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RESEARCH ARTICLE

Control of Movement

Human short-latency reflexes show precise short-term gain adaptation after prior motion

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Abstract

The central nervous system adapts the gain of short-latency reflex loops to changing conditions. Experiments on biomimetic robots showed that reflex modulation could substantially increase energy efficiency and stability of periodic motions if, unlike known mechanisms, the reflex modulation both acted precisely on the muscles involved and lasted after the motion. This study tests the presence of such a mechanism by having participants repeatedly rotate either their right elbow or shoulder joint before perturbing either joint. The results demonstrate a mechanism that modulates short-latency reflex gains after prior motion with joint-specific precision. Enhanced gains were observed hundreds of milliseconds after movement cessation, a timescale well suited to quickly adapt overall periodic motion cycles. A serotonin antagonist significantly decreased these postmovement gains diffusely across joints. But blocking serotonin did not affect the joint specificity of the gain scaling more than a placebo, suggesting that serotonin sets the overall reflex gain across joints after movement by an effect that is modulated in a joint-specific manner by an unidentified neural circuit. These results confirm the existence of a new, joint-specific, fast, persistent adaptation of short-latency reflex loops induced by motion in human arms.

NEW & NOTEWORTHY Our results expose a new spinal cord mechanism that modulates motoneuron gains, uniquely equipped to adapt movement in changing environments: it acts with joint-specific precision, reacts quickly to mechanical changes, and still persists long enough to accumulate information across movement cycles. The overall motoneuron gain across joints can be scaled down by an antagonist to serotonergic neuromodulation, whereas its joint specificity is unaffected by the antagonist and thus due to a complementary, unknown spinal mechanism.

CNS motor feedback; compliant movements; serotonergic neuromodulation; short-latency reflex adaptation

INTRODUCTION

During strong, fast, repetitive movements like locomotion, humans and other animals use their compliant muscles and tendons to cushion impacts with the environment, store the impact energy, and convert it back to kinetic energy for acceleration (1, 2). When the environment changes, the central nervous system (CNS) must precisely adapt the compliance of the musculoskeletal system so that the stretch occurs largely within the passive compliant tendons. The CNS achieves this through cocontraction of antagonistic muscles (3, 4) and task-dependent excitability of the neuronal circuitry (5, 6). For this adaptation, many studies have elaborated how cortical feedback loops use internal models

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of the biomechanical system to modify the long-latency stretch feedback gains (7, 8). In contrast, short-latency spinal feedback loops are only known to change with background muscle activity (9, 10) or through extensive long-term training (11).

However, two recent papers have raised the intriguing possibility that short-latency reflexes also can be modified, allowing rapid tuning of joint compliance. The short-latency reflex gain can accordingly change during ongoing gamma motor neuron drive (12, 13) and for ongoing sensory input signaling different postures (14), potentially by presynaptic inhibition (15). The raphe nuclei in the medulla can additionally modulate the gain beyond cessation of sensory and motor signals (16), as they receive proprioceptive motor feedback (17) and consequently release serotonin onto motoneurons (18) to increase their excitability (19, 20). But the low precision of monoaminergic neuromodulation in other CNS regions (21) has shaped the view that the spinal serotonergic system also acts merely through diffuse modulation that affects all joints simultaneously (16, 20).

In past research, we proposed another pathway that modulates the short-latency stretch reflex gain (22, 23), which quickly adapts motoneuronal gains to sensory motor feedback, maintains information beyond the movement that triggers it, and acts on individual joints. This hypothesis emerged from the functional advantage of such a control mechanism for robots that mimic the compliant properties of muscles and tendons (24, 25). For such robots, we developed a control algorithm that was not biologically inspired but resembled a gain modulation pathway, as it uses sensory information to adapt joint forces to changing environments, as exemplified in Fig. 1, *B–F*. The multiplicative gain accumulates over several seconds, long enough to regard the overall movement cycle and yet fast enough to react, e.g., when the ground stiffness changes. The functional advantage of this controller can be intuitively observed for a simple environment where one joint is fully blocked from any movement whereas the second joint can move with little resistance. In this simple environment, which is considered in the present article, the controller would amplify the motor signals of the second joint, to maximize the movement amplitude. For general complex environments, a joint-specific multiplicative gain that increases with the movement amplitude of this joint was shown to excite movement along the optimal, local, linear approximation of the resonance mode of the mechanical system formed by the elastic biomimetic limb and its environment (22). This gain scaling effect can thus automatically adjust motor control as the environment or the limb mechanics change and leverage elastic properties for energy-efficient movement. By building and updating an internal model of the limbs and the environment, the algorithm reached the performance of an optimal controller and increased the energy efficiency of repetitive robotic movements by up to 67% (26). An analogous functionality would give the brain a substantial evolutionary benefit. The algorithm is mathematically equivalent to the dynamics of serotonergic gain modulation (22), but only if serotonergic neuromodulations acted separately on individual joints.

