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Primary motor cortex underlies multi-joint integration for fast feedback control

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Abstract

A basic difficulty for the nervous system is integrating locally ambiguous sensory information to form accurate perceptions about the outside world[1–4]. This local-to-global problem is also fundamental to motor control of the arm since complex mechanical interactions between the shoulder and elbow allow a particular amount of motion at one joint to arise from an infinite combination of shoulder and elbow torques[5] (Fig. 1a). Here we show that a transcortical pathway through primary motor cortex (M1) resolves this ambiguity during fast feedback control. We demonstrate that single M1 neurons of behaving monkeys can integrate shoulder and elbow motion information into motor commands which appropriately counter the underlying torque within ~50 ms of a mechanical perturbation. Moreover, we reveal a causal link between M1 processing and multi-joint integration in humans by showing that shoulder muscle responses occurring ~50 ms after pure elbow displacement can be potentiated by transcranial magnetic stimulation. Our results show that M1 underlies multi-joint integration during fast feedback control, demonstrating that transcortical processing permits feedback responses to express a level of sophistication previously reserved for voluntary control and providing neurophysiological

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support for influential theories positing that voluntary movement is generated by the intelligent manipulation of sensory feedback[6,7].

Keywords

feedback; primary motor cortex; single-unit recording; transcranial magnetic stimulation

MAIN TEXT

Extensive research has shown that some of our fastest motor reactions express a degree of sophistication which rivals voluntary actions[8–10] but little is known about the neural substrates which underlie this sophistication[11]. The present monkey and human studies test whether primary motor cortex (M1) provides a neural substrate for integrating shoulder and elbow motion information for fast feedback control, a key ability for generating fast and accurate corrections[8,12,13]. M1 is a prime candidate to mediate this ability because: 1) M1 forms part of a transcortical feedback pathway, giving it access to the required afferent information[14,15]; 2) M1 is a key node for voluntary control, which appropriately incorporates shoulder and elbow information when generating commands for voluntary actions[16,17]; and 3) influential theories posit that voluntary movement involves the sophisticated manipulation of sensory information[6], suggesting substantial functional and anatomical overlap between voluntary and feedback control[7].

We first determined whether individual neurons in monkey M1 exhibit a pattern of activity consistent with multi-joint motion integration during fast feedback control. Two rhesus monkeys were trained to counter unpredictable step-torque perturbations applied at the shoulder and/or elbow which displaced their hand from a central target. To receive water reward, the monkeys needed to return their hand to the target within 750 ms and remain within it for an additional 3 s, allowing us to analyze both fast feedback responses (<100 ms post-perturbation) and steady-state motor outputs (last 1s of stabilization) to the applied torque within the same trial.

Since our paradigm (Fig. 1a) was specifically designed to examine sensorimotor control of the shoulder joint, we were principally interested in neurons whose steady-state motor outputs varied with the exerted shoulder torque (i.e. shoulder-like neurons). As in our previous studies, we found that the population of neurons was biased towards combined shoulder and elbow torques (Rayleigh Test for Bimodality, $P < 0.05$) making shoulder-like neurons relatively rare[18]. In total, 25 of 356 M1 neurons were categorized as shoulder-like because they exhibited significant directional tuning to steady-state loads (plane-fit, $P < 0.05$) and a preferred torque direction within 15° of either shoulder flexion or shoulder extension torque (Supplementary Fig. 1).

The key question is how quickly shoulder-like neurons become selectively tuned to shoulder torque following an unexpected torque perturbation. This is not a mere restatement of our selection criteria because local shoulder information is sufficient for countering the underlying shoulder torque in the steady-state. In contrast, the only way that fast feedback

responses can account for the ambiguous relationship between local joint motion and global torque is by integrating information from both the shoulder and elbow.

The need to resolve ambiguous motion information for fast feedback control is exemplified in our first experiment where we applied either shoulder torque or elbow torque perturbations (Fig. 1b). These perturbations caused substantially different amounts of elbow motion but nearly identical shoulder motion (Fig 1c). If shoulder-like neurons integrate both shoulder and elbow motion information, then they should differentiate between the two conditions and respond more strongly to the shoulder torque perturbation than the elbow torque perturbation. Fig. 2a presents an exemplar neuron which follows this pattern. It was maximally active during steady-state compensation of shoulder-extension torque and it responded more strongly to the shoulder-extension torque perturbation than the elbow-flexion torque perturbation (t-test, $t_{18} = 2.2$, $P < 0.05$) within ~60 ms of perturbation onset. Moreover, the population of shoulder-like neurons (Fig. 2b, Supplementary Fig. 2a) also quickly expressed greater activity for shoulder torque perturbations than elbow torque perturbations (paired t-test, $t_{24} = 2.7$, $P < 0.01$; 15 of 20 neurons in Monkey P and 4 of 5 neurons in Monkey X show the expected trend).

