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## Context-dependent inhibition of unloaded muscles during the long-latency epoch

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**Nashed JY, Kurtzer IL, Scott SH.** Context-dependent inhibition of unloaded muscles during the long-latency epoch. *J Neurophysiol* 113: 192–202, 2015. First published October 1, 2014; doi:10.1152/jn.00339.2014.—A number of studies have highlighted the sophistication of corrective responses in lengthened muscles during the long-latency epoch. However, in various contexts, unloading can occur, which requires corrective actions from a shortened muscle. Here, we investigate the sophistication of inhibitory responses in shortened muscles due to unloading. Our first experiment quantified the inhibitory responses following an unloading torque that displaced the hand either into or away from a peripheral target. We observed larger long-latency inhibitory responses when perturbed into the peripheral target compared with away from the target. In our second experiment, we characterized the degree of inhibition following unloading with respect to different levels of preperturbation muscle activity. We initially observed that the inhibitory activity during the short-latency epoch scaled with increased levels of preperturbation muscle activity. However, this scaling peaked early in the R2 epoch (~50 ms) but then quickly diminished through the rest of the long-latency epoch. Finally, in *experiment 3*, we investigated whether inhibitory perturbation responses consider intersegmental dynamics of the limb. We quantified unloading responses for either pure shoulder or pure elbow torques that evoked similar motion at the shoulder but different elbow motion. The long-latency inhibitory response in the shoulder, unlike the short-latency, was greater for the shoulder torque compared with the response following an elbow torque, as previously observed for a loading response. Taken together, these results illustrate that the long-latency unloading response is capable of a similar level of complexity as observed when loads are applied to the limb.

feedback; unloading; inhibition; long-latency; stretch response

COUNTERING MECHANICAL DISTURBANCES during motor actions often requires corrective responses from the lengthening muscle such as when someone bumps your arm when reaching toward an object in the environment. It is well-known that mechanical perturbations applied to the limb or joint evoke a stereotypical pattern of muscle activity in a loaded muscle that is commonly divided into two components: the short-latency (20–45 ms) and the long-latency (50–105 ms) response (Hammond 1956; Lee and Tatton 1975). A wealth of studies over the last 50 years has uncovered the neural substrates and relative capabilities of these two fast muscle responses. In brief, the short-latency response is generated by the spinal cord and is relatively inflexible, whereas the long-latency response in-

cludes contributions from a transcortical feedback pathway and displays capabilities comparable with voluntary action (for review, see Pruszynski and Scott 2012).

Corrective responses commonly require increases in muscle activity generated by applied loads. However, in many behavioral contexts, unloading can occur. For example, a waiter holding a tray of food must rapidly respond if a second server unexpectedly removes objects from the tray. In this situation, afferents in the inactive muscle increase their activity during the unloading, whereas afferents in the active muscle reduce their activity or may even become silent.

Previous work has shown that unloading can initiate activity in a preinhibited, stretched muscle during the long-latency time period (Crevecoeur et al. 2013; Pruszynski et al. 2009). However, it is less clear how the shortened but still loaded muscle contributes during unloading. The problem is that unloading of the limb can quickly silence (reduce activity to 0) the shortened muscle during the short- and long-latency time periods. One possibility is that long-latency inhibitory response in the shortened muscle also expresses task-dependent responses. In this case, both agonist and antagonist muscles contribute to the corrective response. However, previous work has noted a rapid inhibitory response during unloading of a transient perturbation (Kurtzer et al. 2010). This inhibitory response occurs within 30 ms of unloading and can terminate either short- or long-latency responses. Such a powerful spinal inhibitory response may always occur during unloading and not just at the end of a transient load. In this case, context-dependent responses to unloading would only be generated by the initially inactive stretched muscle.

There are only a few studies that have examined unloading responses, although in many cases they have focused on steady state responses well beyond the long-latency time period using the “do not intervene” paradigm (Archambault et al. 2005; Asatryan and Feldman 1965; Levin and Dimov 1997). Two studies have examined the potential flexibility of rapid inhibitory responses during unloading, but they have generally failed to observe any modulation based on verbal instruction (Angel and Weinrich 1986; Miscio et al. 2001). However, failure to observe task-dependent inhibitory responses during unloading may reflect features of the task design. The use of short force pulses (Angel and Weinrich 1986) commonly fails to elicit long-latency and voluntary responses (Kurtzer et al. 2010; Lee and Tatton 1982). As well, limited preexcitation of the shortened muscle (Miscio et al. 2001) will make it more difficult to quantify any inhibitory response reliably.

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Here, we examine whether inhibitory responses during the long-latency epoch modulate according to task demands as observed for excitatory responses. In each experiment, we preexcited the muscle and used a small step-down perturbation to maximize the opportunity to observe task-dependent inhibitory responses. In our first experiment, we examined whether long-latency inhibitory responses are modulated by the location of the spatial goal when the unloading instructs the subject to attain that spatial goal (Pruszynski et al. 2008). In our second experiment, we examined whether long-latency inhibitory responses appropriately compensate for changes in preperturbation muscle activity (Pruszynski et al. 2009). In our final experiment, we examined whether unloading responses consider intersegmental dynamics of the limb (Kurtzer et al. 2008, 2009; Pruszynski et al. 2011). Specifically, we examined whether elbow or shoulder unloading, both of which deviated the shoulder by similar amounts, influenced the long-latency inhibitory response of shoulder muscles. Our results illustrate that, like excitatory responses, inhibitory responses during unloading are task-dependent and consider the influence of limb dynamics.

## METHODS

### Participants

A total of 16 subjects (10 men and 6 women, aged 22–34 yr) participated in 1 of 2 experimental sessions. Eight subjects participated in the first experimental session, which consisted of *experiment 1*. Eight additional subjects participated in the second experimental session, consisting of both *experiments 2* and *3*, which were interleaved. All subjects were neurologically healthy and gave informed, written consent according to a protocol approved by the Queen's University Research Ethics Board. Experiments lasted ~2 h, and subjects were financially compensated for their time.

### Apparatus and Experimental Design

Experiments used a robotic device (KINARM Exoskeleton; BKIN Technologies, Kingston, Ontario, Canada) permitting elbow and shoulder movement in the horizontal plane (Scott 1999). In addition to recording flexion/extension movement of each joint, the KINARM robot can displace the arm by applying joint or hand-based mechanical loads. Projected target lights and hand feedback (radius = 0.2 cm) were presented in the plane of the arm using a television monitor and a semitransparent mirror. A physical barrier occluded direct vision of the hand.

### Experiment 1: Influence of Target Location

We modified the experimental paradigm of Pruszynski et al. (2008) to examine whether unloading elicits rapid target-dependent modulation of the muscle activity in a shortened muscle. All trials began with the gradual onset (rise time = 500 ms) of a background load of  $\pm 3$  Nm that elicited either elbow flexor or extensor muscle activity. Subjects ( $n = 8$ ) were required to counter the background load and maintain their hand within a small circular start target (radius = 0.3 cm) such that the shoulder and elbow were positioned at 45 and 90°, respectively. Subjects were presented with a peripheral target (radius = 20 cm) positioned orthogonal to the forearm either to the right or left side of their hand (Fig. 1A). Movement toward the peripheral target required elbow extension or flexion for the left or right targets, respectively. Following a random hold period within the start target (1–4 s), visual feedback of the hand was removed and a rapid step-torque perturbation of  $\pm 1.25$  Nm was applied to the elbow,

which displaced the hand either into or away from the peripheral target. Subjects were instructed not to anticipate the perturbations. Following perturbation onset, subjects were instructed to move into the peripheral target as accurately and rapidly as possible and maintain their hand in the peripheral target for 1,000 ms postperturbation. On trial completion, subjects were notified as to whether they attained predetermined speed and accuracy criteria through visual feedback of the peripheral target. Trials were deemed successful when the hand entered the peripheral target in  $< 300$  ms postperturbation (peripheral target filled green). Failures occurred when the hand entered the peripheral target  $> 300$  ms postperturbation (peripheral target filled red). Trials were presented in a random order (perturbations toward or away from the goal target) so subjects could not anticipate the perturbation onset or direction. Furthermore, the placement of the peripheral target was also randomly chosen for each trial. Subjects performed 30 successful repeats of each condition (2 muscles, 2 targets, and 2 perturbation directions) for a total of 240 trials. Although subjects could rest at any time, breaks were enforced every 80 correct trials. The experiment lasted ~2 h.

