

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

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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, because complex mechanical interactions between shoulder and elbow allow a particular amount of motion at one joint to arise from an infinite combination of shoulder and elbow torques⁵. Here we show, in humans and rhesus monkeys, 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 that appropriately counter the underlying torque within about 50 milliseconds 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 milliseconds after pure elbow displacement can be potentiated by transcranial magnetic stimulation. Taken together, our results show that transcortical processing through M1 permits feedback responses to express a level of sophistication that rivals voluntary control; this provides neurophysiological support for influential theories positing that voluntary movement is generated by the intelligent manipulation of sensory feedback^{6,7}.

Extensive research has shown that some of our fastest motor reactions express a degree of sophistication that rivals voluntary actions^{8–10}, but little is known about the neural substrates that underlie this sophistication¹¹. The present monkey and human studies test the hypothesis that 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) it forms part of a transcortical feedback pathway, giving it access to the required afferent information^{14,15}; (2) it 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 information⁶, suggesting substantial functional and anatomical overlap between voluntary and feedback control⁷.

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 male 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 analyse both fast feedback responses (<100 ms post-perturbation) and steady-state motor outputs (last 1 s of stabilization) produced in response to the applied torque within the same trial.

Because our experimental scheme (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 (that is, 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 rare¹⁸. 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

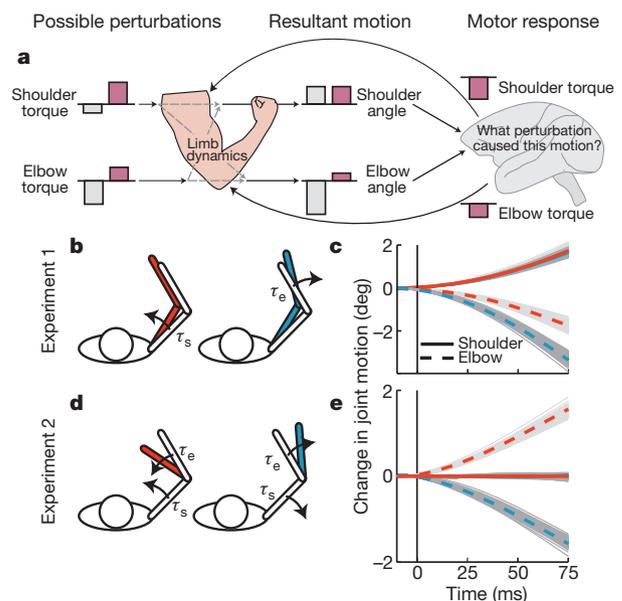


Figure 1 | Experimental methods. **a**, Because of the mechanical properties of the limb, an infinite combination of possible shoulder and elbow torque perturbations can cause the same resultant shoulder motion. Generating the shoulder motor response which counters the applied shoulder torque perturbation requires integrating elbow information. **b**, Limb configuration before (unfilled) and after (filled) a torque perturbation was applied at either the shoulder (τ_s) or elbow (τ_e) as in experiment 1. 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 as in experiment 2. **e**, The perturbations shown in **d** caused substantial elbow motion but almost no shoulder motion.

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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. Figure 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 out of 20 neurons in monkey P and 4 out of 5 neurons in monkey X show the expected trend).

Our hypothesis makes the additional prediction that different amounts of inhibition should occur to torque perturbations that are opposite to 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 to 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).

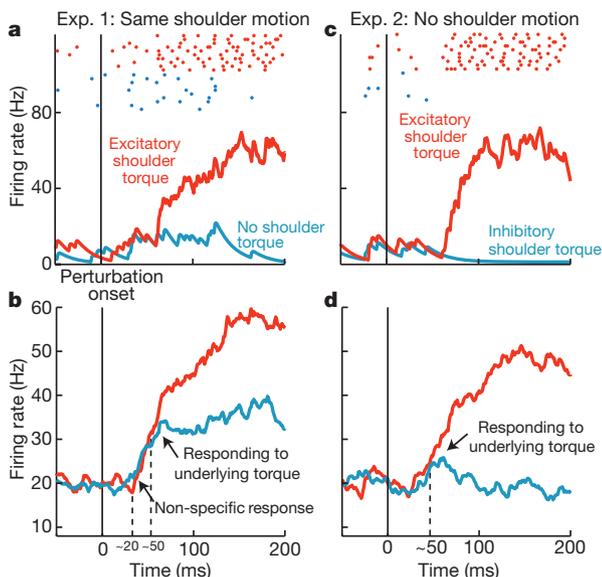


Figure 2 | Neurons in primary motor cortex. **a**, Responses of an exemplar shoulder-like neuron to either an elbow (blue) or shoulder (red) torque perturbation in experiment 1 where shoulder or elbow torque perturbations yielded the same shoulder motion. Data aligned on perturbation onset. Dots represent single action potentials and the trace depicts the average response. **b**, Same format as **a** but representing the population response across shoulder-like neurons. The arrows indicate when neural activity is non-specific to the underlying shoulder torque perturbation and then when it begins to respond appropriately to the underlying shoulder torque. **c**, **d**, Same format as **a** and **b** but for experiment 2 where combined shoulder and elbow torque perturbations yielded no shoulder motion.

