Rapid feedback responses are flexibly coordinated across arm muscles to support goal-directed reaching

Jeffrey Weiler[1-3], Paul L. Gribble[1-3], J. Andrew Pruszynski[1-4]

[1] Brain and Mind Institute, Western University, London, Ontario, Canada
[2] Dept. of Psychology, Western University, London, Ontario, Canada
[3] Dept. of Physiology and Pharmacology, Western University, London, Ontario, Canada
[4] Robarts Research Institute, Western University, London, Ontario, Canada

Running head: flexible routing of rapid feedback responses

Correspondence to:
Jeffrey Weiler
The Brain and Mind Institute
Western University
1151 Richmond Street
London, Ontario, Canada
N6A 3K7
Email: jeffweilerphd@gmail.com

May 26th, 2017

Abstract

Rapid feedback responses can be evoked in wrist muscles when elbow muscles are unexpectedly stretched during goal-directed reaching. Here we examined the flexibility of this coordination. Participants used a planar three degree-of-freedom (shoulder, elbow, wrist) exoskeleton robot to move a cursor to a target following an elbow flexion perturbation. In our first experiment, the cursor was mapped to the veridical position of the robot handle, but participants grasped the handle with two different hand orientations (thumb pointing upward or thumb point downward). We found that large long-latency stretch responses (i.e., muscle activity 50-100 ms following a perturbation) were evoked in wrist extensor muscles when wrist extension helped move the cursor to the target (i.e., thumb upward), and in wrist flexor muscles when wrist flexion helped move the cursor to the target (i.e., thumb downward). In our second experiment, participants grasped the robot handle with their thumb pointing upward, but the cursor's movement was either veridical, or was mirrored such that flexing the wrist moved the cursor as if the participant extended their wrist, and vice versa. We found that, after extensive training, large long-latency stretch responses were evoked in wrist flexor muscles when wrist flexion helped move the cursor to the target (i.e., mirror mapping), and in wrist extensor muscles when wrist extension helped move the cursor to the target (i.e., veridical mapping). Taken together, our findings highlight the flexible routing of long-latency stretch responses and how this coordination supports goal-directed reaching.

New and Noteworthy

We show that the same elbow perturbation evokes long-latency stretch responses in either wrist flexor or extensor muscles depending on which of these muscle groups help achieve the goal of a reaching task. Our findings add to the growing body of work detailing how rapid feedback responses support purposeful goal-directed movement.

Introduction

Rapidly stretching a muscle evokes a multiphasic response in homonymous and/or heteronymous muscles. The first phase of this response occurs approximately 25-50 ms following a perturbation and is often referred to as the short-latency stretch response. The short-latency stretch response is mediated exclusively by spinal circuitry (Pierrot-Deseilligny and Burke, 2005), and is sensitive to factors such as the rate at which the muscle is stretched (Gottlieb and Agarwal, 1979) and the excitability of the motorneuron pool (Beddingham and Tatton, 1984; Capaday et al, 1994). The next phase of the response occurs approximately 50-100 ms following a perturbation and is generated by inputs from spinal circuits (Tracey et al, 1980), as well as brainstem (Shemmell et al, 2009) and cortical circuits (Cheney and Fetz 1984; Evarts and Fromm 1977; Evarts and Tanji 1976; Omrani et al, 2014, 2016; Picard and Smith 1992; Pruszynski et al, 2011, 2014). This response – commonly referred to as the long-latency stretch response – has received a great deal of attention because, unlike the short-latency stretch response, it is modulated by factors that also influence voluntary goal-directed actions, such as volitional intent (Colebatch et al, 1979; Crago et al, 1976; Evarts and Granit 1976; Hammond 1956; Omrani et al, 2013; Pruszynski et al, 2008), motor learning (Cluff and Scott 2013), decision-making (Nashed et al, 2014; Selen et al, 2012; Yang et al, 2011) and environmental dynamics (Ahmadi-Pajouh et al, 2012; Kimura et al, 2006; Krutky et al, 2010).

An interesting feature of the long-latency stretch response is that it can be flexibly coordinated between arms to support goal-directed actions (Dimitru et al, 2012; Marsden et al, 1981; Mutha and Sainburg, 2009). For instance, Mutha and Sainburg (2009) had participants move a cursor to a target, and the cursor was mapped to a location of one hand or the average position

4

of both hands. When a mechanical perturbation was unexpectedly applied to one limb during the reaching movement, long-latency stretch responses were evoked in muscles of the non-perturbed limb, but only if the cursor's location was represented by the average position of both hands – when movement of the non-perturbed limb supported moving the cursor to the goal-location. We have recently been using a three degree-of-freedom (shoulder, elbow and wrist) planar exoskeleton robot to test how long-latency stretch responses are coordinated across multiple muscles of the same limb during goal-directed reaching (Weiler et al, 2015, Weiler et al, 2016). In this work, participants moved their hand to a target following a mechanical perturbation that flexed or extended their elbow, and we placed the target in various locations where both elbow and wrist movement helped transport the hand to the desired location — a simple form of kinematic redundancy (Bernstein 1967). We found that participants coordinated movement at both the elbow and wrist joints to move their hand to the target. More interestingly, long-latency stretch responses were not only evoked in the stretched elbow muscles but were also evoked in wrist muscles that helped transport the hand to the target.

Here we test whether long-latency stretch responses are flexibly routed across arm muscles to support goal-directed reaching. That is, following the same perturbation, can long-latency stretch responses be evoked in different muscles as a function of how those muscles contribute to the success of the reaching movement? We addressed this question with two experiments where participants moved a cursor to a target following a mechanical perturbation that flexed the elbow, and we manipulated how wrist movement helps transport the cursor to the target.

In our first experiment the cursor was mapped to the veridical position of the robot handle, and participants performed reaching movements by holding the handle using two different hand

orientations. In one orientation participants grasped the handle with their thumb pointing upwards (i.e., Upright Orientation), and in the other orientation participants rotated their arm such that they grasped the handle with their thumb pointing downwards (i.e., Flipped Orientation). If the long-latency stretch response can be flexibly routed to wrist muscles, then elbow flexion perturbations that displace the cursor away from the target should evoke large long-latency stretch responses in the wrist extensor muscles when the arm is in the Upright Orientation, and in the wrist flexor muscles when the arm is in the Flipped Orientation. Such flexible coordination, however, may not be possible because previous work suggests that commonly co-recruited muscles are grouped into functional synergies to reduce computational control complexity (Drew et al, 2008; Overduin et al, 2014; Waters-Metenier et al, 2014).