Our hypothesis makes the additional prediction that differential amounts of inhibition should occur to torque perturbations opposite a neuron's steady-state preference. That is, a neuron which is maximally active during steady-state compensation of shoulder-extension torque should quickly express more inhibition to shoulder-flexion torque perturbations than elbow-extension torque perturbations. This prediction was verified across the population (paired t-test, $t_{24} = 2.1$, $P < 0.05$) demonstrating that shoulder-like neurons possess a pattern of multi-joint integration appropriate for both excitatory and inhibitory perturbations (Supplementary Fig. 2a).

Another situation where the nervous system must resolve locally-ambiguous information is exemplified in our second experiment where torque perturbations at both the shoulder and elbow cause substantial elbow motion but no shoulder motion (Fig. 1d,e). If fast feedback responses of shoulder-like neurons appropriately integrate shoulder and elbow motion to counter the underlying torque then they should respond to this perturbation even though the shoulder joint is not displaced and no local shoulder sensor (in the muscle, joint or skin) can signal the event. Indeed, the exemplar neuron (Fig. 2c) increased its activity within ~60 ms of pure elbow extension motion which is appropriate for countering the underlying shoulder extensor torque and consistent with its response in Experiment 1 (t-test, $t_{18} = 5.1$, $P < 10^{-3}$). The population of shoulder-like neurons also quickly expressed the predicted response pattern (Fig. 2d, Supplementary Fig. 2b; paired t-test, $t_{24} = 4.4$, $P < 10^{-3}$; 15 of 20 neurons in Monkey P and 4 of 5 neurons in Monkey X show the expected trend).

The above analysis established that M1 neurons integrate shoulder and elbow motion to counter the underlying torque perturbation within 50–100 ms of perturbation onset (Fig. 3a). The response of shoulder-like neurons in this epoch paralleled the response of monkey shoulder muscles in the same epoch (Fig. 3b) suggesting that M1 contributes to the observed muscle activity. To provide further evidence of a functional link, we calculated the temporal evolution of multi-joint integration for both neurons and muscles using an ROC analysis[9,19].

We found that multi-joint integration occurred in the population of M1 neurons 8–20 ms before it occurred in muscles (Fig. 3c). Although this temporal lead is substantially shorter than typical measurements of M1-to-muscle latency at the initiation of voluntary movement (~60 ms)[20], it is consistent with the known conduction delay between M1 neurons and muscles of the monkey upper-limb[15,21].

Interestingly, shoulder-like M1 neurons did not immediately account for the limb's mechanical properties, displaying a non-specific response to the torque perturbations from ~20 to 50 ms following perturbation onset (Fig. 2b,d). A similar non-specific response was observed across our whole population of M1 neurons (Supplementary Fig. 2c,d). For example, neurons which preferentially responded to steady-state elbow torque (elbow-like neurons, Supplementary Fig. 1) initially exhibited the same response whether the perturbation flexed or extended the elbow joint as in Experiment 2 (Fig. 3d). This non-specific response is strikingly similar to a population of neurons in primary visual cortex (V1) which initially respond ambiguously to objects placed in their receptive field and become sensitive to motion direction only after 20–30 ms[2], a delay attributed to interactions among V1 neurons[22]. The temporal evolution of multi-joint integration that we observe may also reflect processing intrinsic to M1 or it may be caused by delayed contributions from other neural structures such as somatosensory cortex and cerebellum, an important issue that warrants further investigation.