In this article, we experimentally show that when human subjects perform strong, fast, repetitive movements of an individual joint, the CNS specifically increases the short-latency stretch reflex feedback pathway of the respective joint with topographic precision. The excitability change is observable long after the cessation of the motor signals and the movements that triggered it. A second set of experiments then tests the role of serotonin by administering cyproheptadine, an antagonist to metabotropic serotonergic receptors on motoneurons. The antagonist downscales the overall gain adaptation effect across all joints in comparison to a placebo. But the joint-specific precision in the gain adaptation shows a similar change in amplitude as after placebo administration and is even enhanced after antagonist administration.

MATERIALS AND METHODS

The present article summarizes two studies that search for a novel mechanism in the human CNS that adapts gains of motor pools to sensory feedback. The studies consider multijoint movements in humans that were actively driven, fast, strong, and repetitive, because the gain adaptation mechanism was predicted based on functional insights in the control of biomimetic robots during such movements (22, 23). The hypothesis stated that already after a few tens of seconds, such movement leads to higher gains of short-latency reflexes for muscles innervating joints that are strongly involved than for joints that are scarcely involved. This effect should be observable even after cessation of the movement and the muscle activity that triggered it. *Study 1* tested functionally whether the CNS provides this joint-specific, fast, persistent adaptation of short-latency reflex gains. *Study 2* investigated the influence of serotonin on this adaptation. The experimental procedure is illustrated in Fig. 1. Both studies were approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich.

Subjects

In *study 1*, 16 subjects [aged 17–30 yr, mean 26 ± 4 (SD); 12 male] participated. Only healthy, right-handed subjects were recruited who did not suffer from impairments of the neuromuscular or musculoskeletal system. All subjects were naive to the purpose of the study and provided written informed consent before participating.

For *study 2*, 16 different subjects [aged 22–30 yr, mean 26 ± 3 (SD); 12 male] were recruited who had not participated in the first study. In addition to the recruitment requirements above, the participants were screened by a licensed physician to detect possible contradictions against the administered serotonin antagonist, cyproheptadine.

Experimental Apparatus

For both experimental studies, a custom-built apparatus called a manipulandum (cf. Fig. 1*B*) guided the right arm of subjects during active movement and perturbed the arm to excite short-latency reflexes. Being particularly stiff, fast, and strong, the manipulandum delivers high forces and precise movements in a horizontal plane to control even fast and strong human arm movements and to induce fast perturbations (27). Participants wore a stiff splint on the right arm to prevent any wrist movement. The splint was firmly attached through a magnetic clutch to the end point of the manipulandum, with the participant's palm facing downward. As a safety measure, the participant was coupled