In our second experiment, participants always held the robot handle in the Upright Orientation, but the motion of the cursor was mapped to the veridical movement of the wrist (i.e., Veridical Mapping) or to the opposite movement of the wrist (i.e., Mirror Mapping). If long-latency stretch response can be flexibly routed to wrist muscles, then elbow flexion perturbations that displace the cursor away from the target should evoke large long-latency stretch responses in the wrist extensor muscles for the Veridical Mapping, and to the wrist flexor muscles for the Mirror Mapping. However, such flexible coordination may not be possible as previous work has shown that learning to execute movements that dissociate the veridical relationship between body and effector movement (e.g., visual rotation) depend on specific cortical networks (Mutha, Sainburg, Haaland, 2011a; 2011b; Taubert et al, 2010), and these networks may not overlap with the cortical networks that help generate the long-latency stretch response (Cheney and Fetz 1984; Evarts and

Fromm 1977; Evarts and Tanji 1976; Omrani et al, 2014, Omrani et al, 2016; Picard and Smith 1992; Pruszynski et al, 2011; Pruszynski et al, 2014).

Methods

Participants

Twenty individuals volunteered for *Experiment 1* (14 males, 6 females; mean age 21 years old) and 10 individuals volunteered for *Experiment 2* (5 males, 5 females, mean age 22). All participants reported having normal or corrected-to-normal vision and provided informed written consent prior to data collection. This study was approved by the Office of Research Ethics at Western University and was conducted in accordance with the Declaration of Helsinki.

Apparatus

Participants grasped the handle of a three degree-of-freedom exoskeleton robot (Interactive Motion Technologies, Boston, MA). The robot allows participants to flex or extend their shoulder, elbow and/or wrist in a horizontal plane, is equipped with motors to produce flexion or extension torques at these joints and encoders to measure joint kinematics. Visual stimuli were presented downward by a 46-inch LCD monitor (60 Hz, 1,920 x 1,080 pixels, Dynex DX-46L262A12, Richfield, MN) onto a semi-silvered mirror that occluded vision of the participant's arm. Participants were comfortably seated in a height adjustable chair and the lights in the experimental suite were extinguished for the duration of data collection.

General Procedure

Participants began each trial by moving a cursor (turquoise circle: 1 cm diameter; see below for cursor mapping) to a red circle (i.e., the home position: 2 cm diameter) located at a position where the shoulder, elbow and wrist were at 70°, 60° and 10° of flexion (external angle coordinate system). After maintaining the cursor at this location for 1500 ms the robot applied a linearly increasing load at the elbow joint for 2000 ms that plateaued at ±3Nm (i.e., the pre-load). Participants were required to keep the cursor at the home position during this time. When the pre-load plateaued the cursor was extinguished and a white target circle (10 cm diameter) was presented adjacent to the home location in one of two positions: at a location where elbow flexion would displace the hand directly into the target, or at a location where elbow flexion would displace the hand directly away the target (see Figure 1C from Weiler et al, 2015). Participants maintained this arm position for a randomized foreperiod (1000 – 2500 ms) after which a commanded step-torque (i.e., the perturbation) of ±3Nm was applied at the elbow. Each perturbation moved the participant's hand either into the target (IN condition) or away from the target (OUT condition) depending on the target's location. The participant's task was to move their arm such that the cursor, if visible, would enter the target in less than 375 ms. The cursor reappeared 100 ms after the perturbation, the commanded step torque was rapidly ramped down 1000 ms after the perturbation and movement feedback was provided on each trial. If the cursor entered the target after 375 ms, or never entered the target, the target changed from white to red – otherwise the target changed from white to green.

Mapping of the cursor

We used two different methods to map the position of the cursor relative to the robot handle. In one condition (i.e., Veridical Mapping) the cursor simply reflected the Cartesian coordinates of the robot handle.   In the other condition (i.e., Mirror Mapping) the cursor reflected the Cartesian coordinates of the robot handle only when the participant's wrist was at 10° of flexion. When participant's wrist was not at 10° of flexion, we mapped the cursor to the Cartesian coordinates of the robot handle as if the participant flexed their wrist when they extended their wrist, and vice versa. For example, the cursor was presented as if the participant's wrist was at 30° of extension when in fact their wrist was at 40° of flexion. We selected 10° of flexion as our reference point so that a similar arm orientation would be used to position the cursor over the home location regardless of the mapping condition (i.e., Veridical or Mirror). We used the Veridical Mapping across *Experiment 1 and 2*, whereas the Mirror Mapping was only used in *Experiment 2*.

Experiment Specific Procedures

Experiment 1 consisted of two blocks of trials, which differed by how participants physically grasped the handle of the robot. For one block of trials (i.e., Upright Orientation) participants naturally grasped the handle such that their forearm was in a semi-supine position (thumb pointing upwards; see top of Figure 1). For this orientation, flexing the wrist and elbow moved the cursor in a similar direction, as did extending the wrist and elbow. For the other block of trials (i.e., Flipped Orientation) participants grasped the handle once they rotated their forearm into a fully pronated position (thumb point downwards; see bottom of Figure 1B). Notably, for this orientation, extending the elbow and flexing the wrist moves the cursor in a similar direction, as does flexing

9

the elbow and extending the wrist. Each block consisted of 8 different trial-types (2 pre-loads: flexion, extension; 2 target locations: IN, OUT; 2 perturbations: flexion, extension). Each trial-type was repeated 30 times in a randomized order totaling 240 trials per block. The ordering of blocks was randomized across participants. Rest breaks were given approximately every 20 minutes during data collection or when requested.

Experiment 2 took place over the course of five days and participants always grasped the robot handle with the normal Upright Orientation. For the first four days of the experiment participants practiced the same reaching task used in *Experiment 1*, but this time the movement of the cursor was mapped to the opposite movement of the wrist (i.e., Mirror Mapping). Each practice session required participants to complete 40 trials for each of the 8 trial-types (see above) in a randomized order, totaling 1280 practice trials across the four days. On the last day of the experiment participants completed two blocks of trials that differed by how the cursor was mapped with respect to the robot handle (i.e., Veridical or Mirror Mapping). Each block consisted of the 8 different trial-types, which were repeated 30 times in a randomized order totaling 240 trials per block. The ordering of blocks was randomized across participants. Rest breaks were given approximately every 20 minutes during data collection or when requested.

Muscle Activity

Participants' skin was cleaned with rubbing alcohol and EMG surface electrode (Delsys Bagnoli-8 system with DE-2.1 sensors, Boston, MA) contacts were coated with a conductive gel. EMG electrodes were then placed on the belly of six muscles (pectoralis major, posterior deltoid, biceps brachii long heads, triceps brachii lateral head, flexor carpi radialis, extensor carpi ulnaris) at an

10

orientation that runs parallel to the muscle fiber. A reference electrode was placed on participants' left clavicle. EMG signals were amplified (gain = 10^3), and then digitally sampled at 2,000 Hz.

Data Reduction and Analysis

Angular position of the shoulder, elbow and wrist were sampled at 500 Hz. EMG data were band-pass filtered (20 - 250 Hz, 2-pass 2nd-order Butterworth) and full-wave rectified. Muscle activity was normalized to their own mean activity 200 ms prior to perturbation onset when the TRI was pre-loaded by the robot (i.e., flexion pre-load). Joint kinematics and EMG were recorded from -200 ms to 400 ms relative to perturbation onset.