Although the activity of single neurons in monkeys provides evidence that M1 is functionally linked to multi-joint integration for fast feedback control, the data are ultimately correlational and cannot establish whether M1 causes the co-varying pattern of shoulder muscle activity. We addressed this issue by directly influencing the processing of M1 in human participants while they generated feedback corrections similar to the monkey study. Applying a single pulse of magnetic stimulation (TMS) over M1 will excite its intrinsic circuits and evoke a synchronous burst of muscle activity. When TMS is applied in conjunction with a joint perturbation the response in the stretched muscle is much larger than the linear sum of the response to TMS alone and the perturbation alone[23–25]. These supra-linear effects – previously demonstrated in the finger, wrist, and elbow muscles – occur only when TMS is timed to evoke a response >50 ms following the perturbation, suggesting that the two stimuli interact through a common cortical circuit and that feedback control at latencies >50 ms reflects processing in M1. We established the validity of this technique for shoulder muscles since a supra-linear response occurred when TMS was delivered ~65 ms after the shoulder muscle was stretched (i.e. during the long-latency reflex; t-test; Extensor: $t_9 = 6.7$, $P < 10^{-3}$; Flexor: $t_8 = 6.0$, $P < 10^{-3}$) but not 25 ms after the muscle was stretched (i.e. during the short-latency reflex; Extensor: $t_9 = -0.5$, $P > 0.5$; Flexor: $t_8 = 0.5$, $P > 0.5$) when only spinal processes could contribute (Supplementary Fig. 3, Left Column).

The critical question is whether M1 causally contributes to multi-joint integration for fast feedback control. We tested this hypothesis by applying TMS in conjunction with the torque perturbation that causes pure elbow displacement (Fig. 1d,e). Any supra-linearity of the shoulder muscle response in this condition must reflect afferent information from the elbow joint onto cortical circuits controlling shoulder muscles since local shoulder afferents are not

physically affected by pure elbow motion. The predicted supra-linear effect was observed for both shoulder flexors and extensors (Fig. 4, Supplementary Fig. 3, Right Column) with TMS delivered at 65 ms (Extensor: $t_9 = 3.8$, $P < 0.01$; Flexor: $t_8 = 5.3$, $P < 10^{-3}$) but not at 25 ms (Extensor: $t_9 = -2.7$, $P > 0.5$; Flexor: $t_8 = -0.1$, $P > 0.5$). The observed supra-linearity likely reflects latency-specific engagement of M1 rather than a general change in motor neuron excitability since we found no correlation between the magnitude of perturbation-evoked activity and the amount of supra-linearity at either latency ($P > 0.1$, Supplementary Fig. 4). Taken together, these results provide strong evidence that M1 causally underlies multi-joint integration for fast feedback control.

Previous studies have demonstrated that fast feedback responses in M1 are scaled by task-constraints such as movement amplitude[26], surface texture[27] and intended vigor[14,28]. Our results show that M1 also integrates locally-ambiguous motion information into a global response that accounts for the limb's mechanical properties, a more complex capability that is central to successfully guiding whole-arm movements[17]. It is well established that the voluntary motor system accounts for the mechanical properties of the limb and that this capability is expressed in the activity of M1 neurons[29]. We have previously argued that the functional similarity of voluntary and feedback control is not an accident and likely arises because of a common neural implementation that includes M1[7]. This expectation is consistent with recent theories of sensorimotor control which posit that voluntary behavior involves the sophisticated manipulation of sensory information[6]. If our suggestion is true then feedback processing in M1 should possess all the capabilities of voluntary processing in M1 and, likewise, studying feedback processing may provide a useful window into voluntary control.

METHODS

Participants and Apparatus

The studies presented in this paper were approved by the Queen's University Research Ethics Board. All monkey (n = 2, macaca mulatta, ~10 Kg, male) procedures were approved by the Queen's University Animal Care Committee. Human subjects (6 females, 4 males, median age = 27) were neurologically unimpaired, had normal/corrected vision and provided informed consent. Human and monkey experiments were performed using different versions of the same robotic exoskeleton (KINARM, BKIN Technologies, Kingston, ON) which allows combined flexion and extension movements of the shoulder and elbow in the horizontal plane and can independently apply mechanical loads to the shoulder and/or elbow[30]. Target lights and simulated hand feedback were presented in the horizontal plane of the task via a virtual reality display and direct vision of the hand was limited either by a physical barrier (humans) or by a lack of ambient light (monkeys).