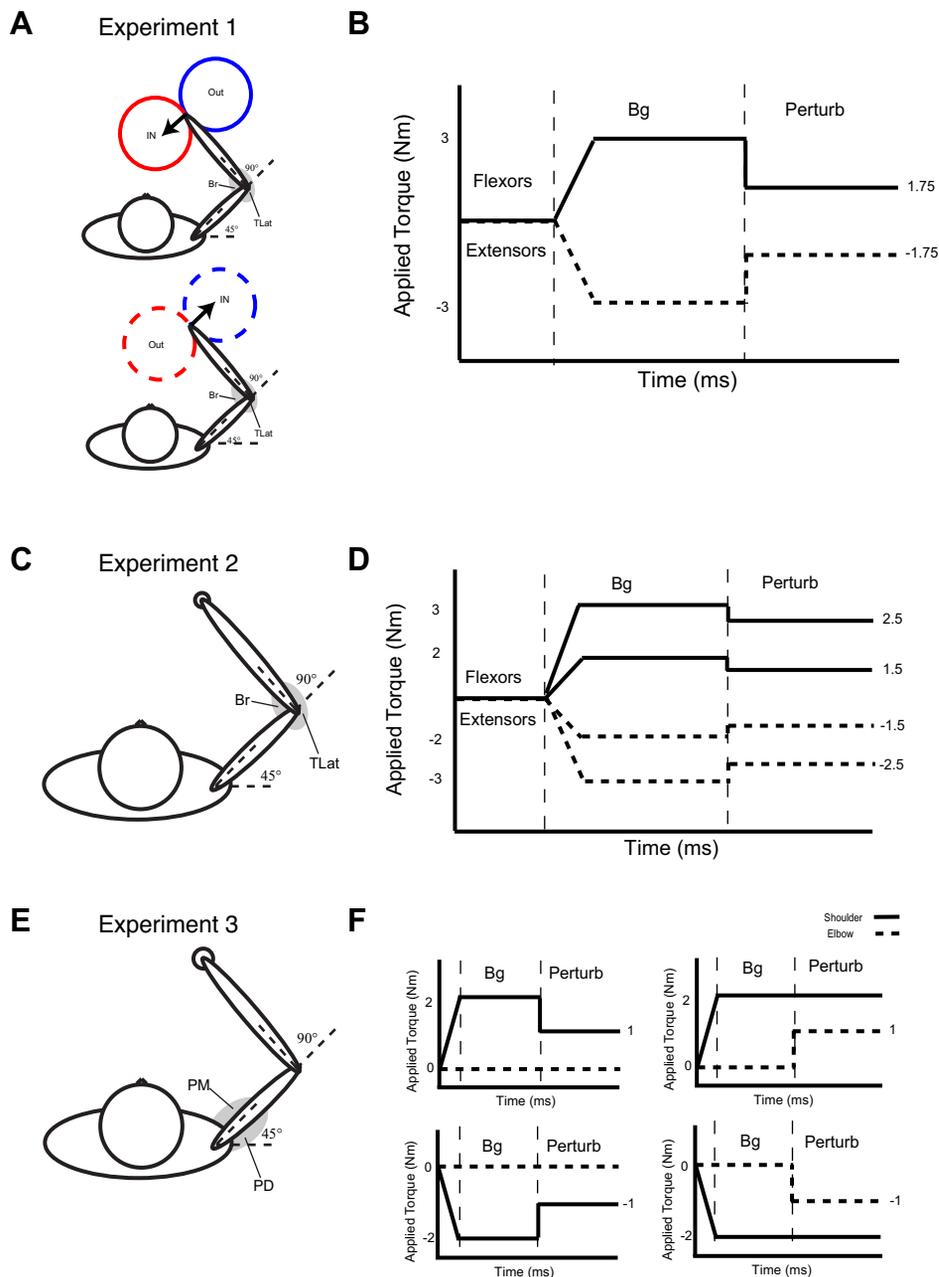
### Experiment 2: Influence of Preperurbation Muscle Activity

We modified the experimental paradigm of Pruszynski et al. (2009) to examine whether muscle activity following unloading is related to the magnitude of the preperturbation muscle activity. All trials began with the gradual onset (rise time = 500 ms) of a background load ( $\pm 2$  or  $\pm 3$  Nm at the elbow) to elicit elbow flexor or extensor muscle activity. Subjects ( $n = 8$ ) were required to stabilize against the background load and maintain their hand within a small circular start target (radius = 0.5 cm) such that the shoulder and elbow were positioned at 45 and 90°, respectively. After a random hold period within the start target (1–4 s), visual feedback of the hand was removed and a rapid unloading step-torque perturbation of 0.25 Nm was applied to the elbow. The unloading perturbation magnitude was chosen to ensure that muscle activity did not saturate, that is, evoke zero muscle activity (i.e., completely inhibited). Subjects were instructed not to anticipate the perturbations and to avoid cocontraction before the perturbation. Following perturbation onset, subjects were instructed to return to the start target as accurately and rapidly as possible and stabilize for 800 ms postperturbation. On trial completion, subjects were notified as to whether they attained predetermined speed and accuracy criteria through visual feedback of the start target. Trials were deemed successful when the hand entered the peripheral target in  $< 700$  ms postperturbation (peripheral target filled green). Failed trials occurred when the hand entered the peripheral target  $> 700$  ms postperturbation (peripheral target filled red). Similar to *experiment 1*, trials were presented in a random order and subjects performed 30 successful repeats of each condition (2 muscles and 2 background loads) for a total of 120 trials.

### Experiment 3: Influence of Limb Mechanics

We modified the experimental paradigm of Kurtzer et al. (2008) to examine whether shoulder muscle activity following unloading reflects the underlying torques that produce movement. All trials began with the gradual onset (rise time = 500 ms) of a background load ( $\pm 2$  Nm at the shoulder) that elicited either shoulder flexor or extensor muscle activity. Subjects ( $n = 8$ ) were required to stabilize against the background load and maintain their hand within a small circular start target (radius = 1 cm) such that the shoulder and elbow were positioned at 45 and 90°, respectively. After a random hold period within the start target (1–4 s), visual feedback of the hand was removed and an unloading step-torque perturbation of  $\pm 1$  Nm was applied to either the elbow or shoulder. The applied unloading torque produced similar shoulder movements but different degrees of elbow movement. Subjects were instructed not to anticipate the perturbations and to avoid any cocontraction. Following perturbation onset, subjects