We analyzed mean kinematic and EMG data from trials in which the TRI was pre-loaded and the mechanical perturbation flexed the elbow. Trials in which the perturbation extended the elbow were excluded from analyses because these perturbations could elicit responses in the pronator teres muscle to counteract unwanted forearm supination – an action generated by biceps brachii recruitment (see Gielen et al, 1988). This is important because responses in pronator teres may masquerade as activity from flexor carpi radialis as these two muscles lie in close proximity to one another. Although not analyzed, the remaining trials were included so that participants were unable to predict what response would be required on a trial-by-trial basis.

We were interested in assessing how long-latency stretch responses were modulated in wrist muscles following elbow perturbations and therefore primarily focused our analyses on the mean activity of flexor carpi ulnaris (a wrist flexor: WF) and extensor carpi radialis (a wrist extensor: WE) from 50-100 ms following the perturbation (i.e., the long-latency stretch response).

11

WF activity from three participants in *Experiment 1* was excluded because the robot dislodged the EMG electrode during data collection. We used paired sample t-tests to compare IN and OUT condition trials for the WE and WF across both experiments. Experimental results were considered reliably different if $p < 0.05$.

Results

Experiment 1: Changing arm orientation

The objective of *Experiment 1* was to test whether long-latency stretch responses evoked in wrist muscles were appropriately modulated to account for the orientation of the arm. Participants adopted one of two arm orientations (i.e., Upright or Flipped Orientation) and quickly moved the cursor into a target following a mechanical perturbation that displaced the cursor into the target (IN condition) or away from the target (OUT condition).

Features of Wrist Behaviour

Figure 2A displays group mean wrist kinematics for the Upright Orientation block, which shows that the wrist initially moved into extension for both IN and OUT condition trials following the elbow flexion perturbation. This was expected as flexing the elbow in this arm configuration generates torque that extends the wrist. Notably, the wrist then moved further into extension for OUT condition trials compared to their IN condition counterparts ~175 ms after the perturbation. The same basic pattern was observed when participants adopted the Flipped Orientation, but in the opposite direction. Figure 2B shows that the wrist initially moved into flexion for both IN and OUT condition trials following the perturbation, and then the wrist moved further into flexion for

12

OUT condition trials compared to their IN condition counterparts ~175 ms after the perturbation. All participants displayed these general patterns of wrist motion across the two arm orientations despite not receiving explicit instructions about how to use their wrist to move the cursor towards the target. This is highlighted in Figure 2C – 2F, which shows trial-by-trial wrist motion of four exemplar participants for IN and OUT condition trials for the Upright and Flipped orientations.

We first tested if the onset of wrist movement that helped transport the hand to the target differed between the two arm orientations. We used each participant's wrist kinematic data from IN and OUT trials to compute a time-series receiver operator characteristic (ROC) curve from 0 – 400 ms relative to perturbation onset for the Upright and Flipped Orientations. In brief, ROC curves denote the probably an ideal observer can discriminate responses (e.g., wrist displacement) that come from two discrete categories (e.g., conditions; Green and Swets 1966). We then fit these time-series ROC curves with a segmented linear regression to estimate when IN and OUT condition trials began to differ (see Weiler et al, 2015 for full description of this regression technique and MATLAB code). A paired sample t-test showed that there was no reliable difference of these estimates between the Upright and Flipped Orientations, t(19) = 0.75, p = 0.46.

Flexible routing of long-latency stretch responses to wrist muscles

Figure 3 shows mean EMG activity from the WE and WF for the Upright and Flipped Orientations. For the Upright Orientation, mean EMG activity of the WE increases within the long-latency stretch epoch for the OUT compared to IN condition trials, whereas the mean EMG activity of the WF appears to be matched at all time points. For the Flipped Orientation, mean EMG activity of the WE appears to decrease within the long-latency stretch epoch for the OUT compared to IN

13

condition trials, whereas the mean EMG activity of the WF appears to increase within the long-latency stretch epoch for the OUT compared to IN condition trials.

We used paired sample t-tests to compare mean EMG activity within the long-latency stretch epoch between IN and OUT condition trials from the WE and WF for both the Upright and Flipped Orientation. For the Upright Orientation, we found that WE long-latency stretch responses were larger for OUT condition trials compared to their IN condition trial counterparts, t(19) = 4.70, p < 0.001, whereas there was no reliable difference in long-latency stretch responses between IN and OUT condition trials for the WF, t(16) = 0.29, p = 0.78. For the Flipped Orientation, we found that WE long-latency stretch responses were smaller for OUT condition trials compared to their IN condition trial counterparts, t(19) = -2.11, p = 0.041, and that WF long-latency stretch responses were larger for OUT condition trials compared to their IN condition trial counterparts, t(16) = 2.72, p < 0.015.

Experiment 2: Changing visual mapping

The objective of *Experiment 2* was to test whether long-latency stretch responses evoked in wrist muscles were appropriately modulated to account for a non-veridical mapping between wrist movement and cursor movement. To test this, we mapped the movement of the cursor such that it moved as if the participant extended their wrist when if fact they flexed their wrist, and vice versa (i.e., Mirror Mapping). Our initial pilot testing, however, demonstrated that participant's were generally unable to account for this mapping within a single experimental session. That is, participant's had great difficulty using their wrist to help move the cursor to the target with the Mirror Mapping. We therefore trained individuals for four days to complete the reaching task with

14

the Mirror Mapping, and then assessed long-latency stretch responses in the wrist muscles on the 5th day.

Features of Wrist Behaviour

We present two figures that highlight how participants used their wrist to help move the cursor towards the target over the course of the experiment. Figure 4 shows three exemplar participants' trial-by-trial wrist kinematics, as well as group mean wrist kinematics, across the four days of practice and the final testing session. Participants frequently made inappropriate extension wrist movements for OUT condition trials during the initial training sessions, progressively showed improvement over the four days of practice and were consistently using the wrist in an appropriate fashion to move the cursor towards the target on the final testing day. Figure 5 shows the median movement time (MT) for participants to rotate their wrist 10 degrees in a direction that moved the cursor towards the target across the four days of practice of the Mirror Mapping condition, the final testing day of both the Mirror and Veridical Mapping conditions, as well as the Upright and Flipped Orientations from *Experiment 1*. As shown in the figure, the MT on the final testing session for the Mirror Mapping was comparable to the MTs from the other experimental conditions (i.e., Veridical Mapping, Upright and Flipped Orientation).

Flexible but partially erroneous routing of long-latency stretch responses to wrist muscles

Mean EMG responses of the WE and WF from the Veridical and Mirror Mapping blocks on the final testing day are shown in Figure 6. For the Mirror Mapping block, WE long-latency stretch responses did not differ between OUT and IN condition trials, $t(9) = 1.00$, $p = 0.34$, whereas WF

15

long-latency stretch responses for OUT condition trials were reliably larger than IN condition trials, t(9) = 4.65, p = 0.001. This pattern of EMG activity is consistent with participants accounting for the non-veridical mapping of the cursor.