Neural, Muscle and Kinematic Recordings

Recording chambers were surgically implanted under inhalation anesthetic and neural recordings were performed according to standard techniques[18,29]. Single tungsten microelectrodes (FHC, Bowdoin, ME) were advanced until neural activity was observed. Individual neurons were then isolated and neural activity was recorded from those neurons

with clear responses to either passive or active movements of the shoulder and/or elbow. Neurons which primarily responded to motion of the wrist or fingers were not recorded. Neurons recorded in the task (n = 356) were located in the rostral bank of the central sulcus as well as more superficial sites where previous mapping efforts showed that trains of electrical stimulation (11 pulses, 333Hz, 0.2ms pulse width, <50uA) could elicit shoulder and/or elbow movement. Post-mortem histology confirmed that recording sites from Monkey P were located in M1.

Monkey muscle activity was acquired from mono-articular shoulder muscles (Anterior Deltoid, Middle Deltoid, Posterior Deltoid, Pectoralis Major; n = 34) using fine-wire electrodes. Electrodes consisted of two single-strand wires and were individually inserted into the muscle belly spaced ~5 mm apart. Insertion was guided by anatomical landmarks and was confirmed by microstimulation. Human experiments used surface electrodes (DE-2.1, Delsys, Boston, MA) and focused on those mono-articular muscles which could be readily recorded from the surface (Posterior Deltoid, Pectoralis Major; n = 19). Muscle activity was recorded at either 4 KHz (monkey) of 1 KHz (human), aligned on perturbation onset and full-wave rectified prior to analysis[9]. Only those muscles with clear phasic responses to the mechanical perturbation were analyzed. Kinematic data and applied torques were acquired directly from the KINARM device and were sampled at the same rate as the muscle activity.

Transcranial Magnetic Stimulation

We followed standard procedures in the TMS portion of the study[23–25]. Single pulses of TMS (MES-10, Cadwell, Kennewick, WA) were applied over left M1 with a posterior orientation of 30–45°. Placement and orientation of the double coil was chosen to evoke the largest response from the muscle of interest, ~4.5cm lateral from vertex. Stimulation magnitude was selected to deliver the smallest-possible consistent response (evoked response on seven consecutive stimulations, average of 40% and 51% of the stimulator's maximum output for the posterior deltoid and pectoral major, respectively) when the muscle of interest actively countered a 3 Nm background load (i.e. active motor threshold).

Experimental Paradigm

The experimental procedure and logic have been previously described[8]. The major difference in the human portion of this study was the parallel implementation of TMS. Briefly, subjects stabilized their hand in a small central target while countering a steady state shoulder torque (3 Nm) which activated either the shoulder flexor or extensor muscles. After a random hold time (1–4 s), an unpredictable torque pulse (100 ms duration) was introduced and the trial ended when the subjects re-stabilized in the target for 500 ms.

In total, four torque perturbations were used in the human study. Two single-joint torque perturbations (3 Nm shoulder-flexion for shoulder flexor muscles and 3 Nm shoulder-extension for shoulder extensor muscles) made up Experiment 1 and two multi-joint torque perturbations (3Nm shoulder-flexion / 3Nm elbow-flexion for shoulder flexor muscles; 3Nm shoulder-extension / 3Nm elbow-extension for shoulder extensor muscles) made up Experiment 2. Perturbation only, TMS only and combined TMS and perturbation trials were

randomly interleaved. In combined TMS and perturbation trials, the TMS was timed to evoke shoulder muscle activity either ~25 ms or ~65 ms after perturbation onset.

The perturbation, TMS placement and TMS intensity were chosen for the shoulder flexor muscle and shoulder extensor muscle in two successive blocks. Half the subjects began with the conditions for the shoulder flexor muscle and half the subjects began with the conditions for the shoulder extensor muscle. Thirty repeats of the 14 conditions were collected for a total of 420 trials in a session that lasted about 2.5 hours.

Monkeys performed a similar paradigm with ~10x smaller loads. Unlike humans, the monkeys did not counter a pre-perturbation background load and they were exposed to eight randomly-interleaved step-torque perturbations ([Shoulder Torque, Elbow Torque], applied flexion/extension = positive/negative: 1. [0.28 Nm, 0 Nm], 2. [0.24, 0.24], 3. [0, 0.24], 4. [−0.2, 0.2], 5. [−0.28, 0], 6. [−0.24, −0.24], 7. [0, −0.24], 8. [0.2, −0.2]) and catch trials where no perturbations occurred. Four of these perturbations (1,3,5,7) formed Experiment 1 and two (2,6) formed Experiment 2. All eight conditions were used to calculate the steady-state tuning of each neuron by performing a planar regression on the neural activity when the monkey had re-stabilized their hand at the central target[18]. To receive water reward, the monkeys needed to return their hand to the target within 750 ms and remain within it for an additional 3 s, allowing us to analyze both fast feedback responses (<100 ms post-perturbation) and steady-state motor outputs (last 1s of stabilization) to the applied torque within the same trial. Five to 20 repeats were collected per experimental condition.