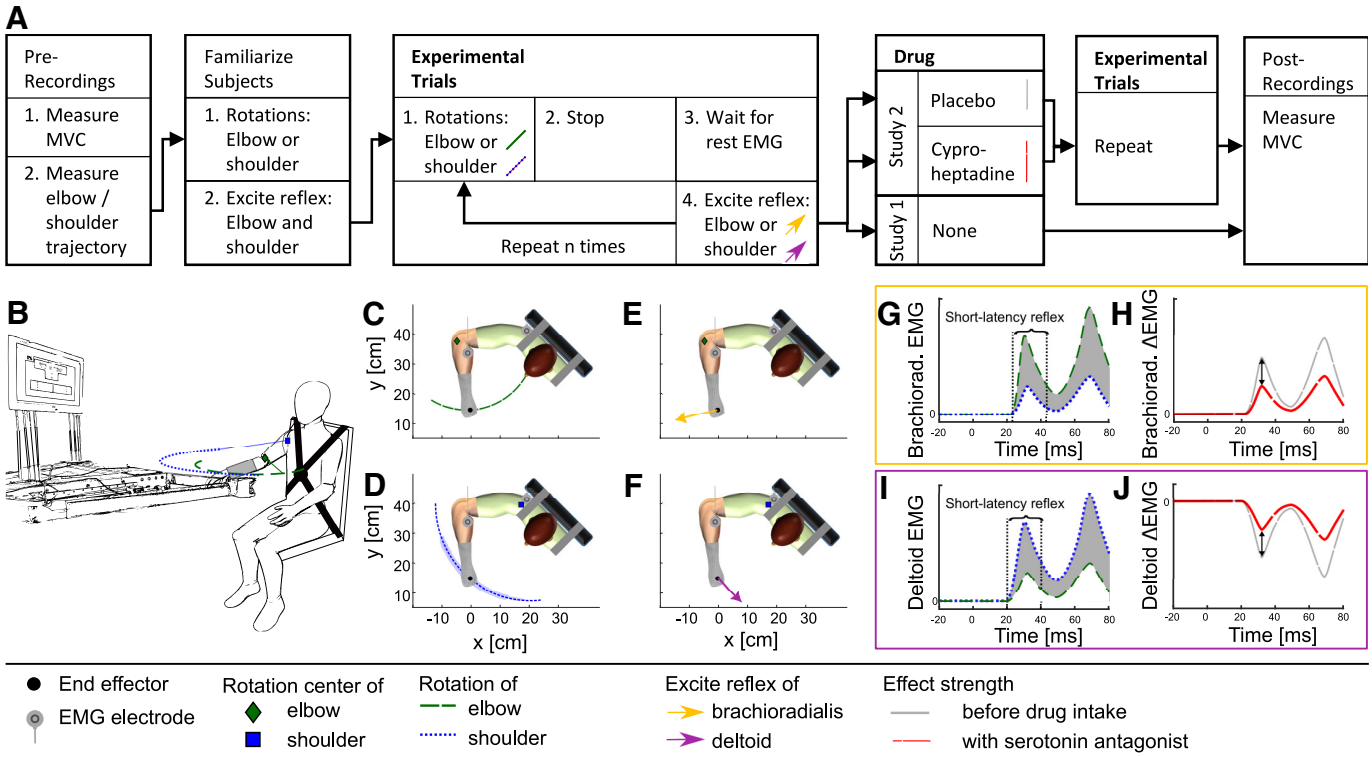

Figure 1. Overview of the conducted experiments. *A*: experimental protocol for each subject. MVC, maximum voluntary contraction. *B*: during the experiments, a manipulandum guided the arm movement of subjects while a monitor provided feedback on the movement. The wrist was immobilized throughout the study by a stiff splint. *C* and *D*: in each trial, the subject actively rotated either the elbow (*C*) or shoulder (*D*) joint in a horizontal plane, while movement of the other joint was blocked by the manipulandum. The schematics show the exemplary end-effector trajectories recorded for 300 s for 1 subject as a shaded area. *E* and *F*: after stopping the rotation at a constant point, the arm was rapidly perturbed to excite a short-latency stretch reflex in either the brachioradialis (*E*) or posterior deltoid (*F*). *G*–*J*: qualitatively sketch the expected results of the experiments. *G*: for elbow muscles like the brachioradialis, the study hypothesis predicted the short-latency stretch reflex to be higher after elbow rotation than after shoulder rotation. *H*: the strength of this joint-specific effect was defined as the gray area between the curves. This effect strength was expected to be diminished after intake of a serotonin antagonist. *I*: for shoulder muscles like the deltoid, the hypothesis predicted that the short-latency reflex shows the opposite effect to that in *G*, i.e., is lower after elbow than after shoulder rotation, leading to an expected negative subtracted change in electromyogram (EMG) (ΔEMG) in *J*. *J*: intake of a serotonin antagonist was expected to decrease the amplitude of the joint-specific effect for the deltoid, making ΔEMG less negative.

through a clutch that automatically detached when a predefined maximal force was exceeded. Participants were seated in an adjustable chair facing the manipulandum, with their trunk tightly restrained by seat belts. Their right arm was supported against gravity by a horizontally moving armrest and by the manipulandum handle.

The handle exerted forces onto the human arm to guide its movement along either the elbow or shoulder trajectory and precisely moved its spatial position for perturbations. For this, the handle was actuated by two linear actuators (Linmot PS01-48x360F-C; NTI AG, Switzerland) and controlled by an algorithm detailed in the Supplemental Methods. Details about the movement patterns are given in *Experimental Protocol*. A computer screen indicated the beginning of trials and the remaining time of a trial and provided visual feedback on movements.