For the Veridical Mapping block, WE long-latency stretch responses for OUT conditions were reliably larger than their IN condition counterparts, t(9) = 4.65, p = 0.001. Notably, and in contrast to *Experiment 1* as well as our previous work (Weiler et al, 2015; Weiler et al, 2016), WF long-latency stretch responses were also larger for OUT condition trials compared to IN condition trials, t(9) = 2.85, p = 0.02. One possible explanation for this unexpected result is that the extensive training of the Mirror Mapping block conditioned WF long-latency stretch responses to be elicited independent of the participants' volitional movement. We tested this idea by comparing the WF long-latency stretch responses for OUT condition trials between the Veridical and Mirror Mapping blocks, as well as mean EMG activity within the voluntary epoch (i.e., 100-300 ms following perturbation onset) for OUT condition trials between the Veridical and Mirror Mapping blocks (see Figure 7). Note that the need to flex the wrist following an elbow flexion perturbation for OUT condition trials is different between the Veridical and Mirror Mapping blocks – in the Veridical Mapping block one should extend the wrist, whereas in the Mirror Mapping block one should flex the wrist. Consistent with these requirements, we found that WF muscle activity in the voluntary epoch was larger for OUT condition trials in the Mirror Mapping block compared to the Veridical Mapping block, t(9) = 6.24, p < 0.001 (see Figure 7*ii*). In contrast, long-latency stretch responses of the WF for OUT condition trials in the Mirror Mapping block did not reliably differ from the Veridical Mapping block, t(9) = 0.19, p = 0.85 (see Figure 7*i*). Thus, long-latency stretch responses evoked in the WF within the Veridical Mapping block were similar to the how these

responses were evoked in the WF within the Mirror Mapping block, and did not support how participants voluntarily moved their wrist to help transport the cursor to the target.

Discussion

We designed two experiments to test the flexibility in which long-latency stretch responses are routed to wrist muscles to support a goal-directed reaching task. In our first experiment participants physically changed how they grasped the handle of a robotic exoskeleton, which in turn changed how the wrist moved the cursor towards the target. We found that participants rapidly altered their wrist behaviour to account for the different arm orientations, and that long-latency stretch responses were evoked in the wrist muscles appropriate for generating this behaviour. In the second experiment, participants grasped the robot's handle with the thumb pointing upward, but we changed how wrist movement was mapped to the movement of the cursor. We found that participants initially had great difficultly changing their wrist behaviour to account for a non-veridical (i.e., Mirror) mapping between wrist and cursor movement, but were able to learn this mapping over the course of four days of practice. After training, long-latency stretch responses were evoked in the wrist muscles that appropriately accounted for the non-veridical mapping of the cursor, but were erroneously evoked for the Veridical Mapping.

Coordinating rapid feedback responses across multiple muscles for goal-directed movement

Long-latency stretch responses are mediated – at least in part – by cortical regions involved in sensorimotor control (e.g., primary motor cortex: Cheney and Fetz 1984; Evarts and Fromm 1977; Evarts and Tanji 1976; Omrani et al, 2014, Omrani et al, 2016; Picard and Smith 1992; Pruszynski et

17

al, 2011; Pruszynski et al, 2014; pre-motor cortex: Omrani et al, 2016, parietal cortex: Omrani et al, 2016). Therefore, assessing how these responses are flexibly routed to multiple muscles provides insight into how cortical sensorimotor circuits process incoming somatosensory information to flexibly coordinate purposeful motor output. Several groups have leveraged this approach. For instance, in the seminal 'teacup' experiment – wherein no teacup was ever used (Marsden et al, 1981) – Marsden showed that after the left arm was rapidly pulled, long-latency stretch responses were flexibly routed to the right arm's triceps or biceps depending on whether the person was holding onto a table or a 'teacup' with their right hand. More recently, Mutha and Sainburg (2009), as well as Dimitriou and colleagues (2011), demonstrated that long-latency stretch responses could be flexibly routed to muscles of a non-perturbed arm if the success of an ongoing action depends on the collective movement of both arms. This series of results indicate that the rapid processing of somatosensory information can flexibly generate coordinated muscle activity between different limbs in order to help achieve a desired behavioural goal.

The goal of our work is to understand how somatosensory information is rapidly processed to support reaching actions. We have often approached this work by applying a mechanical perturbation to the elbow and assessed how long-latency stretch responses are evoked in multiple muscles of the upper-limb. One interesting finding we and others have extensively documented is that long-latency stretch responses are evoked in shoulder muscles to precisely counteract torques that are generated at the shoulder joint as a result of rapid elbow motion (Crevecoeur et al, 2012; Kurtzer et al, 2008, Kurtzer et al, 2009; Maeda et al, 2017; Pruszynski et al, 2011). Thus, in addition to coordinating muscle activity between different limbs, rapid feedback responses also account for the biomechanical complexities associated with controlling a multi-joint linkage like the arm (see

also Gielen et al 1988; Koshland et al, 1991; Latash, 2000; Soechting and Lacquaniti 1988). More recently, we have shown that individuals utilize elbow and wrist movement to move their hand to a goal-location following an elbow perturbation, and that long-latency stretch responses are not only evoked in the elbow muscles, but also evoked in the wrist muscles that support this wrist behaviour (Weiler et al, 2015; Weiler et al, 2016). Here we demonstrated that these responses are evoked in wrist muscles based on the manner in which wrist movement contributes to the success of the reaching action. These findings add to an expansive list documenting the functional capacity of the long-latency stretch response (for review see: Cluff et al, 2015; Pruszynski and Scott, 2012), and indicates that the rapid processing of somatosensory information also accounts for how the movements of multiple joints are linked together to produce purposeful actions.

Long-latency stretch responses for movements with veridical and non-veridical mappings

The Flipped Orientation from *Experiment 1* and Mirror Mapping from *Experiment 2* were designed so that participants had to flex their wrist to help transport the cursor towards the target. A noticeable difference between *Experiment 1* and *2* was how quickly participants modulated their wrist behaviour to account for these experimental manipulations. For *Experiment 1*, all participants easily modified their wrist movements when they adopted the Flipped Orientation to help transport the cursor towards the target. Furthermore, our time-series ROC analysis indicated that the arm's orientation did not influence the timing of incorporating wrist movement into the reaching action. These findings may not be overly surprising as a prerequisite for producing effective and efficient movement is accounting for the orientation of the body in external space. What is more interesting, however, is that the rapid computations that underlie the generation

and routing of the long-latency stretch response also account for the body's orientation, consistent with the idea that these computations depend on an estimate of current static or dynamical state of the body (Crevecoeur and Scott, 2013; Scott 2004; Todorov and Jordan 2002;).