Population responses for both muscles and neurons were calculated by collapsing across shoulder flexion and extension conditions according to their predicted excitatory and inhibitory effects. That is, applied shoulder-flexion torque perturbations were excitatory for shoulder extensor muscles/neurons and inhibitory for shoulder flexor muscles/neurons. Applied shoulder-extension torque perturbations were excitatory for shoulder flexor muscles/neurons and inhibitory for shoulder extensor muscles/neurons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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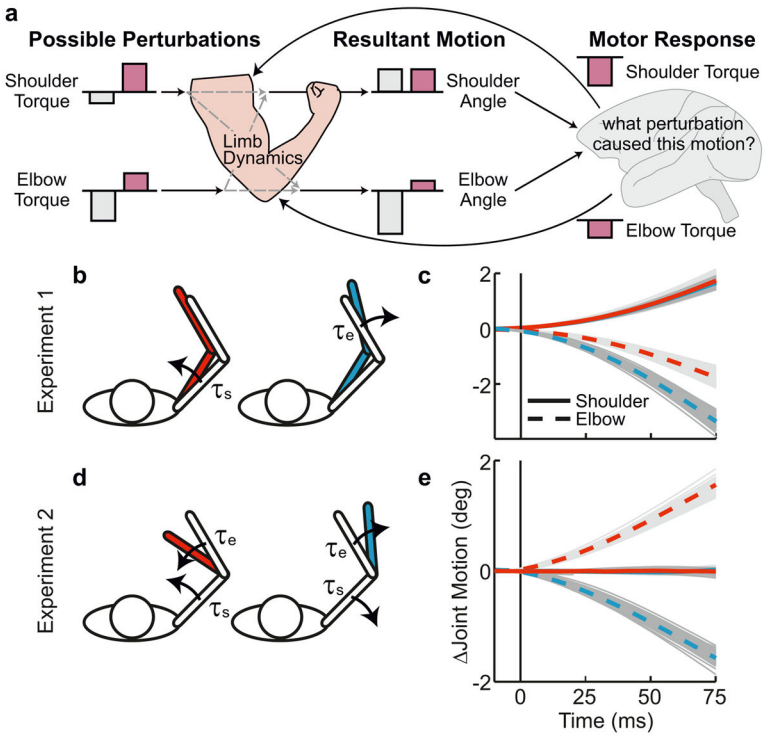

Figure 1. Experimental methods

a, Because of the mechanical properties of the limb, an infinite combination of shoulder and elbow torques can cause the same shoulder motion. Determining which torque perturbation caused the observed shoulder motion requires integrating elbow information. **b**, Limb configuration before (unfilled) and after (filled) a torque perturbation was applied at either the shoulder or elbow. Opposite conditions (shoulder-extensor / elbow-flexor torque) not shown. **c**, Joint displacement resulting from the shoulder (red) and elbow (blue) perturbation conditions in **b**. The perturbations yielded similar shoulder motion but substantially different elbow motion. Solid lines represent the mean displacements and the grey lines show individual trials. **d**, Limb configuration before and after a multi-joint flexion or multi-joint extension torque perturbation. **e**, The perturbations caused substantial elbow motion but almost no shoulder motion.