Fig. 1. Task apparatus and experimental setup. *A: experimental 1* setup: the top and bottom figure represent the elbow flexor and extensor conditions, respectively. Initially, subjects were presented with a start target (radius = 0.3 cm). The start target was located such that the elbow and shoulder angles were located at 90 and 45°, respectively. Subjects were presented with 1 of 2 large peripheral targets (radius = 20 cm) located to the left or right of the start target (radius = 0.3 cm). Peripheral target location was chosen such that applied flexion or extension elbow torques deviated the hand either into (IN) or away from (OUT) the target. Br, brachioradialis; TLat, lateral triceps. *B: schematic* of applied loads: a background load (Bg) of  $\pm 3$  Nm was slowly introduced (ramp up = 250 ms), which primed either the elbow flexors (solid line) or extensors (dotted line). After a random hold period (1–4 s), a 1.25-Nm unloading perturbation (Perturb) was applied. *C: experimental 2* setup: subjects were presented with a visual target (radius = 0.5 cm) positioned such that the elbow and shoulder angles were located at 90 and 45°, respectively. Subjects were required to return to maintain their hand within the visual target after perturbation onset. *D: schematic* of applied loads: 1 of 2 background loads of either  $\pm 2$  or  $\pm 3$  Nm was slowly introduced (ramp up = 250 ms), which primed either the elbow flexors (solid line) or extensors (dotted line). After a random hold period (1–4 s), a 0.5-Nm unloading perturbation was applied. *E: experimental 3* setup: subjects were presented with a visual target (radius = 1 cm) positioned such that the elbow and shoulder angles were located at 90 and 45°, respectively. Subjects were required to return to maintain their hand within the visual target after perturbation onset. PM, pectoralis major; PD, posterior deltoid. *F: schematic* of multijoint loads applied in each experimental condition: a background load of  $\pm 2$  Nm was slowly introduced (solid line; ramp up = 250 ms), which primed either the shoulder flexors or extensors. After a random hold period (1–4 s), a 1-Nm unloading perturbation was applied to either the shoulder or elbow (dashed line).



were instructed to return to the start target as accurately and rapidly as possible and stabilize for 800 ms postperturbation. On trial completion, subjects were notified as to whether they attained predetermined speed and accuracy criteria through visual feedback of the start target. Trials were deemed successful when the hand entered the peripheral target in  $<700$  ms postperturbation (peripheral target filled green). Failed trials occurred when the hand entered the peripheral target  $>700$  ms postperturbation (peripheral target filled red). Trials were presented in a random order and were interleaved with *experiment 2*. Subjects performed 30 successful repeats of each condition (2 muscles and 2 background loads) for a total of 120 trials. Breaks were enforced every 40 correct trials, and the session lasted 2 h.

### Muscle Recordings

Surface electromyographic (EMG) recordings were obtained from 2 elbow muscles in *experiments 1* and 2, the lateral triceps (an elbow extensor) and brachioradialis (an elbow flexor). In *experiment 3*, we

collected muscle activity from 2 shoulder muscles, posterior deltoid (a shoulder extensor) and pectoralis major (a shoulder flexor). Full details of the procedures are described in our earlier study (Nashed et al. 2012).

### Data Analysis

**Filtering and normalization.** All data were aligned on perturbation onset. Muscle activity was normalized according to the procedures from previous studies. For *experiment 1*, the EMG of each muscle was normalized to its mean response during the preperturbation stabilization period in the start target in which the muscle actively countered a 3-Nm load. For *experiment 2*, EMG was normalized to the mean response obtained from a small normalization block at the end of the experimental session in which subjects maintained a constant posture against the  $\pm 1$ -Nm torques applied to the elbow. For *experiment 3*, the EMG of each muscle was normalized to its mean response during the preperturbation stabilization hold period in the start target when

the muscle actively countered a 2-Nm load. In all cases, the normalization window was a length of 100 ms. Full details of the filtering procedures are described in our earlier studies (Nashed et al. 2012, 2014; Pruszynski et al. 2008).

**Kinematics.** We used a receiver operating characteristic (ROC) technique to determine when the hand, elbow, and shoulder positions were reliably different between experimental conditions (Green and Swets 1974). For each time step (1 ms), we generated an ROC curve representing the probability of discrimination between the two movements for the same perturbation to different target locations. Values of 0 and 1 indicate perfect discrimination, whereas a value of 0.5 indicates performance at chance. We determined that movement was reliably different when the ROC curve surpassed a threshold of 0.75 for 5 ms consecutively. We generated an ROC curve for each subject, which were then used to produce a mean ROC across subjects to determine kinematic differences between experimental conditions. Furthermore, in *experiment 1*, we quantified the terminal hand position (350 ms postperturbation) using principal component analysis to generate 95% confidence ellipses of final hand position (Pruszynski et al. 2008).

### Muscle Activity

Perturbation-related response epochs to quantify muscle activity were based on earlier reports: baseline (pre) = -100 to 0; R1 = 20–45 ms; R2 = 45–75 ms; R3 = 75–105 ms; and early voluntary = 105–135 (Crago et al. 1976; Lee and Tatton 1975; Mortimer et al. 1981; Nakazawa et al. 1997; Nashed et al. 2012, 2014; Pruszynski et al. 2008). The early voluntary epoch was chosen such that it was similar in size (30 ms) to the long-latency epochs.

Our experimental design allowed us to make straightforward comparisons between conditions to determine whether inhibitory responses were modulated as a function of task demands. Specifically, *t*-tests using subject means were used to determine changes in muscle activity across experimental conditions. Additionally, we used the ROC technique to determine when the muscle activity was reliably different between experimental conditions.

**Gain-scaling.** We defined gain-scaling (GS) as 1 plus the change in the evoked response for the same perturbation across background loads normalized by the difference in preperturbation muscle activity between these background loads. Note that this equation is a modified version of the equation reported in Pruszynski et al. (2009) and can be used to quantify GS of both excitatory and inhibitory responses. In the present manuscript, we calculated the GS across a 2- and 3-Nm background load with a 0.25-Nm unloading perturbation:

$$GS = 1 + \frac{\text{abs}[\Delta A(t)_{bg3} - \Delta A(t)_{bg2}]}{[A(\text{pre})_{bg3} - A(\text{pre})_{bg2}]}$$

where  $\Delta A(t)$  is the change in evoked muscle activity relative to the preperturbation muscle activity at a particular time,  $A(\text{pre})$  is the mean preperturbation muscle activity, and the subscripts refer to the background load level (bg). Note that GS of 1 signifies no effect of background load on the inhibitory activity, that is, no GS.

## RESULTS

### Experiment 1: Influence of Target Location

This experiment examined whether unloading elicits rapid target-dependent inhibition within the shortened muscle. Subjects had little difficulty learning and completing the task. Unloading joint torques applied to the elbow caused multijoint movement that ultimately deviated the hand from the start target either into (IN) or away from (OUT) a peripheral target (Fig. 1A). Figure 2A illustrates the mean hand paths and endpoint variability across all subjects for the IN and OUT conditions following the application of an elbow extension torque. Although the hand paths initially overlapped considerably, they rapidly deviated within 5 cm of the initial limb position and with significantly different terminal hand positions. We used ROC analysis to quantify the timing of the corrective actions in the shoulder and elbow motions following an elbow extensor torque (Fig. 2B). We observed target-

