysiol 100:224–238.

Pruszynski JA, Omrani M, Scott SH (2014) Goal-dependent modulation of fast feedback responses in primary motor cortex. J Neurosci 34:4608–4617.

Pruszynski JA, Scott SH (2012) Optimal feedback control and the long-latency stretch response.

Exp Brain Res 218:341–359.

Richardson AG, Borghi T, Bizzi E (2012) Activity of the same motor cortex neurons during repeated experience with perturbed movement dynamics. J Neurophysiol 107:3144–3154.

Russo AA, Bittner SR, Perkins SM, Seely JS, London BM, Lara AH, Miri A, Marshall NJ, Kohn A, Jessell TM, Abbott LF, Cunningham JP, Churchland MM (2018) Motor Cortex Embeds Muscle-like Commands in an Untangled Population Response. Neuron 97:953–966.e8.

Sadtler PT, Quick KM, Golub MD, Chase SM, Ryu SI, Tyler-Kabara EC, Yu BM, Batista AP (2014) Neural constraints on learning. Nature 512:423–426.

Scott SH (1997) Comparison of onset time and magnitude of activity for proximal arm muscles and motor cortical cells before reaching movements. J Neurophysiol 77:1016–1022.

Scott SH (1999) Apparatus for measuring and perturbing shoulder and elbow joint positions and torques during reaching. J Neurosci Methods 89:119–127.

Scott SH (2004) Optimal feedback control and the neural basis of volitional motor control. Nat Rev Neurosci 5:532–546.

Scott SH (2016) A Functional Taxonomy of Bottom-Up Sensory Feedback Processing for Motor Actions. Trends Neurosci 39:512–526.

Shadmehr R, Smith MA, Krakauer JW (2010) Error correction, sensory prediction, and adaptation in motor control. Annu Rev Neurosci 33:89–108.

Soechting JF, Lacquaniti F (1988) Quantitative evaluation of the electromyographic responses to multidirectional load perturbations of the human arm. J Neurophysiol 59:1296–1313.

Sussillo D, Churchland MM, Kaufman MT, Shenoy KV (2015) A neural network that finds a naturalistic solution for the production of muscle activity. Nat Neurosci 18:1025–1033.

Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor coordination. Nat Neurosci 5:1226–1235.

Vyas S, Even-Chen N, Stavisky SD, Ryu SI, Nuyujukian P, Shenoy KV (2018) Neural Population Dynamics Underlying Motor Learning Transfer. Neuron 97:1177–1186.e3.

Vyas S, O'Shea DJ, Ryu SI, Shenoy KV (2020) Causal Role of Motor Preparation during Error-Driven Learning. Neuron 106:1-11.

Wagner MJ, Kim TH, Kadmon J, Nguyen ND, Ganguli S, Schnitzer MJ, Luo L (2019) Shared Cortex-Cerebellum Dynamics in the Execution and Learning of a Motor Task. Cell 177:669–682.e24.

Wagner MJ, Smith MA (2008) Shared internal models for feedforward and feedback control. J Neurosci 28:10663–10673.

Wang T, Dordevic GS, Shadmehr R (2001) Learning the dynamics of reaching movements results in the modification of arm impedance and long-latency perturbation responses. Biol Cybern

85:437–448.

Wolpaw JR (1980) Amplitude of responses to perturbation in primate sensorimotor cortex as a function of task. J Neurophysiol 44:1139–1147.

Wolpert DM, Kawato M (1998) Multiple paired forward and inverse models for motor control. Neural Netw 11:1317–1329.

Wolpert DM, Miall RC, Kawato M (1998) Internal models in the cerebellum. Trends Cogn Sci 2:338–347.

Yousif N, Diedrichsen J (2012) Structural learning in feedforward and feedback control. J Neurophysiol 108:2373–2382.

Zhou X, Tien RN, Ravikumar S, Chase SM (2019) Distinct Types of Neural Reorganization During Long-Term Learning. J Neurophysiol 121:1329–1341.