The arm movement and muscular activation of subjects were recorded with multiple sensors. The position of the manipulandum handle was measured using the position sensors built into the linear actuators. The forces that both participants and the linear motors exerted onto the manipulandum handle were measured by a six-axis force-torque sensor (mini45; ATI Industrial Automation, United States). A force exerted on the manipulandum end point caused a change in position readings <1 ms after being detected by the force-torque sensor. Muscular activation of the subjects was measured by wireless electrodes (Trigno Avanti; Delsys, United States) that were attached to the participants' skin and measured muscular surface electromyogram (EMG) (cf. Fig. 1*B*). The muscle chosen to quantify the elbow joint activation was the brachioradialis, and for the shoulder movement the posterior deltoid muscle was used. Attachment sites were chosen according to recommendations by the SENIAM project (28). The Trigno Avanti electrodes could additionally record accelerations, so that electrodes on the brachioradialis and on the biceps were used to detect the horizontal acceleration of the lower and upper arm, respectively. To get information about the joint angles of the elbow and shoulder, additional wireless goniometers (SG110 and SG150B; Biometrics, United States) were mounted over each joint. The EMG electrodes recorded data with an intrinsic delay of 48 ms and the accelerometers and goniometers with a delay of 96 ms, according to the manufacturer manuals. The analysis corrected for this delay by subtracting the respective delay from the timestamp of each recorded data point. This aligned the timestamps of the different sensors. All signals were sampled at 2 kHz.

Experimental Protocol

Both studies followed a similar experimental protocol, illustrated in Fig. 1*A*. A range of preliminary recordings were used to set up the apparatus and to validate a clean setup. The participants were then familiarized with the experimental tasks. The main experimental trials differed between *studies 1* and *2* to test the respective hypotheses. A final set of recordings ensured that the electrodes had remained properly attached.

Experimental trials.

In *study 1*, a sequence of trials tested whether the short-latency reflex of the brachioradialis is stronger after elbow than after shoulder movement and weaker for the posterior deltoid. *Study 2* investigated the influence of serotonin on the gain scaling effect observed in *study 1*. To test the effect of serotonin, a new set of participants repeated the sequence of trials in an almost identical manner; however, it was repeated twice per participant, once unmedicated and once after administration of either a placebo or a serotonin antagonist.

Each trial consisted of four stages. First, the participant performed repeated rotations of either the elbow or shoulder joint, which was predicted to increase predominantly the excitability of motoneurons driving the elbow or shoulder muscles, respectively (cf. Fig. 1, *C*–*J*). Second, the controller smoothly stopped the handle after 30 s of movement at a constant point by exponentially increasing a virtual stiffness (see Supplemental Methods for more details). Third, the motoneuron excitability of either the brachioradialis or deltoid muscle was measured. For this, the controller waited until the movement had stopped and until the EMG of the respective muscle remained below its resting value for 100 ms, which introduced an average delay of 0.27 ± 0.20 s (SD; more precise statistics in the Supplemental Results). The manipulandum then either extended the elbow or flexed the shoulder by 10° within 60 ms to excite the short-latency stretch reflex in the brachioradialis or posterior deltoid, respectively. The reflex EMG was measured to quantify the motoneuron excitability. Fourth, a delay of 30 s between trials allowed restoration of motoneuron excitability and provided time for the manipulandum to move the handle back to its initial position. In summary, there were four possible trial conditions, defined by the two joints that could be rotated and the two muscles that could be stretched for a reflex response:

1) Rotate elbow → excite brachioradialis reflex
2) Rotate shoulder → excite brachioradialis reflex
3) Rotate elbow → excite deltoid reflex
4) Rotate shoulder → excite deltoid reflex

Catch trials were introduced that omitted the reflex perturbation but were otherwise identical to normal trials. These catch trials ensured that participants could not expect perturbations to happen, to alleviate effects induced by training and expectation on the measured motoneuron excitability. Subjects received no prior information about the perturbation direction or occurrence of catch trials.