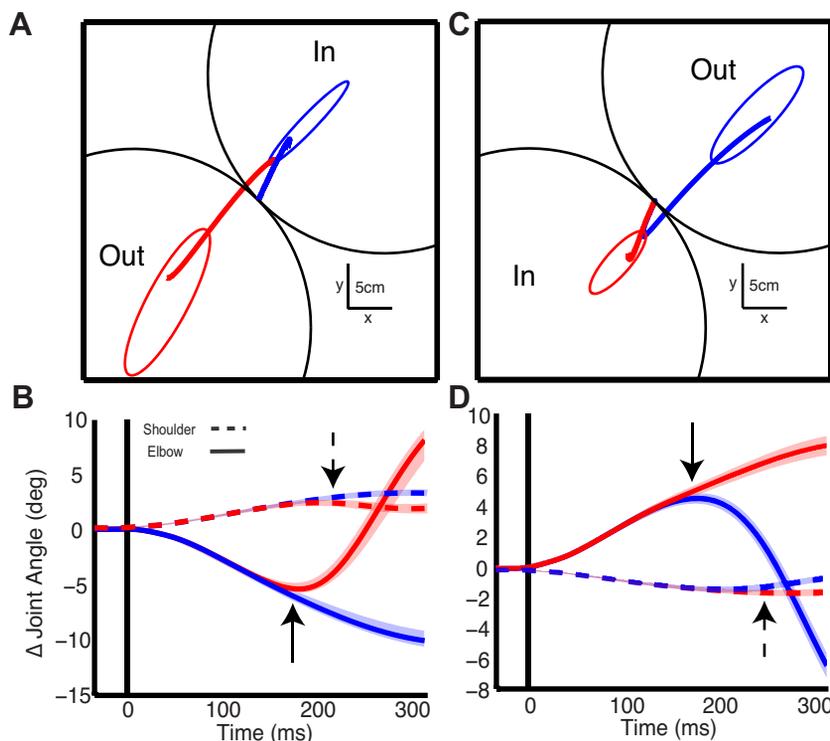


Fig. 2. *Experiment 1* hand and joint kinematics. **A:** traces correspond to the mean hand movement across subjects from the IN (blue) and OUT (red) conditions for extensor unloading. Endpoint ellipses represent the SD of hand position 300 ms postperturbation. **B:** traces represent the mean change in elbow (solid) and shoulder (dashed) motion for the extensor unloading for the IN (blue) and OUT (red) target conditions. Data are aligned to perturbation onset, and the vertical line (0 ms) represents perturbation onset. The solid and dashed arrows indicate the 1st point of statistical difference of elbow and shoulder movement, respectively, determined by the receiver operating characteristic (ROC). deg, Degrees. **C:** traces correspond to the mean hand movement across subjects from the IN (red) and OUT (blue) conditions for flexor unloading. Endpoint ellipses represent the SD of hand position 300 ms postperturbation. **D:** joint kinematics of elbow and shoulder for flexor unloading: traces represent the mean change in elbow (solid) and shoulder (dashed) motion for the flexor unloading for the IN (red) and OUT (out) target conditions. The solid and dashed arrows indicate the 1st point of statistical difference of elbow and shoulder movement, respectively, determined by the ROC analysis.

dependent differences at  $188 \pm 19$  and  $210 \pm 31$  ms for the elbow and shoulder, respectively. Similar results were observed following flexor unloading torque perturbations (Fig. 2C). ROC analysis revealed target-dependent changes at  $181 \pm 24$  and  $241 \pm 46$  ms for the elbow and shoulder, respectively (Fig. 2D).

The effects of elbow extensor unloading produced a decrease in muscle activity of the preexcited lateral triceps and an increase in muscle activity of the preinhibited brachioradialis (Fig. 3). Brachioradialis produced no significant differences in muscle activity related to target location during the R1 epoch [Fig. 3, A and B;  $t_{(9)} = 0.82$ ,  $P = 0.433$ ]. In contrast, the R2, R3, and voluntary epochs were all elevated from baseline and exhibited larger increases for the OUT compared with the IN target [R2:  $t_{(9)} = 2.41$ ,  $P = 0.04$ ; R3:  $t_{(9)} = 2.54$ ,  $P = 0.03$ ; voluntary:  $t_{(9)} = 4.12$ ,  $P < 0.01$ ]. Target-dependent differences started at  $52 \pm 8$  ms using ROC analysis (Fig. 3C).

As mentioned above, extensor unloading resulted in a shortening of the lateral triceps, producing a decrease in its muscle activity. The onset of inhibition began at  $\sim 20$  ms at the start of

the R1 epoch (Fig. 3, D and E), but there were no target-dependent changes [ $t_{(9)} = 0.51$ ,  $P = 0.62$ ; Fig. 3F]. However, the R2, R3, and voluntary epochs [R2:  $t_{(9)} = 2.33$ ,  $P = 0.04$ ; R3:  $t_{(9)} = 2.72$ ,  $P = 0.02$ ; voluntary:  $t_{(9)} = 3.61$ ,  $P < 0.01$ ] all exhibited target-dependent modulation such that muscle activity in the IN condition produced more inhibition than the OUT condition. ROC analysis revealed target-dependent differences starting at  $58 \pm 14$  ms postperturbation (Fig. 3F).

We found essentially the same results for the flexor unloading perturbation, which stretched the preinhibited lateral triceps and shortened the preexcited brachioradialis. Excitation in lateral triceps began at  $\sim 20$  ms but did not display any target dependency until the R2, R3, and voluntary response [R1:  $t_{(9)} = 0.98$ ,  $P = 0.352$ ; R2:  $t_{(9)} = 2.77$ ,  $P = 0.02$ ; R3:  $t_{(9)} = 2.78$ ,  $P = 0.02$ ; voluntary:  $t_{(9)} = 2.98$ ,  $P = 0.02$ ]. Differences in the amount of inhibition for the two targets began at  $53 \pm 13$  ms (ROC analysis). In brachioradialis, rapid inhibition occurred at  $\sim 20$  ms, but there were no target-dependent differences in the R1 epoch [R1:  $t_{(9)} = 1.11$ ,  $P = 0.295$ ]. We again observed significantly greater inhibition in the R2, R3, and voluntary