In contrast to *Experiment 1*, participants took several days practicing the Mirror Mapping condition from *Experiment 2* to produce wrist movements appropriate for transporting the cursor to the target. This likely reflects the time course for learning the non-veridical relationship between movement of the arm and the movement of the cursor. Although dissociating arm and cursor movement is commonly used in motor learning experiments, there are differences in how such manipulations are employed. For example, many experiments have used manipulations that displace the cursor by a specified angle with respect to the veridical reaching direction (i.e., visual rotation; Harris 1965; Redding and Wallace 1990) and participants adjust their movements relatively quickly to account for this non-veridical relationship. However, this was not the type of non-veridical manipulation we employed. In this work we mirrored the movement of the cursor with respect to the wrist – a manipulation that is fundamentally different from a visual rotation. Indeed, previous work has shown that participants take longer to learn mirror reversals compared to visual rotations (Lillicrap et al, 2013) and reaction times associated with mirror reversals are delayed compared to visual rotations (Telgen et al, 2014). These behavioural differences may be due to distinct mechanisms that underlie how these two non-veridical relationships are learned (Lillicrap et al, 2013; Telgen et al, 2014). Learning a visual rotation requires the recalibration of an existing control policy, which is a relatively quick and likely depends on neural processing within the parietal (Mutha et al, 2011a; Mutha et al, 2011b) and premotor cortices (Krakauer et al, 2004). In contrast, learning a mirror reversal requires the acquisition of a completely new control policy,

20

which is a relatively slow process and likely depends on processing within the basil ganglia (Gutierrez-Garralda et al, 2013) and the cerebellum (Sanes et al, 1990; Vaca-Palomares et al, 2013).

Once participants learned the mirrored relationship between wrist and cursor movement, long-latency stretch responses were appropriately evoked in the WF, which produced the wrist flexion movement that helped transport the cursor to the target. This is consistent with previous work showing that long-latency stretch responses are modulated in a manner that reflects the learning of a novel motor response (Ahmadi-Pajouh et al, 2012; Cluff and Scott, 2013). Large long-latency stretch responses were then also evoked in the WF for OUT condition trials when the cursor was mapped to the veridical wrist movement. This is an interesting finding, as this response is inappropriate to produce the wrist extension movement that helps transport the cursor to the target. One potential explanation is that long-latency stretch responses were habitually routed to the WF following the extensive training of the Mirror Mapping block. Indeed, this routing was not observed in experiments where mirror training was not a part of the protocol (i.e., Upright Orientation from *Experiment 1*, and Weiler et al, 2015; Weiler et al, 2016), and long-latency stretch responses evoked in the WF during OUT condition trials were indistinguishable between the Veridical and Mirror Mapping blocks. An intriguing possibility is that the well-learned mirrored wrist movements influenced how the neural networks that generate and route the long-latency stretch response processed incoming somatosensory information in the Veridical Mapping block.
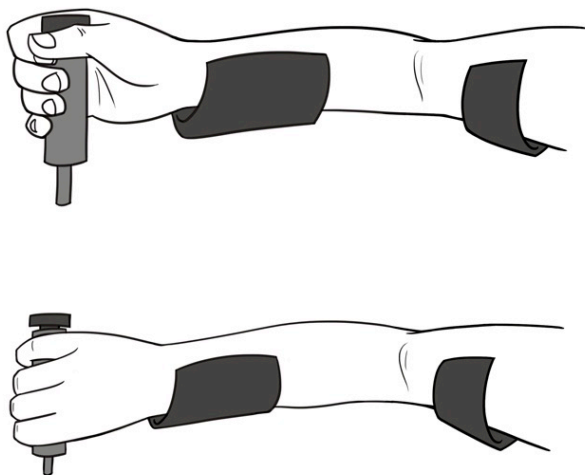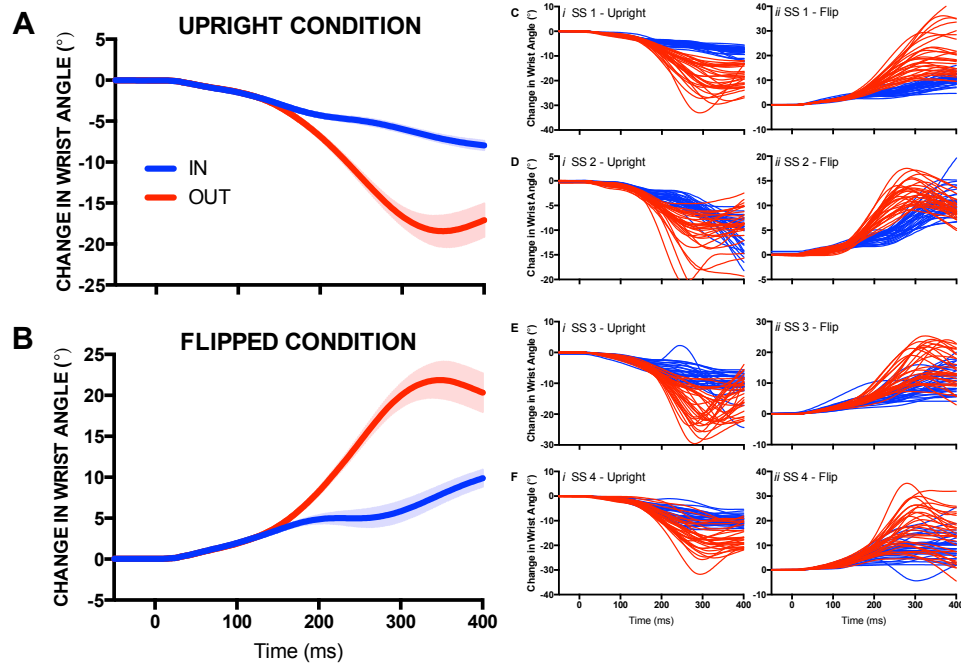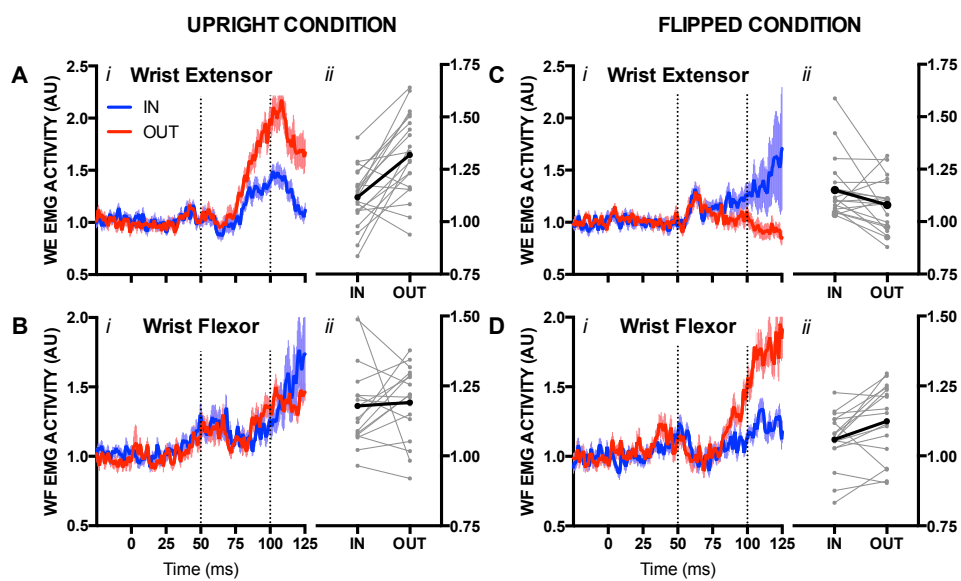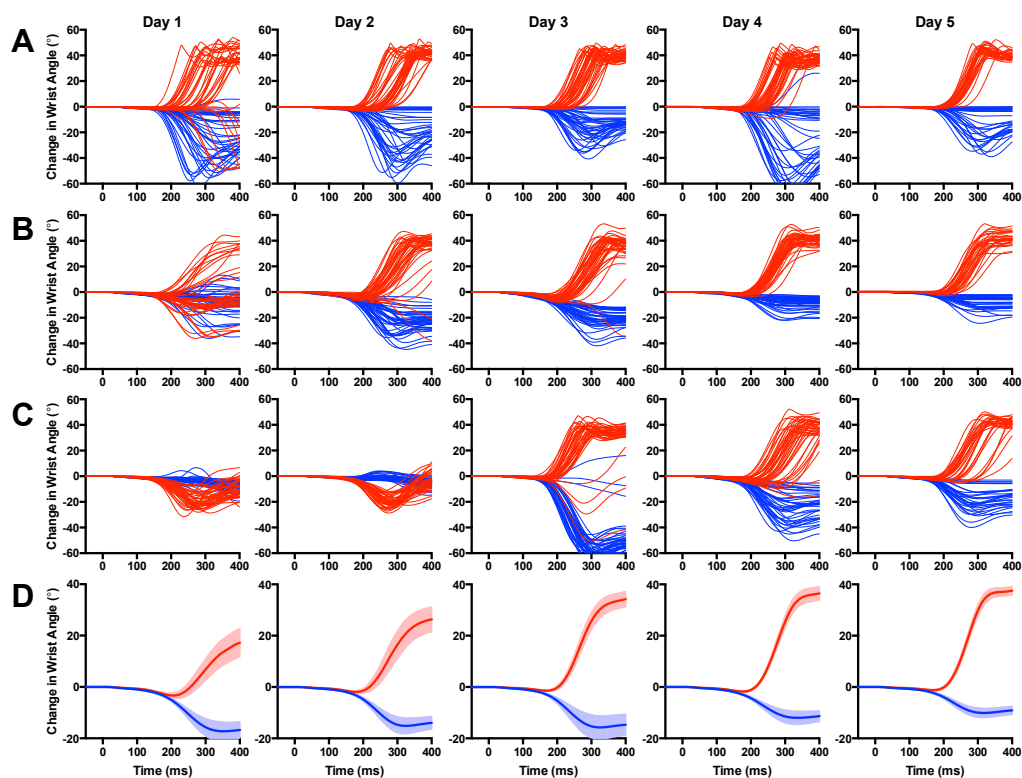
Figures