While the subjects actively performed rotations, the manipulandum exerted forces that guided the desired rotation of a single joint. The applied manipulandum controller was developed based on the theoretical work by de Luca et al. (29). It is detailed in the Supplemental Methods and particularly prevented interference from the mechanical manipulandum design, as verified in Supplemental Fig. S1. Visual feedback stipulated a rotation amplitude around the equilibrium of 0.105 rad m^{-1}/r_0 for elbow and 0.15 rad m^{-1}/r_0 shoulder rotation, where r_0 is the radius of the circular elbow or shoulder movement (cf. Fig. 1, *C* and *D*). The screen provided visual feedback to the participants on the current and desired movement amplitude and the remaining duration of the trial. A characterization of the resulting rotations is provided in RESULTS, showing that the participants performed strong, fast, and clean movements of either the elbow or the shoulder, as stated by the study hypotheses.

Importantly, in our experiments we did not have a background load of the muscles that were to be stretched before the perturbation. A background load is often used in studies that investigate modulation of stretch reflexes to ensure strong but matched gain scaling across all conditions (6, 9, 30). This is due to a long-standing belief that some modulation of short-latency stretch reflexes could potentially be due to small subthreshold changes in the motor neuron pool (9, 31, 32). However, here we do not load the muscles before perturbations for three reasons. First, loading specific muscles could indicate the direction of the upcoming perturbation or would double the length of the experiment. It is critical that the specific perturbation or even the presence of a perturbation is not indicated to the participants. As we wait until participants are fully relaxed, there is little reason to suggest that a specific preset level of background activity below threshold is specifically responsible for our effects. Second, with a background load, it would not be possible to confirm that any EMG due to the movement itself has disappeared before the perturbation, which is an important control in our study. Third, recent work (33) has argued against using a background load. This work suggests that a background load will likely recruit strong gain scaling that could mask any modulation of stretch reflexes in our study.

In *study 1*, every participant completed each of the four trial conditions 15 times. In addition, the same number of catch trials was introduced, resulting in 120 trials per participant. The sequence of 120 trials was constrained such that at each of the 120 steps two subjects completed a trial from each of the four groups and eight subjects performed catch trials. This design determined the chosen number of 16 subjects. Apart from this constraint, trials from the four groups were randomly distributed along the sequence for each subject. Each participant completed the full experiment lasting ~4.5 h on a single day.

In *study 2*, the participants completed the sequence in an identical manner; however, it was repeated twice per participant, once unmedicated and once after administration of either a placebo or a serotonin antagonist. Between the two sequences, participants took a 2-h break to recover from the first sequence of trials and for the medication to reach peak concentration. A pill with a dose of 8 mg cyproheptadine (tradename Peritol) served as serotonin antagonist, as proposed by Wei et al. (16), who showed that reflex modulation after strong proprioceptive input can be scaled up and down by serotonin agonists and antagonists. As the placebo, a pill

with color and dimension identical to the serotonin antagonist was chosen (white, 8-mm diameter; produced by Zentiva). This pill contained no active substance, solely consisting of filling material, namely lactose monohydrate, cellulose powder, magnesium stearate, and microcrystalline cellulose. The experiment was carried out double-blinded. To ensure that measured EMG signals remained comparable, the unmedicated control and medicated test trial sequences were carried out on the same day without detaching the electrodes. The control experiment thus had to be carried out first, since it takes multiple hours until cyproheptadin is fully eliminated by the body. To increase the statistical power, each trial sequence consisted of 20 trials per trial condition. In return, catch trials were omitted to avoid an excessive burden on the participants. Thus, each subject performed a total of 80 trials before and 80 trials after drug administration. The total experimental procedure took ~6 h per participant.

Preexperimental recordings.

Before the experimental trials, each participant underwent two preliminary recordings. The first of these measured the EMG signals of the brachioradialis and deltoid at maximum voluntary contraction (MVC) three times each.

The second recording characterized the elbow and shoulder movement of each participant as shown in Fig. 1, *B*–*F*. The manipulandum used these measurements to guide pure elbow and shoulder rotations. For this, the shoulder and elbow were sequentially immobilized by custom-made splints and the subject rotated the free joint back and forth in a horizontal circle for a total of 300 s. The resulting manipulandum end-effector trajectory was recorded and fitted by a circle to determine the center and radius r_0 of rotation of the target trajectory. Figure 1, *C* and *D*, show the exemplary recorded end-effector trajectories of one subject. For each subject, the standard error in the center position of the shoulder joint was <5 mm, and the standard error in the lower and upper arm radii was <4 mm and 6 mm, respectively. The crossing position of the elbow and shoulder motions was defined as both the equilibrium position of the rotation and the initial position for perturbations. At the equilibrium position, the elbow was flexed by 54 ± 8° and the shoulder horizontally adducted by 47 ± 6° (SD) relative to a position where the arm was horizontally stretched to the side, which differed slightly across participants.