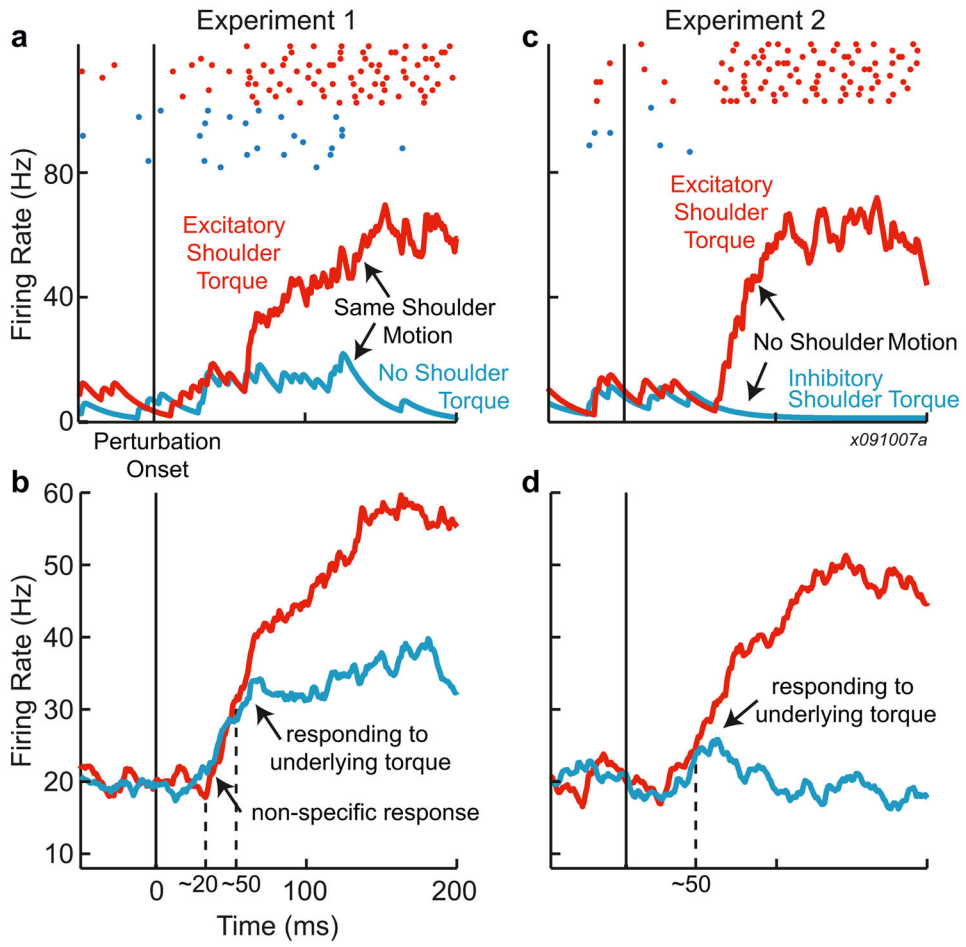

Figure 2. Neurons in primary motor cortex

a, Responses of an exemplar shoulder-like neuron to either an elbow (blue) or shoulder (red) torque perturbation in Experiment 1. Data aligned on perturbation onset. Tick marks represent single action potentials and the trace depicts the average response. **b,** Same format as **a** but representing the population response across shoulder-like neurons. **c** and **d**, Same format as **a** and **b** but for Experiment 2.