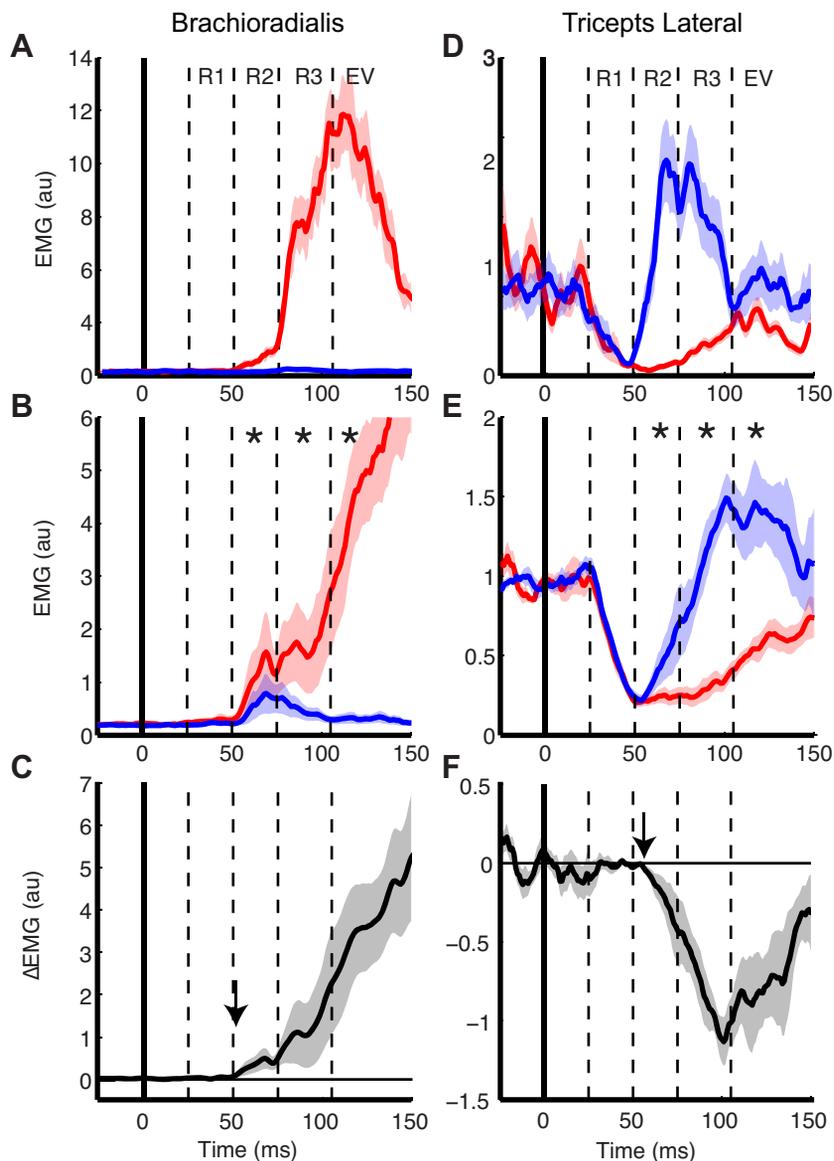


Fig. 3. Muscle activity of brachioradialis (left column) and triceps lateral (right column) following extensor unloading in *experiment 1*. **A**: mean and SE brachioradialis muscle activity from an exemplar subject aligned to perturbation onset (vertical line); blue and red traces indicate the mean muscle activity for the IN and OUT conditions, respectively. R1, 20–45 ms; R2, 45–75 ms; R3, 75–105 ms; EV, early voluntary; EMG, electromyography; au, arbitrary units. **B**: mean (solid) and SE (shaded) brachioradialis muscle activity of the group ( $*P < 0.05$ ). **C**: difference in muscle activity between the 2 responses in **B** (mean  $\pm$  SE). The arrow indicates the 1st point of significance determined by ROC analysis. **D**: mean and SE triceps lateral muscle activity from an exemplar subject aligned to perturbation onset (vertical line); blue and red traces indicate the mean muscle activity for the IN and OUT conditions, respectively. **E**: mean (solid) and SE (shaded) triceps lateral muscle activity of the group ( $*P < 0.05$ ). **F**: difference in muscle activity between the 2 responses in **E** (mean  $\pm$  SE). The arrow indicates the 1st point of significance determined by ROC analysis.

epochs [R2:  $t_{(9)} = 2.37$ ,  $P = 0.04$ ; R3:  $t_{(9)} = 3.10$ ,  $P = 0.01$ ; voluntary:  $t_{(9)} = 3.77$ ,  $P < 0.01$ ] for the IN compared with the OUT target, which began at  $54 \pm 6$  ms.

### Experiment 2: Influence of Preperturbation Muscle Activity

Here, we examined how the level of background muscle activity influenced inhibitory responses during unloading. An unloading torque was applied to the elbow that produced a shortening of the preexcited muscle. Similar to *experiment 1*, subjects had little difficulty learning and completing the task.

Figure 4A illustrates mean hand paths across all subjects for both the flexor and extensor unloading torques for each background load. ROC analysis revealed a small but significant difference in elbow motion for different background loads. Differences in elbow motion during unloading were observed between the 2- and 3-Nm background loads at  $131 \pm 24$  ms for flexor unloading and  $149 \pm 21$  ms for extensor unloading (Fig. 4C).

We observed rapid inhibition in lateral triceps that again began in the R1 epoch for each unloading (Fig. 5, A and B). Figure 5, A and B, illustrates the unloading responses of an individual subject and the group, respectively. Critically, inhibition never saturated, that is, motor responses never decreased to zero muscle activity (Fig. 5, A and B;  $P > 0.05$ ). Figure 5C illustrates the amount of inhibition in the 2- and 3-Nm conditions after subtracting the preperturbation muscle activity. We quantified the amount of GS and observed a significant increase in inhibition with increased preperturbation muscle activity (Fig. 5D). We found significant GS began in the R1 epoch [R1:  $t_{(7)} = 5.26$ ,  $P < 0.01$ ] and was maintained in the R2 epoch [R2:  $t_{(7)} = 5.63$ ,  $P < 0.01$ ] before rapidly reducing in the R3 epoch [R3:  $t_{(7)} = 4.97$ ,  $P < 0.01$ ]. GS was effectively diminished at the onset of the voluntary epoch [Fig. 5, C and D;  $t_{(7)} = 0.51$ ,  $P = 0.62$ ].

Similar results were observed in the flexor unloading condition. Specifically, we observed that GS began in the R1 epoch [R1:  $t_{(7)} = 4.81$ ,  $P < 0.01$ ], which was maintained in the R2 epoch [R2:  $t_{(7)} = 6.81$ ,  $P < 0.01$ ] before reducing in the R3 epoch [R3:  $t_{(7)} = 5.05$ ,  $P < 0.01$ ]. There was no significant GS in the voluntary epoch [ $t_{(7)} = 0.64$ ,  $P = 0.54$ ].

### Experiment 3: Influence of Limb Mechanics

This experiment examined whether muscle activity in the shoulder following unloading reflects the underlying torques that produce movement. Similar to the experiments above, subjects were introduced to a background load that preexcited either the shoulder flexors or extensors. Unloading torques were applied at either the shoulder or elbow, such that the preexcited shoulder muscle was shortened. These perturbations resulted in kinematic deviations that displaced the hand from the initial start target (Fig. 6, A and D). Subjects readily countered the perturbations and easily returned the hand to the target. Critically, the applied shoulder or elbow torques each induced a similar amount of (shortening) shoulder joint motion (Fig. 6B) but resulted in different degrees of elbow motion (Fig. 6C).

By unloading either the shoulder extensors or elbow flexors, we induced similar amounts of shoulder extension (Fig. 6, B and C). ROC analysis confirmed that both unloading torques evoked similar amounts of shoulder extension motion within

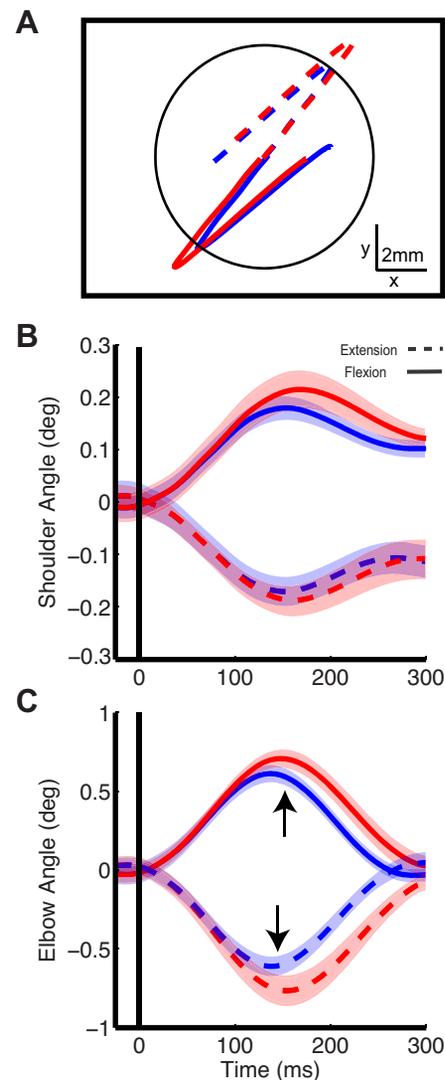


Fig. 4. *Experiment 2* hand and joint kinematics. A: traces correspond to the mean hand movement across subjects from the flexor (solid) and extensor (dashed) unloading for both the small (blue) and large (red) background loads. Red and blue traces correspond to the small and large background loads, respectively. B: traces represent the mean ( $\pm$  SE) change in shoulder (dashed) motion following the flexor (solid) and extensor (dashed) unloading conditions. Red and blue traces correspond to the small and large background loads, respectively. Data are aligned to perturbation onset (vertical line). Note: ROC analysis did not determine a point of significance between the different background loads for both the flexor and extensor groups. C: traces represent the mean change in elbow (dashed) motion following the flexor (solid) and extensor (dashed) unloading conditions. Red and blue traces correspond to the small and large background loads, respectively. Data are aligned to perturbation onset (vertical line). The arrows indicate the 1st point of significance between background loads following unloading determined by ROC analysis.

the 1st  $200 \pm 14$  ms (Fig. 6B). In contrast, differences in elbow motion were observed as early as  $23 \pm 6$  ms (Fig. 6C). The evoked shoulder extension movement resulted in a stretch of the preinhibited pectoralis major muscle (Fig. 7, A and B). Consistent with our previous studies, the perturbations failed to produce significant torque-related modulation in the R1 epoch [R1:  $t_{(7)} = 0.48$ ,  $P = 0.65$ ]. However, muscle activity during the R2, R3, and voluntary epochs all exhibited increases for the shoulder unloading torque relative to the elbow unloading torque [R2:  $t_{(9)} = 2.39$ ,  $P = 0.04$ ; R3:  $t_{(9)} = 2.89$ ,  $P = 0.02$ ; voluntary:

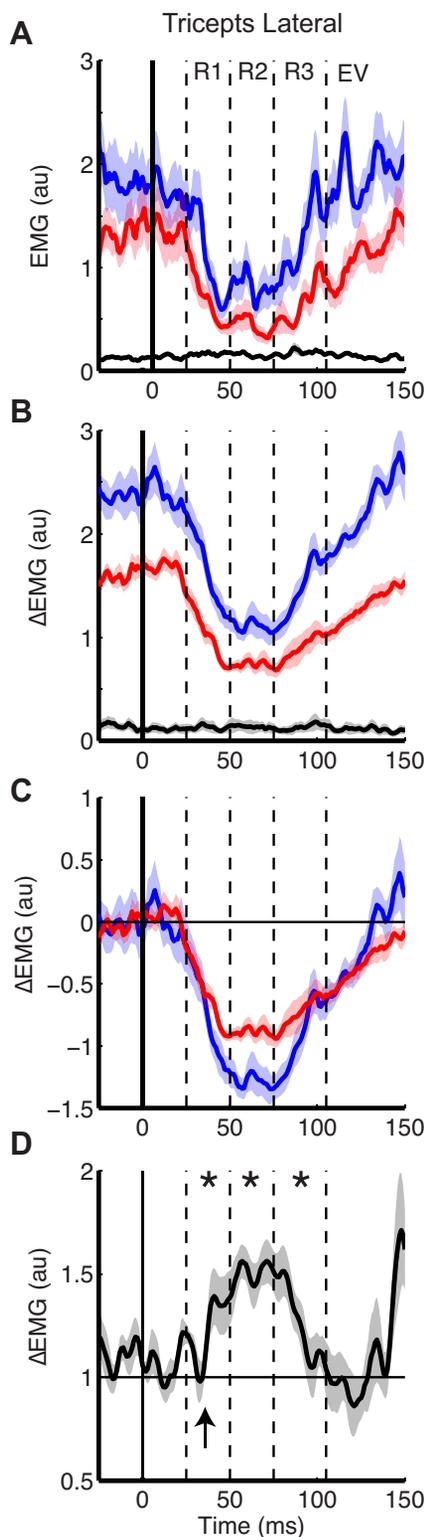


Fig. 5. Muscle activity of triceps lateral following extensor unloading in *experiment 2*. *A*: mean and SE triceps lateral muscle activity from an exemplar subject aligned to perturbation onset (vertical line); red and blue traces indicate the mean muscle activity for the small and large background load conditions, respectively. The black line indicates the muscle activity of triceps lateral when brachioradialis is loaded. *B*: mean (solid) and SE (shaded) triceps lateral muscle activity of the group. *C*: same as *B* except baseline reduced. *D*: difference in muscle activity between the 2 responses in *B* (mean  $\pm$  SE). The arrow indicates the 1st point of significance determined by ROC analysis (\* $P < 0.05$ ).

$t_{(9)} = 3.03, P = 0.01$ ]. The onset of these task-specific changes in muscle activity occurred at  $54 \pm 6$  ms (Fig. 7C).

We were most interested in the inhibitory responses observed in the preexcited shoulder muscle (posterior deltoid). The inhibition occurred in the R1 epoch but failed to show any torque-related differences [Fig. 7, *D* and *E*; R1:  $t_{(7)} = 0.67, P = 0.52$ ]. In contrast, we observed torque-related differences in the subsequent epochs, beginning at  $46 \pm 9$  ms, with greater modulation related to the shoulder unloading torque compared with the elbow torque [Fig. 7F; R2:  $t_{(9)} = 3.11, P = 0.01$ ; R3:  $t_{(9)} = 3.21, P = 0.01$ ; voluntary:  $t_{(9)} = 3.22, P = 0.01$ ].

We found essentially the same results for the unloading torques that evoked shoulder flexion that stretched the preinhibited posterior deltoid and shortened the preexcited pectoralis major. Similar to above, the reduction of either the shoulder flexion torque or elbow extension torque resulted in similar amounts of shoulder flexion motion over the  $1st\ 228 \pm 22$  ms postperturbation (Fig. 6E). In contrast, differences in elbow motion were evident at  $22 \pm 4$  ms postperturbation (Fig. 6F). We failed to observe torque-related differences in the R1 response of the preinhibited muscle (posterior deltoid) that was stretched [R1:  $t_{(7)} = 0.78, P = 0.46$ ]. In contrast, the R2, R3, and voluntary epochs all exhibited increases in muscle activity that were consistently larger following a shoulder torque compared with the elbow torque [R2:  $t_{(9)} = 2.91, P = 0.02$ ; R3:  $t_{(9)} = 2.95, P = 0.02$ ; voluntary:  $t_{(9)} = 3.01, P = 0.02$ ]. We observed task-specific changes in muscle activity related to the underlying applied torques that occurred at  $52 \pm 7$  ms.

Although rapid inhibition occurred during the R1 epoch, we failed to observe torque-related modulation of the shortened preexcited muscle (pectoralis major) during this time frame [R1:  $t_{(7)} = 0.80, P = 0.45$ ]. However, the R2, R3, and voluntary epochs all modulated significantly and displayed greater inhibition for unloading shoulder torques compared with unloading elbow torques [R2:  $t_{(9)} = 3.02, P = 0.02$ ; R3:  $t_{(9)} = 3.15, P = 0.02$ ; voluntary:  $t_{(9)} = 3.33, P = 0.01$ ]. The onset of this task-specific modulation occurred at approximately  $51 \pm 5$  ms.

## DISCUSSION

Many studies have examined the sophistication of evoked activity in lengthened muscles following loading of the arm (Crago et al. 1976; Day et al. 1991; Hammond 1956; Kimura and Gomi 2009; Lacquaniti and Soechting 1984; Lewis et al. 2006, 2010; Pruszynski and Scott 2012; Rothwell et al. 1980; Shemmell et al. 2009, 2010; Soechting and Lacquaniti 1988). Here, we examined whether similar responses occurred when an active muscle was abruptly unloaded. In all cases, the unloading elicited inhibition of the shortened muscle that began during the short-latency epoch. We showed that inhibitory responses during the short-latency epoch were relatively fixed and only modulated with changes in the level of pre-perturbation muscle activity (*experiment 2*). In contrast, inhibitory responses during the long-latency epoch depended on the location of the spatial goal (*experiment 1*), compensated for GS that began in the short-latency epoch (*experiment 2*), and considered intersegmental dynamics of the limb (*experiment 3*). These results highlight the flexibility of inhibitory responses during the long-latency time period.