Familiarization of subjects.

Subjects were further familiarized with the movement conditions and the perturbations. The subjects performed one trial each with elbow and shoulder rotation, both without perturbation. These movements were recorded and used to test whether subjects guided by the manipulandum performed joint-specific rotations and to quantify the movements as reported in RESULTS.

The participants were further habituated to perturbations of the brachioradialis and the deltoid by exerting 15 perturbations each in an alternating fashion. Between two successive perturbations, the arm was moved back to the equilibrium, before the next perturbation started after a random duration between 5 and 10 s.

Postexperimental recordings.

After the main experiments, the MVC recordings were repeated to ensure that the electrodes had remained properly attached.

Analysis of EMG Data

All data were analyzed in MATLAB. The processing of the EMG data served two purposes: to determine the short-latency reflex response to mechanical perturbations and to ensure that the EMG of the observed muscle was at rest before this response. The EMG electrodes provided signals with a bandwidth of 20–450 Hz, which were demeaned, rectified, and normalized to the subject-specific MVC measurements.

The short-latency reflex responses of the brachioradialis and deltoid muscles were quantified based on their EMG signals after perturbation of the corresponding joint. The reflex response occurred after a time delay composed of the mechanical delay between the manipulandum handle movement and the joint movement and the neuronal transduction delay. Both delays are illustrated in Fig. 3, *G* and *H*, for two exemplary reflex responses. The neuronal transduction delays of the brachioradialis and deltoid were set to 25 ms and 20 ms (30, 34), respectively. The mechanical delays were determined from the accelerometers on the lower and upper arm for the elbow and shoulder perturbations, respectively. The perturbation onset was detected when the accelerometer readings exceeded their resting value by three standard deviations. To account for interfering oscillations of the accelerometers after movement, the mechanical delays for each subject were averaged over all trials where perturbation and rotation direction differed. After the reflex delay, the EMG response was averaged over a time window of 25 ms and normalized by subtracting its resting EMG averaged over the 25 ms preceding the perturbation. The natural logarithm of these strictly positive values was defined as reflex response for the statistical analysis.

Perturbations were initiated once the EMG signal had remained at its resting value for 100 ms. If the EMG did not reach its resting value within 3 s after movement cessation, the perturbation was omitted and the respective trial repeated. Any information that distinguished trials with omitted perturbation from catch trials was withheld from the subjects. The resting detection was based on three recordings of the mean and maximum unprocessed EMG signals, termed EMG_{mean} and EMG_{max}, respectively, over a 1-s period before an individual trial. The recording with the smallest EMG_{max} was chosen to prevent any measurement artifacts resulting from brief unintended muscle contractions. The EMG recordings within the range EMG_{max}–EMG_{mean} around EMG_{mean} were defined as the resting EMG. If the EMG exceeded its resting value by >20% over a defined time period during the trials, trials were neglected in the data analysis. This period started 48 ms before a perturbation, corresponding to the delay of the EMG electrodes. It ended 10 ms after the perturbation, since this is the minimal possible neuronal transduction delay of short-latency stretch reflexes (35).

To ensure that the observed changes in motoneuron gain did not result from any muscle activation remaining after a

movement, the prereflex activity was matched between the different rotation conditions for each subject. Accordingly, the EMG signal of the brachioradialis was averaged within the first 10 ms after the onset of elbow perturbations, as determined by the accelerometer. Elbow rotation trials were sorted from highest to lowest remaining muscle activation and iteratively excluded until the average muscle activation equaled at most the average muscle activation of shoulder rotation trials. The converse procedure was applied to the recordings of deltoid perturbations.

Figure 3, *A* and *D*, illustrate the reflex responses of the brachioradialis and deltoid, respectively, after both rotation types. The responses were averaged over all trials of all subjects. To make the EMG responses comparable across subjects for these plots, the muscular responses of the individual subjects were normalized to a z score. The z scores for the brachioradialis and deltoid muscles were calculated from the EMG over the first 50 ms and 45 ms after perturbation onset, respectively. The different durations account for the different neuronal transduction delays between the two muscles. The normalized values were averaged across all subjects in steps of 0.5 ms.