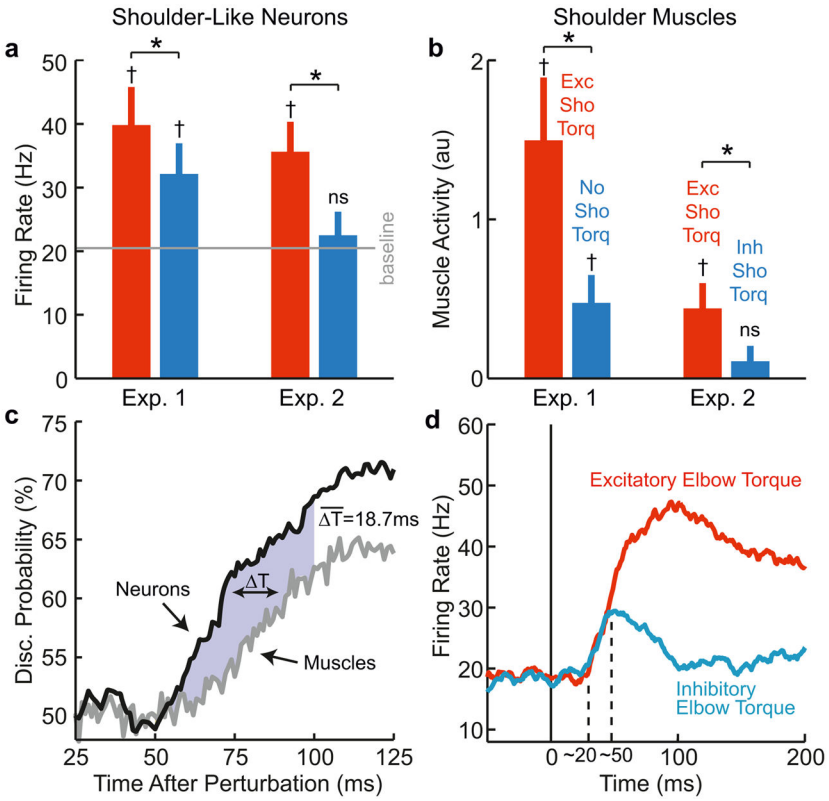

Figure 3. Population analysis of neurons and muscles

a, Binned response (50–100 ms post-perturbation) across shoulder-like neurons. For Experiment 1, the red and blue bars represent responses to shoulder and elbow torque perturbations, respectively. For Experiment 2, the red and blue bars depict responses to pure elbow motion caused by a torque perturbation aligned with or opposite to the neuron's steady-state preference, respectively. Error bars indicate SEM, the (*) indicates significant differences between conditions (paired t-test, $p < 0.05$) and the (†) denotes significant differences from baseline. **b,** Same format as **a** but for the population of muscles. Because of the normalization procedure, muscle baseline activity is 0 au. **c,** Average ROC over time for the population of neurons and muscles. Conditions are collapsed across experiments such that the vertical axis is a metric of multi-joint integration. On average, the neurons led the muscles by ~18 ms as estimated by the average temporal difference between the neural and muscle ROC curves from 50 to 100 ms post-perturbation (filled area). **d**, Same format as Fig. 2d but for elbow-like neurons.

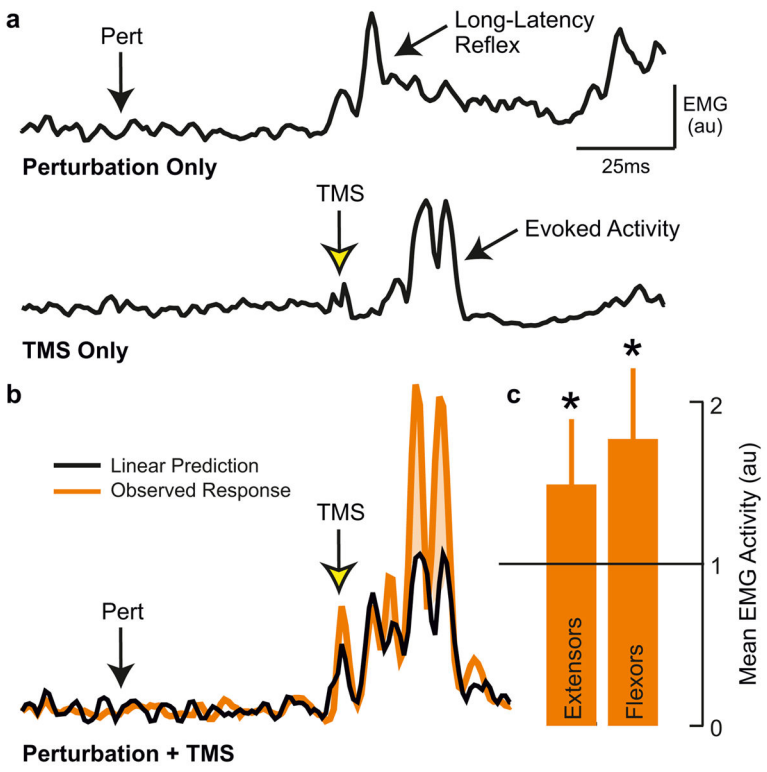

Figure 4. TMS and perturbation evoked activity in human shoulder muscles

a, Response evoked in an exemplar shoulder muscle (Posterior Deltoid) when a mechanical perturbation or TMS was applied in isolation. **b**. Observed response (orange) and linear prediction (sum of responses in **a**, black) when the mechanical perturbation and TMS were applied in the same trial. **c**. Group muscle response (mean and STD) when TMS was paired with the perturbation normalized by the sum of their separate effects ($E_{norm} = E_{TMS,pert} / (E_{TMS} + E_{pert})$). Values above 1 indicate supra-linearity.