Figure 1

Figure 2

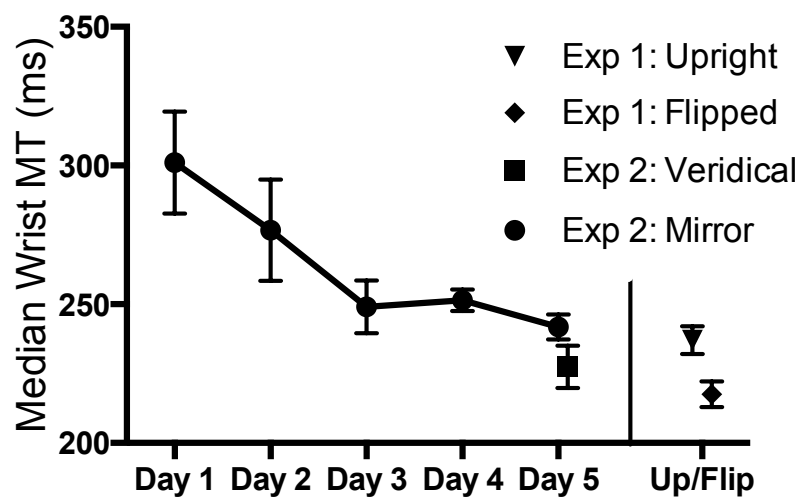Figure 3

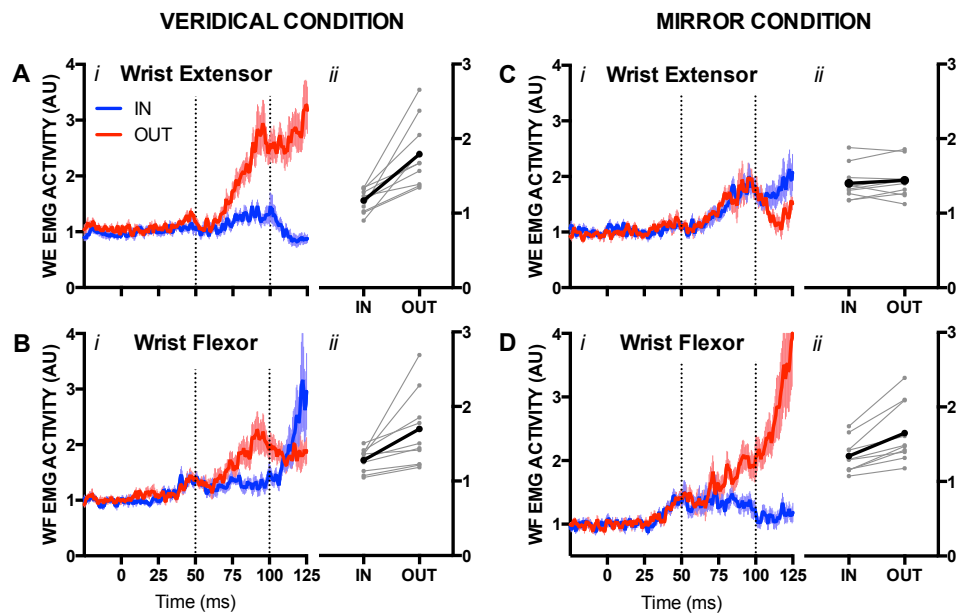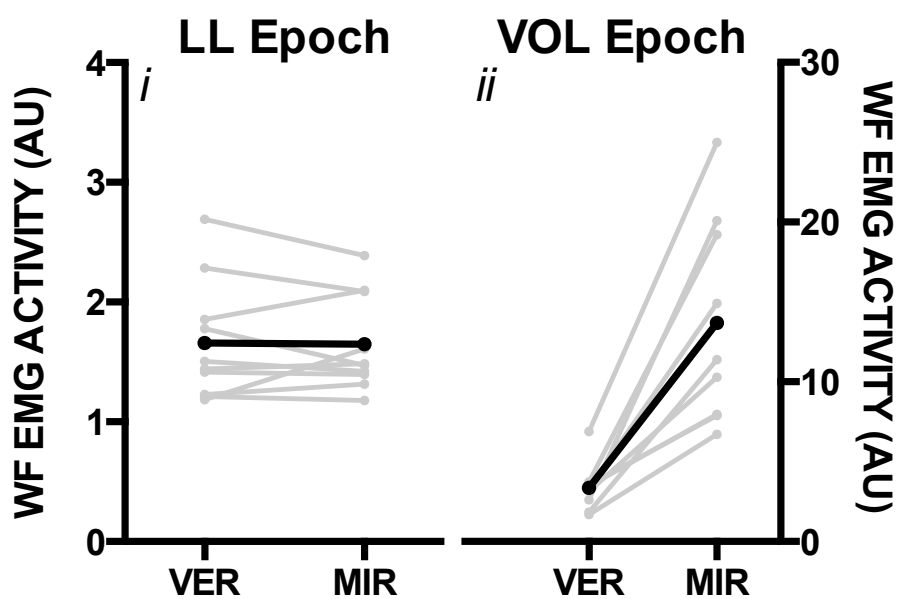Figure 4