Statistics and Reproducibility

Study 1.

The hypothesis for the first study stated that the gain of motoneurons is higher after movement of a joint that is innervated by these motoneurons than after movement of other joints. For the brachioradialis, this hypothesis was tested on $n_e = 172$ trials with prior elbow rotation and $n_s = 209$ trials with prior shoulder rotation, which had passed the stated exclusion criteria. For the deltoid, the respective number of trials amounted to $n_e = 203$ and $n_s = 137$. The hypothesis was tested by the linear mixed-effects model

$$r_i = \beta_0 + \beta_1 \cdot \mathrm{rot}_i + b_{0,m} + b_{1,m} \cdot \mathrm{rot}_i + \epsilon_{im} \quad (1)$$

that was individually fitted to the observed reflex responses r_i of the brachioradialis and deltoid. In this model, β_0 and β_1 denote the fixed-effect regression coefficients, $b_{0,m}$ and $b_{1,m}$ are the random-effect regression coefficients, and ϵ_{im} denotes residuals. The subjects were denoted by m, and differences between them were considered as random effects. The fixed effect rot_i describes the joint rotated in trial number i,

$$\mathrm{rot}_i = \begin{cases} +1 & \text{if shoulder was rotated} \\ -1 & \text{if elbow was rotated} \end{cases} \quad (2)$$

The assumption that the reflex response in either of the two muscles is higher after its innervated joint has moved implies that $\beta_1 > 0$ for the deltoid muscle that innervates the shoulder and $\beta_1 < 0$ for the brachioradialis that innervates the elbow. The corresponding null hypothesis $\beta_1 = 0$ was tested by a two-tailed t test. The hypothesis predicts that the effect must be significant in both muscles simultaneously. The linear mixed-effects model assumes that the residuals ϵ_{im} are normally distributed, consistent with the histograms in Fig. 3, *C* and *D*.

To test whether the perturbation delays were significantly different after an elbow and shoulder rotation, the same linear mixed-effects model in *Eq. 1* was applied. Here, the dependent response variable r_i was chosen as the natural logarithm of the delay between the movement cessation and the perturbation onset in all trials. The logarithm accounted for the fact that the delay is restricted to positive values.

Study 2.

The second study tested whether the topographically precise gain scaling effect is linked to serotonergic neuromodulation. The new group of participants first performed the same set of trials as above. Then half of the group received a placebo or the serotonin antagonist cyproheptadine, respectively.

The effect of serotonin on either individual muscle was tested using the linear mixed-effect model

$$r_i = \beta_2 \cdot \mathrm{rot}_i \cdot \mathrm{med}_i + \beta_{11} \cdot \mathrm{rot}_i + \beta_{12} \cdot \mathrm{med}_i + \beta_0 + b_{1,m} \cdot \mathrm{rot}_i + b_{0,m} + \epsilon_{im} \quad (3)$$

where

$$\mathrm{med}_i = \begin{cases} +1 & \text{after cyproheptadine administration} \\ +2 & \text{control group} \end{cases} \quad (4)$$

Hereby, the control group can refer either to all participants before any intake or to the placebo subgroup.

The main question of the second study was whether β_2 differed between the brachioradialis and the deltoid. This was accounted for by introducing a third factor,

$$\mathrm{refl}_i = \begin{cases} -1 & \text{trial excited the brachioradialis reflex} \\ +1 & \text{trial excited the deltoid reflex} \end{cases} \quad (5)$$

resulting in the linear mixed-effect model

$$r_i = \beta_3 \cdot \mathrm{rot}_i \cdot \mathrm{med}_i \cdot \mathrm{refl}_i + \quad (6)$$

$$\beta_{21} \cdot \mathrm{rot}_i \cdot \mathrm{med}_i + \beta_{22} \cdot \mathrm{rot}_i \cdot \mathrm{refl}_i + \beta_{23} \cdot \mathrm{med}_i \cdot \mathrm{refl}_i + \quad (7)$$

$$\beta_{11} \cdot \mathrm{rot}_i + \beta_{12} \cdot \mathrm{med}_i + \beta_{13} \cdot \mathrm{refl}_i + \beta_0 + \quad (8)$$

$$b_{1,m} \cdot \mathrm{rot}_i + b_{0,m} + \quad (9)$$

$$\epsilon_{im} \quad (10)$$

The hypothesis states that

$$\beta_3(\text{control} = \text{no intake}) \neq 0 \quad (11)$$

$$\beta_3(\text{control} = \text{placebo}) \neq 0 \quad (12)$$

$$\mathrm{sign}(\beta_3(\text{control} = \text{placebo})) = \mathrm{sign}(\beta_3(\text{control} = \text{no intake})) \quad (13)$$