Previous studies on muscle responses to mechanical loads applied to the limb, including many of our own, have almost

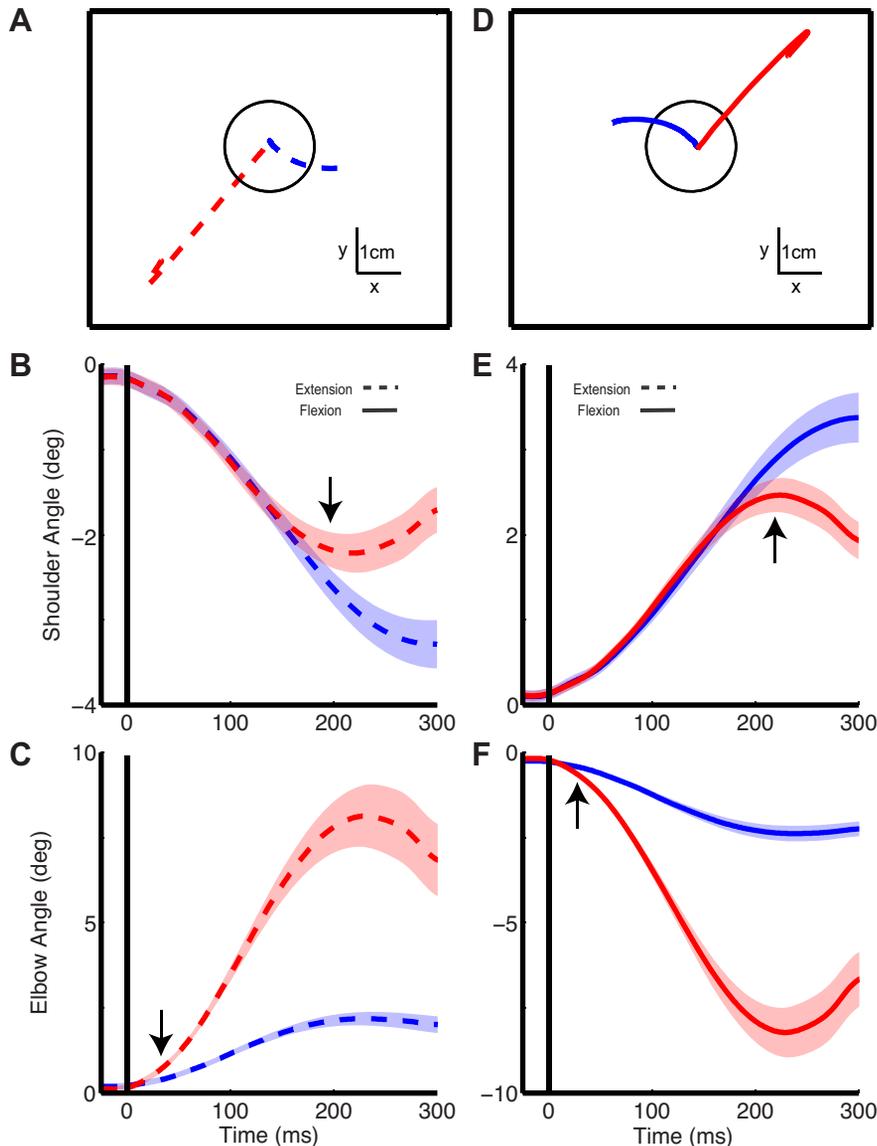


Fig. 6. *Experiment 3* hand and joint kinematics. *A*: traces correspond to the mean hand movement across subjects of the elbow (red) and shoulder (blue) unloading torques for shoulder extension (dashed) unloading condition. *B*: traces represent the mean ( $\pm$  SE) change in shoulder motion following the shoulder extension (dashed) unloading condition. Red and blue traces correspond to the elbow and shoulder unloading torques, respectively. Data are aligned to perturbation onset (vertical line). *C*: traces represent the mean ( $\pm$  SE) change in elbow motion following the shoulder extension (dashed) unloading condition. The arrow indicates the 1st point of significance between unloading conditions determined by ROC analysis. *D*: traces correspond to the mean hand movement across subjects of the elbow (red) and shoulder (blue) unloading torques for shoulder flexion (solid) unloading condition. *E*: traces represent the mean ( $\pm$  SE) change in shoulder motion following the shoulder flexion (solid) unloading condition. Red and blue traces correspond to the elbow and shoulder unloading torques, respectively. Data are aligned to perturbation onset (vertical line). *F*: traces represent the mean ( $\pm$  SE) change in elbow motion following the shoulder flexion (solid) unloading condition. The arrows indicate the 1st point of significance between unloading conditions determined by ROC analysis.

universally focused on motor responses to applied loads that increase muscle activity in a preexcited muscle. From an experimental standpoint, this favored paradigm has many advantages, notably the ease to avoid muscle activity reducing to zero, obfuscating interpretations. This paradigm also likely reflects the obvious fact that muscle afferents increase their firing rate for increases in muscle length and velocity and lead to increases in muscle activity (Crowe and Matthews 1964; Edin and Vallbo 1988, 1990; Matthews 1962). As well, detailed neurophysiological studies exploring synaptic transmission and spinal feedback processes have focused on muscle stretch responses (Hultborn 2006), and so it is natural that human studies also have focused on motor responses to applied loads.

However, motor errors that cause the motor system to over- or undershoot a behavioral goal are both common occurrences, as are mechanical disturbances from the environment that either load or unload the body. Thus appropriate corrective responses require a rich mixture of excitation and inhibition in both preinhibited and preexcited muscles. The present study highlights that the basic pattern for motor responses is ob-

served in preexcited unloaded muscles and preinhibited excited muscles.

A challenge in quantifying inhibitory muscle responses is to ensure that they do not saturate, that is, evoke zero muscle activity. Thus, to prevent the cessation of muscle activity, we selected very small unloading torques relative to the background loads used to preexcite the muscle. A trade-off with using these small unloading torques is that hand deviations were relatively small compared with most previous studies that examined evoked responses during muscle loading. In fact, during *experiment 2*, the unloading torques occasionally failed to deviate the hand outside of the end target. Fortunately, previous work has shown that muscle responses simply scale to the size of the perturbation even for disturbances that approach the natural variability of unperturbed reaching or postural control (Crevecoeur et al. 2012). This scaling of motor responses appears to occur also during unloading given that we observed sophisticated inhibitory processes for these small disturbances.

The unloading responses examined in the present study are different from the unloading responses observed in Kurtzer et