Another situation where the nervous system must resolve locally ambiguous information is exemplified in our second experiment, in which 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 our first experiment (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 out of 20 neurons in monkey P and 4 out 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 a binned epoch from 50 to 100 ms after 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 a receiver operating characteristic (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

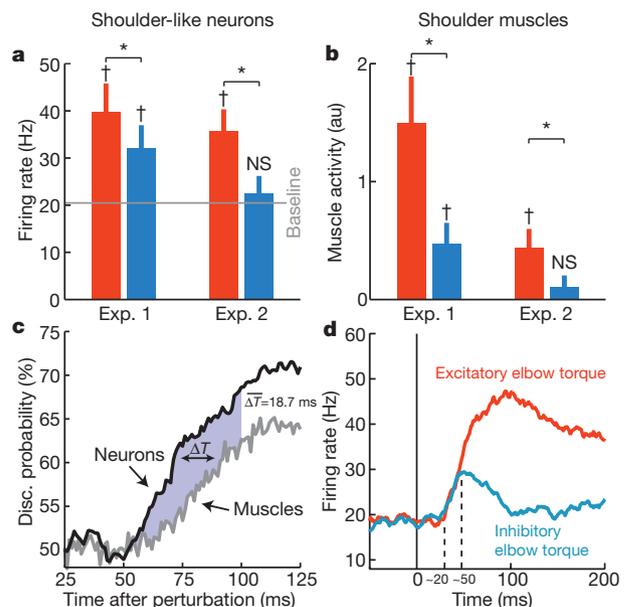


Figure 3 | Population analysis of neurons and muscles. **a**, Binned response (50–100 ms post-perturbation) across shoulder-like neurons. For Experiment 1, the red and blue bars represent responses to shoulder and elbow torque perturbations, respectively. For Experiment 2, the red and blue bars depict responses to pure elbow motion caused by a torque perturbation aligned with or opposite to the neuron's steady-state preference, respectively. Error bars, s.e.m.; *significant differences between conditions (paired t -test, $P < 0.05$); †significant differences from baseline; NS, not significant. **b**, Same format as **a** but for the population of muscles. Because of the normalization procedure, muscle baseline activity is 0 arbitrary units (a.u.). **c**, Average discrimination probability over time for the population of neurons and muscles as determined by ROC analysis. 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 ~ 19 ms as estimated by the mean temporal difference between the neural and muscle ROC curves (ΔT) from 50 to 100 ms post-perturbation (shaded area). **d**, Same format as Fig. 2d but for elbow-like neurons.

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 our second experiment (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 (ref. 2), a delay attributed to interactions among V1 neurons²². 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; this is 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 above 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 those in the monkey study. Applying a single pulse of transcranial magnetic stimulation (TMS) over M1 will excite its intrinsic circuits and, thereby, evoke a 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 after 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, as a supra-linear response occurred when TMS was delivered ~ 65 ms after the shoulder muscle was stretched (that is, 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 (that is, 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, because 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 65 ms after perturbation onset (extensor: $t_9 = 3.8$, $P < 0.01$; flexor: $t_8 = 5.3$, $P < 10^{-3}$) but not 25 ms after perturbation onset (extensor: $t_9 = -2.7$, $P > 0.5$; flexor: $t_8 = -0.1$, $P > 0.5$). The observed supra-linearity probably reflects latency-specific engagement of M1 rather than a general change in motor neuron excitability, because 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.