Figure 5

Figure 6

Figure 7

Figure captions

Fig 1. *Top*. Depiction of how participants grasped the exoskeleton handle for the Upright Orientation. *Bottom*. Depiction of how participants grasped the exoskeleton handle for the Flipped Orientation.

Fig 2. *A*. Mean change in wrist angle following the mechanical perturbation while participants adopted the Upright orientation. Blue and red traces reflect IN and OUT conditions, respectively. Data are aligned to perturbation onset. Shading reflects ± 1 SEM. *B*. Same format as *A* but for the Flipped orientation. *C-Fi*. Trial-by-trial changes in wrist angle for four exemplar participants while in the Upright orientation. Each line reflects a single trial, and blue and red traces reflect IN and OUT condition trials, respectively. Data are aligned to perturbation onset. *C-Fii.* Same format as *C-Fi*, but for the Flipped orientation.

Fig 3. *Ai.* Mean EMG activity of the WE following the mechanical perturbation while participants adopted the Upright orientation. Blue and red traces reflect IN and OUT conditions, respectively. Data are aligned to perturbation onset. Veridical dotted lines reflect the long-latency stretch epoch. Shading reflects ± 1 SEM. *Aii.* Mean EMG activity of the WE in the long-latency stretch epoch for IN and OUT conditions while participants adopted the Upright orientation. Thin grey lines reflect individual participants whereas thick black lines reflect the group mean. *Bi.* Same format as *Ai*, but for the WF. *Bii.* Same format as *Aii*, but for the WF. *Ci.* Same format as *Ai*, but for the Flipped orientation.   *Cii.* Same format as *Aii*, but for the Flipped orientation. *Di*. Same

format as *Bi,* but for the Flipped orientation. *Dii*. Same format as *Bii,* but for the Flipped orientation.

Fig 4. *A-C*: Trial-by-trial changes in wrist angle from three exemplar participants for the Mirror Mapping block across the four days of practice and the final training session. Each line reflects a single trial, and blue and red traces reflect IN and OUT condition trials, respectively. Data are aligned to perturbation onset. *D:* Mean change in wrist angle following the mechanical perturbation for the Mirror Mapping block across the four days of practice and the final training session. Blue and red traces reflect IN and OUT conditions, respectively. Data are aligned to perturbation onset. Shading reflects ± 1 SEM.

Fig 5. Median movement time required for participants to rotate their wrist 10 degrees in a direction that brings the cursor towards the target following a perturbation that displaced the cursor away from the target. Connected circles denote the required movement times over the course of the Mirror Mapping training session and final day of testing, whereas the square, triangle and diamond reflect the movement time required for the Veridical Mapping, Upright Orientation and Flipped Orientation, respectively. Error bars reflect 1 SEM.

Fig 6. *Ai*. Mean EMG activity of the WE following the mechanical perturbation for the Veridical Mapping block. Blue and red traces reflect IN and OUT conditions, respectively. Data are aligned to perturbation onset. Veridical dotted lines reflect the long-latency stretch epoch. Shading reflects ± 1 SEM. *Aii.* Mean EMG activity of the WE in the long-latency stretch epoch for IN and

OUT conditions for the Veridical Mapping block. Thin grey lines reflect individual participants whereas thick black lines reflect the group mean. *Bi.* Same format as *Ai*, but for the WF. *Bii.* Same format as *Aii*, but for the WF. *Ci.* Same format as *Ai*, but for the Mirror Mapping block. *Cii.* Same format as *Aii*, but for Mirror Mapping block. *Di.* Same format as *Bi,* but for Mirror Mapping block. *Dii.* Same format as *Bii,* but for the Mirror Mapping block.

Fig 7. *i.* Mean EMG activity of the WF in the long-latency stretch epoch for OUT condition trials between the Veridical Mapping block (VER) and Mirror Mapping block (MIR). Thin grey lines reflect individual participants whereas thick black lines reflect the group mean. *ii.* Same format as *i*, but for mean EMG activity within the voluntary epoch (i.e., 100-300 ms following perturbation onset). Note the different scales for long-latency and voluntary epochs.

References

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

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

Bernstein NA. The Co-ordination and Regulation of Movements. Pergamon Press; Oxford: 1967.

Capaday C, Forget R, Milner T. A re-examination of the effects of instruction on the long-latency stretch reflex response of the flexor pollicis longus muscle. *Exp Brain Res 100:* 515-521, 1994.

Cheney PD, Fetz EE. Corticomotoneuronal cells contribute to long-latency stretch reflexes in the rhesus monkey. J Physiol 349: 249-272, 1984.

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

Cluff T, Crevecoeur F, Scott SH. A perspective on multisensory integration and rapid perturbation responses. *Vision Res 110:* 215-22, 2015.

Crago PE, Houk JC, Hasan Z. Regulatory actions of human stretch reflex. *J Neurophysiol* 39: 925-935, 1976.

Colebatch JG, Gandevia SC, McCloskey DI, Potter EK. Subject instruction and longlatency reflex responses to muscle stretch. *J Physiol* 292: 527-534, 1979.

Crevecoeur F, Scott SH. Priors engaged in long-latency responses to mechanical perturbations suggest a rapid update in state estimation. *PLoS Comput Biol* 9: e1003177, 2013.

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

Dimitriou M, Franklin DW, Wolpert DM. Task-dependent coordination of rapid bimanual motor responses. *J Neurophysiol.* 107: 890-901, 2012.

Drew T, Kalaska J, Krouchev N. Muscle synergies during locomotion in the cat: a model for motor cortex control. *J Physiol 586:* 1239-1245, 2008.

Evarts EV, Fromm C. Sensory responses in motor cortex neurons during precise motor control. *Neurosci Lett* 5: 267272, 1977.

Evarts EV, Granit R. Relations of reflexes and intended movements. *Prog Brain Res* 44: 1-14, 1976.

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

Gielen CC, Ramaekers L,van Zuylen EJ. Long-latency stretch reflexes as co-ordinated functional responses in man. *J Physiol* 407: 275-292, 1988.