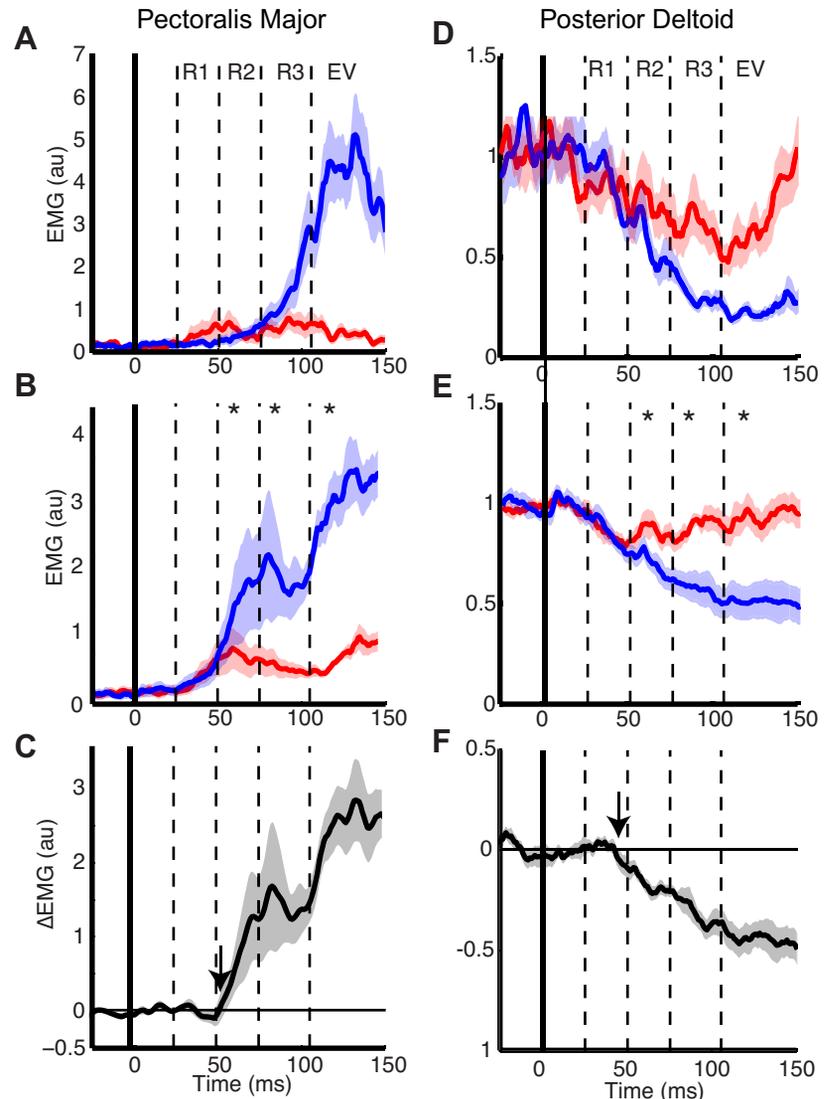


Fig. 7. Muscle activity of pectoralis major (*left column*) and posterior deltoid (*right column*) following shoulder extensor unloading in *experiment 3*. *A*: mean and SE pectoralis major muscle activity from an exemplar subject aligned to perturbation onset (vertical line); blue and red traces indicate the mean muscle activity for the elbow and shoulder applied torques, respectively. *B*: mean (solid) and SE (shaded) pectoralis major muscle activity of the group ( $*P < 0.05$ ). *C*: difference in muscle activity between the 2 responses in *B* (mean  $\pm$  SE). The arrow indicates the 1st point of significance determined by ROC analysis. *D*: mean and SE posterior deltoid muscle activity from an exemplar subject aligned to perturbation onset (vertical line); blue and red traces indicate the mean muscle activity for the elbow and shoulder conditions, respectively. *E*: mean (solid) and SE (shaded) posterior deltoid muscle activity of the group ( $*P < 0.05$ ). *F*: difference in muscle activity between the 2 responses in *E* (mean  $\pm$  SE). The arrow indicates the 1st point of significance determined by ROC analysis.

al. (2010). That study explored how the removal of an applied load generated a powerful reduction in muscle response that occurred in  $\sim 30$  ms. This rapid termination of the stretch response could occur at any time during the short-latency, long-latency, or voluntary time periods and always returned to a response pattern observed for a brief perturbation. Perturbations lasting  $\sim 10$  ms are known to elicit only spinal feedback responses (Kurtzer et al. 2010; Lee and Tatton 1982). Thus cessation of an ongoing perturbation is generated at the spinal level and appears to remove any supraspinal contributions to the perturbation response.

In contrast, the present study examined unloading responses after the subjects were stabilizing their limb at a spatial location. In this steady-state condition, we found unloading responses created strong inhibitory responses at  $\sim 30$  ms as well. However, context-dependent changes were only present during the long-latency time period, implicating transcortical pathways in these more sophisticated feedback responses (Cheney and Fetz 1984; Evarts and Tanji 1976; Pruszynski et al. 2011, 2014; Tanji and Evarts 1976). Corticospinal axons are only excitatory and can synapse directly onto motoneurons (Lemon 2008; Porter and Lemon 1993), whereas the spinal

cord possesses both excitatory and inhibitory circuits (Hultborn 2006; Pierrot-Desseilligny and Burke 2005). Thus inhibitory responses related to transcortical feedback could be generated by decreasing descending drive and/or exploiting inhibitory processes at the spinal level.

Afferent information from spindles in the lengthened muscle likely trigger these inhibitory responses by relaying information back to the central nervous system. A number of studies have highlighted the increased discharge rate of spindles from lengthened muscles during joint displacement (Cordo et al. 2002; Edin and Vallbo 1988, 1990; Roll and Vedel 1982). An alternative possibility is that before unloading, as the pre-excited muscle holds an isometric contraction, spindle sensitivity is heightened due to  $\alpha$ - $\gamma$  coactivation (Stein 1974; Vallbo 1970). Following unloading, the discharge rate of the muscle spindles would suddenly decrease, which could result in a reduction in muscle activity. However, the spindle discharge rates during muscle shortening, even active muscle shortening, have been reported to be weak compared with the spindle responses during muscle lengthening (Burke et al. 1978; Jones et al. 2001). It is difficult to determine from the present study which spindle afferents are responsible for the inhibitory re-

sponses observed in this study. However, it is important to note that studies have shown that during slow movements spindle afferents from both the shortened and lengthened muscles relay afferent information to the central nervous system (Ribot-Ciscar and Roll 1998). Thus it is likely that a combination of the spindle discharges from the shortened and lengthened muscles both contribute to the inhibitory responses noted here.

Previous studies have traditionally used verbal instruction to examine the effect of prior intent on the flexibility of inhibitory responses, but they have generally failed to observe any modulation based on instruction (Angel and Weinrich 1986; Miscio et al. 2001). For example, Angel and Weinrich (1986) used verbal instruction to examine the influence of subject intent on the inhibitory responses of hand muscles. They instructed subjects either to “flex” or “extend” their fingers following unloading pulses. Because the authors used short force pulses, which fail to elicit long-latency and voluntary responses (Kurtzer et al. 2010; Lee and Tatton 1982), subjects were unable to modulate their inhibitory responses. In a similar study, Miscio et al. (2001) also used verbal instruction to examine the influence of subject intent on the shortened muscle. Subjects were instructed either to “oppose the displacement” or “assist the displacement” following a perturbation applied to the finger. Although the authors observed differences in the shortened muscle based on subject intent, they failed to preexcite the shortened muscle and thus were unable to quantify the inhibitory response reliably. We circumvented these issues by preexciting the muscle and then using a small step-down perturbation. Furthermore, we used visual targets to direct behavior and explicitly indicate the position and accuracy constraints of the task as opposed to verbal instruction, which is ambiguous. Importantly, we observed that the unloading responses parallel those observed during loading across all experiments. That is, the responses during the short-latency epoch fail to modulate based on target location, whereas the responses during long-latency epoch are quite flexible.

Background loads were essential in the present study to observe decreases in muscle activity during unloading. Correspondingly, the stretched antagonist muscles were initially inactive before the perturbation. We did not observe robust short-latency stretch (R1) responses in these muscles because the size of the R1 response is sensitive to background load. R1 responses increase with the level of background load, a phenomenon termed GS (Matthews 1986; Pruszynski et al. 2009). When preinhibited, the R1 response is greatly diminished, at least for the size of the perturbations used in these studies (see also Pruszynski et al. 2011). Conceivably, larger R1 responses in a preinhibited muscle may be possible for sufficiently large perturbations. However, such large disturbances would make it difficult or even impossible to continue to perform the instructed motor action. Furthermore, such large disturbances may even override the instructed voluntary motor action with an entirely new defensive response to avoid injury, akin to the stumble-corrective response during walking (Berger et al. 1984; Dietz et al. 1987; Nashner 1980).

Although only three experimental contexts were examined in the present study, it is likely that inhibitory motor responses during the long-latency epoch are capable of all the complexity observed in the excitatory responses, such as stability (Akazawa et al. 1982; Krutky et al. 2010; Nichols and Houk 1976; Shemmell et al. 2010), characteristics of the goal and environ-

ment (Kimura et al. 2006; Kimura and Gomi 2009; Nashed et al. 2012, 2014; Pruszynski et al. 2008; Shemmell et al. 2009), learning (Cluff and Scott 2013), statistical priors (Crevecoeur and Scott 2013), and even decision-making (Nashed et al. 2014; Selen et al. 2012). This general flexibility for excitatory and inhibitory processes is also expected given the likely link between these corrective responses and voluntary control (Scott 2004, 2012).

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#### DISCLOSURES

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

#### AUTHOR CONTRIBUTIONS

J.Y.N., I.L.K., and S.H.S. conception and design of research; J.Y.N. and I.L.K. performed experiments; J.Y.N. analyzed data; J.Y.N., I.L.K., and S.H.S. interpreted results of experiments; J.Y.N. prepared figures; J.Y.N. drafted manuscript; J.Y.N., I.L.K., and S.H.S. edited and revised manuscript; J.Y.N., I.L.K., and S.H.S. approved final version of manuscript.

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