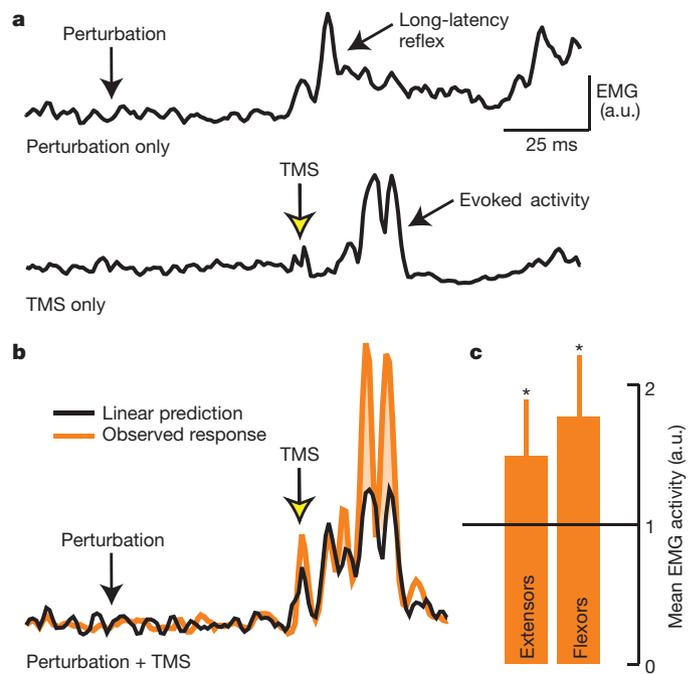


Figure 4 | TMS and perturbation evoked activity in human shoulder muscles. **a**, Response evoked in an exemplar shoulder muscle (posterior deltoid) when a mechanical perturbation or TMS was applied in isolation. Note that the mechanical perturbation yielded a robust long-latency reflex and that the TMS yielded substantial evoked activity. **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 + s.d.) when TMS was paired with the perturbation normalized by the sum of their separate effects ($E_{\text{norm}} = E_{\text{TMS,per}} / (E_{\text{TMS}} + E_{\text{per}})$). Values above 1 indicate supra-linearity; *significant supra-linearity (*t*-test, $P < 0.05$).

Previous studies have demonstrated that fast feedback responses in M1 are scaled by task-constraints, such as movement amplitude²⁶, surface texture²⁷ and intended vigour^{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 movements¹⁷. 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 neurons²⁹. We have previously argued that the functional similarity of voluntary and feedback control is not an accident and probably arises because of a common neural implementation that includes M1⁷. This expectation is consistent with recent theories of sensorimotor control, which posit that voluntary behaviour involves the sophisticated manipulation of sensory information⁶. 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 SUMMARY

Studies were approved by the Queen's University Research Ethics Board and Animal Care Committee. Ten human subjects gave informed consent and completed the experiments as previously described⁸. Two monkeys (*Macaca mulatta*, ~ 10 kg) performed a similar experimental scheme in a miniaturized version of the same apparatus with $\sim 10\times$ smaller loads (KINARM, BKIN Technologies)³⁰. Monkeys did not counter a pre-perturbation background load, and were exposed to eight randomly-interleaved step-torque perturbations, four used in experiment 1 and two used in experiment 2. All eight conditions were used to calculate steady-state tuning by performing a planar regression on the neural activity when the monkey had re-stabilized its hand at the central target¹⁸.

Neural recordings were performed with single electrodes and processed according to standard techniques^{18,29}. Monkey muscle activity was acquired from mono-articular shoulder muscles (anterior/middle/posterior deltoid, pectoralis major;

$n = 34$) using fine-wire electrodes. Human experiments used surface electrodes (posterior deltoid, pectoralis major; $n = 19$). Population responses for both neurons and muscles were collapsed across shoulder flexion and extension conditions according to their predicted excitatory and inhibitory effects (for example, shoulder-flexion torque perturbations were excitatory for shoulder extensor muscles/neurons and inhibitory for shoulder flexor muscles/neurons).

Single pulses of TMS (MES-10, Cadwell) were applied over left M1 with a posterior orientation of 30–45°. Placement/orientation of the double coil was chosen to evoke the largest response from the muscle of interest, ~4.5 cm lateral from vertex. Stimulation magnitude (40–50% of maximum) was selected to deliver the smallest-possible consistent response (evoked activity on seven consecutive trials) when the shoulder muscle countered a steady-state load. TMS only, perturbation only and combined TMS and perturbation trials were randomly interleaved. TMS was timed to evoke shoulder muscle activity either ~25 ms or ~65 ms after perturbation onset.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions J.A.P. collected and analysed the monkey data, helped design the experiments, interpreted the results and helped write the manuscript. I.K. collected and analysed the human data, helped design the experiments, interpreted the results and helped write the manuscript. J.Y.N. helped collect the human data. M.O. helped collect a subset of the monkey data. B.B. helped interpret the human data. S.H.S. helped design the experiments, interpreted the results and helped write the manuscript.

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METHODS

Participants and apparatus. The studies presented 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) 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 elbow³⁰. 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 anaesthetic, and neural recordings were performed according to standard techniques^{18,29}. Single tungsten microelectrodes (FHC) 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, 333 Hz, 0.2 ms pulse width, <50 μ A) 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 (Bortec AMT-8) 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) or 1 kHz (human), aligned on perturbation onset and full-wave rectified before analysis⁹. Only those muscles with clear phasic responses to the mechanical perturbation were analysed. 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) were applied over left M1 with a posterior orientation of 30–45°. Placement and orientation of the double cone coil were chosen to evoke the largest response from the muscle of interest, ~4.5 cm 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 N m background load (that is, active motor threshold).

Experimental scheme. The experimental procedure and logic have been previously described⁸. 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 N m) 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 N m shoulder-flexion for shoulder flexor muscles and 3 N m shoulder-extension for shoulder extensor muscles) made up experiment 1, and two multi-joint torque perturbations (3 N m shoulder-flexion/3 N m elbow-flexion for shoulder flexor muscles; 3 N m shoulder-extension/3 N m 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 h.

Monkeys performed a similar scheme with ~10 \times 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 N m, 0 N m], 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 its hand at the central target¹⁸. 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 analyse both fast feedback responses (<100 ms post-perturbation) and steady-state motor outputs (last 1 s of stabilization) to the applied torque within the same trial. Five to twenty 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.