Gottlieb GL, Agarwal GC. Response to sudden torques about ankle in man: myotatic reflex. *J Neurophysiol* 42: 91-106, 1979.

Green DM, Swets JA. Signal detection and recognition by human observers. Wiley; New York: 1966.

Gutierrez-Garralda JM, Moreno-Briseno P, Boll MC, Morgado-Valle C, Campos-Romo A, Diaz R, Fernandez-Ruiz J. The effect of Parkinson's disease and Huntington's disease on human visuomotor learning. *Eur J Neurosci 38*: 2933-2940, 2013.

Hammond PH. The influence of prior instruction to the subject on an apparently involuntary neuro-muscular response. *J Physiol* 132: 17-18P, 1956.

Harris CS. Adaptation to displaced vision: visual, motor, or proprioceptive change? *Science 17*: 812-813, 1965.

Kimura T, Haggard P, Gomi H. Transcranial magnetic stimulation over sensorimotor cortex disrupts anticipatory reflex gain modulation for skilled action. *J Neurosci* 26: 9272-9281, 2006.

Koshland GF, Hasan Z, Gerilovsky L. Activity of wrist muscles elicited during imposed or voluntary movements about the elbow joint. *J Mot Behav 23*: 91-100, 1991.

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, Ghez C. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. *J Neurophysiol 91:* 924-933, 2004

Krutky MA. Ravichandran VJ, Trumbower RD, Perreault EJ. Interactions between limb and environmental mechanics influence stretch reflex sensitivity in the human arm. *J Neurophysiol* 103: 429-440, 2010.

Kurtzer IL, Pruszynski JA, Scott SH. Long-latency reflexes of the human arm reflect an internal model of limb dynamics. *Curr Biol* 18: 449-453, 2008.

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

Latash ML. The organization of quick corrections within a two-joint synergy in conditions of unexpected blocking and release of a fast movement. *Clin Neurophysiol*, *111*: 975-987, 2000.

Lillicrap TP, Moreno-Briseño P, Diaz R, Tweed DB, Troje NF, Fernandez-Ruiz J. Adapting to inversion of the visual field: a new twist on an old problem. *Exp Brain Res 228:* 327-339, 2013.

Marsden CD, Merton PA, Morton HB. Human postural responses. *Brain* 104: 513–534, 1981.

Mutha PK, Sainburg RL. Shared bimanual tasks elicit bimanual reflexes during movement. *J Neurophysiol.* 102: 3142-3155, 2009.

Mutha PK, Sainburg RL, Haaland KY. Critical neural substrates for correcting unexpected trajectory errors and learning from them. *Brain 134:* 3647-3661, 2011a

Mutha PK, Sainburg RL, Haaland KY. Left parietal regions are critical for adaptive visuomotor control. *J Neurosci 31:* 6972-6981, 2011b.

Nashed JY, Crevecoeur F, Scott SH. Rapid online selection between multiple motor plans. *J Neurosci* 29: 1769-1780, 2014.

Omrani M, Diedrichsen J, Scott SH. Rapid feedback corrections during a bimanual postural task. *J Neurophysiol* 109: 147-161, 2013.

33

Omrani M, Murnaghan CD, Pruszynski JA, Scott SH. Distributed task-specific processing of somatosensory feedback for voluntary motor control. *Elife 5:* p. e13141, 2016.

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

Overduin SA, d'Avella A, Carmena JM, Bizzi E. Muscle synergies evoked by microstimulation are preferentially encoded during behavior. *Front Comput Neurosci 8: 20,* 2014.

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

Pierrot-Deseilligny E, Burke D. The circuitry of the spinal cord: its role in motor control and movement disorders. Cambridge: Cambridge University Press, 2005.

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

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

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

Pruszynski JA, Scott SH. Optimal feedback control and the long-latency stretch response. *Exp Brain Res* 218: 341-359, 2012.

Maeda RS, Cluff T, Gribble PL, Pruszynski JA. Compensating for intersegmental dynamics across the shoulder, elbow and wrist joints during feedforward and feedback control. *bioRxiv* doi: https://doi.org/10.1101/115675

Redding GM, Wallace B. Effects on prism adaptation of duration and timing of visual feedback during pointing. *J Mot Behav 22*: 209-224, 1990.

Sanes JN, Dimitrov B, Hallett M. Motor learning in patients with cerebellar dysfunction. *Brain 113:* 103-120, 1990

Scott SH. Optimal feedback control and the neural basis of volitional motor control. *Nat Rev Neurosci* 5: 532-546, 2004.

Selen LP, Shadlen MN, Wolpert DM. Deliberation in the motor system: reflex gains track evolving evidence leading to a decision. *J Neurosci.* 32, 2276-2286, 2012.

Shemmell J, An JH, Perreault EJ. The differential role of motor cortex in stretch reflex modulation induced by changes in environmental mechanics and verbal instruction. *J Neurosci* 29: 13255-13263, 2009.

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

Taubert M, Dafotakis M, Sparing R, Eickhoff S, Leuchte S, Fink GR, Nowak DA. Inhibition of the anterior intraparietal area and the dorsal premotor cortex interfere with arbitrary visuo-motor mapping. *Clin Neurophysiol 121:* 408-413, 2010

Telgen S, Parvin D, Diedrichsen J. Mirror reversal and visual rotation are learned and consolidated via separate mechanisms: recalibrating or learning de novo? *J Neurosci 34:* 13768-13779, 2014.

Todorov E, Jordan MI. Optimal feedback control as a theory of motor control. *Nat Neurosci* 5: 1226-1235, 2002.

Tracey DJ, Walmsley B, Brinkman J. 'Long-loop' reflexes can be obtained in spinal monkeys. *Neurosci Lett 1*8: 59-65. 1980.

Waters-Metenier S, Husain M, Wiestler T, Diedrichsen J. Bihemispheric transcranial direct current stimulation enhances effector-independent representations of motor synergy and sequence learning. *J Neurosci* 34: 1037-1050, 2014.

Weiler J, Gribble PL, Pruszynski JA. Goal-dependent modulation of the long-latency stretch response at the shoulder, elbow, and wrist. *J Neurophysiol* 114: 3242-3254, 2015.

Weiler J, Saravanamuttu J, Gribble PL, Pruszynski JA. Coordinating long-latency stretch responses across the shoulder, elbow, and wrist during goal-directed reaching. *J Neurophysiol* 116: 2236-2249, 2016.

Vaca-Palomares I, Díaz R, Rodríguez-Labrada R, Medrano-Montero J, Vázquez-Mojena Y, Velázquez-Pérez L, Fernandez-Ruiz J. Spinocerebellar ataxia type 2 neurodegeneration differentially affects error-based and strategic-based visuomotor learning. *Cerebellum 12*: 848-855, 2013.

Yang L, Michaels JA, Pruszynski JA, Scott SH. Rapid motor responses quickly integrate visuospatial task constraints. *Exp Brain Res* 211: 231-242, 2011.