These three claims were tested by separate two-tailed t tests. Combined over all subjects, brachioradialis reflex measurements obtained after elbow movement passed the stated exclusion criteria in 149, 135, and 286 trials under the influence of cyproheptadine, placebo, or no substance, respectively. After shoulder movement, 139, 142, and 299 trials passed the exclusion criteria, respectively. The deltoid reflex was considered after elbow movement for 152, 141, and 284 trials, respectively, and after shoulder movement in 136, 122, and 258 trials. Combined over all conditions, the linear mixed-effect model thus took into account 2,243 trials from the 16 study participants.

RESULTS

The present article summarizes two studies, each including 16 human subjects. The focus of the first study was to test

the hypothesis that the CNS scales motoneuronal gains with topographic precision. Our control algorithm for robotic motion predicts that the gain of motor pools should be higher after rotation of an innervated joint than after rotations of other joints in the same limb (22, 23). The second study investigated the involvement of serotonergic feedback modulation in this gain scaling.

The experimental protocol is illustrated in Fig. 1 and consisted of multiple individual trials for each subject. In each trial, the subject first actively performed strong, fast, repetitive rotations of either the right elbow or the right shoulder joint. After 30 s of movement, the manipulandum stopped the arm in a predefined default posture, and the motoneuron gain was measured in either the brachioradialis or posterior deltoid muscles. Specifically, after the electromyography (EMG) signal of the respective muscle had decayed to its resting value, the motoneuron gain of either muscle was quantified by its short-latency EMG reflex response to a mechanical stretch of the target joint. According to the study hypothesis, rotating a joint should enhance the short-latency reflex response of its associated muscles in comparison to a rotation of another joint. To ensure repeatability of movements, the subjects' motions were guided by a manipulandum, i.e., a machine that applies translational forces to the arm.

Verifying the Assumptions on the Joint Movement

The study design imposes two assumptions on the rotatory movement that triggered the gain scaling: First, the two movement conditions were assumed to be clearly divisible into rotation of the elbow and rotation of the shoulder joint, respectively. Second, the subjects were assumed to perform strong, fast, repetitive movements, which are known to be shaped by compliant elements in the body. These two assumptions were verified by recording rotatory movements of all subjects who participated in the set of experiments without medication intake. Exemplary recordings illustrating the movements of one subject are shown in Fig. 2.

In agreement with the first assumption, the differentiation between elbow and shoulder rotation is evident from the angular trajectory of the elbow and the shoulder joint, measured by goniometers. When the subjects were guided to perform elbow rotations, the peak angles were on average 7.0 ± 2.8 (SD) times higher in the elbow than in the shoulder trajectory. Conversely, when the subjects were guided to perform shoulder rotations, the peak angles were on average 3.5 ± 0.9 (SD) times higher in the shoulder than in the elbow trajectory. The average peak EMG of participants during elbow movements was 22 ± 10% MVC for the brachioradialis and 3.1 ± 36% MVC for the deltoid. During shoulder movement, the ratio reversed as expected, and the average peak EMG of brachioradialis and deltoid amounted to 3.2 ± 31% MVC and 49 ± 20% MVC (SD), respectively. Although the joint angles and EMG signals are only indirect measures of sensory and motor signals, the presented results are sufficient to conclude that the joint-specific gain scaling can mathematically not emerge from diffuse serotonergic neuromodulation, as elaborated in the Supplemental Results. One reason that the EMG signals of the two measured muscles (brachioradialis and posterior deltoid) could so clearly be related to the respective joint movements can be attributed to the guidance of the arm motion through the manipulandum, which counteracted occurring torques on the arm. Additionally, the subjects were trained to focus on moving the respective muscles for each joint and were familiarized with the task, which probably enabled them to relax the rest of the muscles, as has been shown by Maeda et al. (36).

In agreement with the second assumption, all subjects performed strong and fast movements. Participants actuated their brachioradialis with an average peak EMG of 22 ± 10% MVC during elbow movements and their deltoid with an

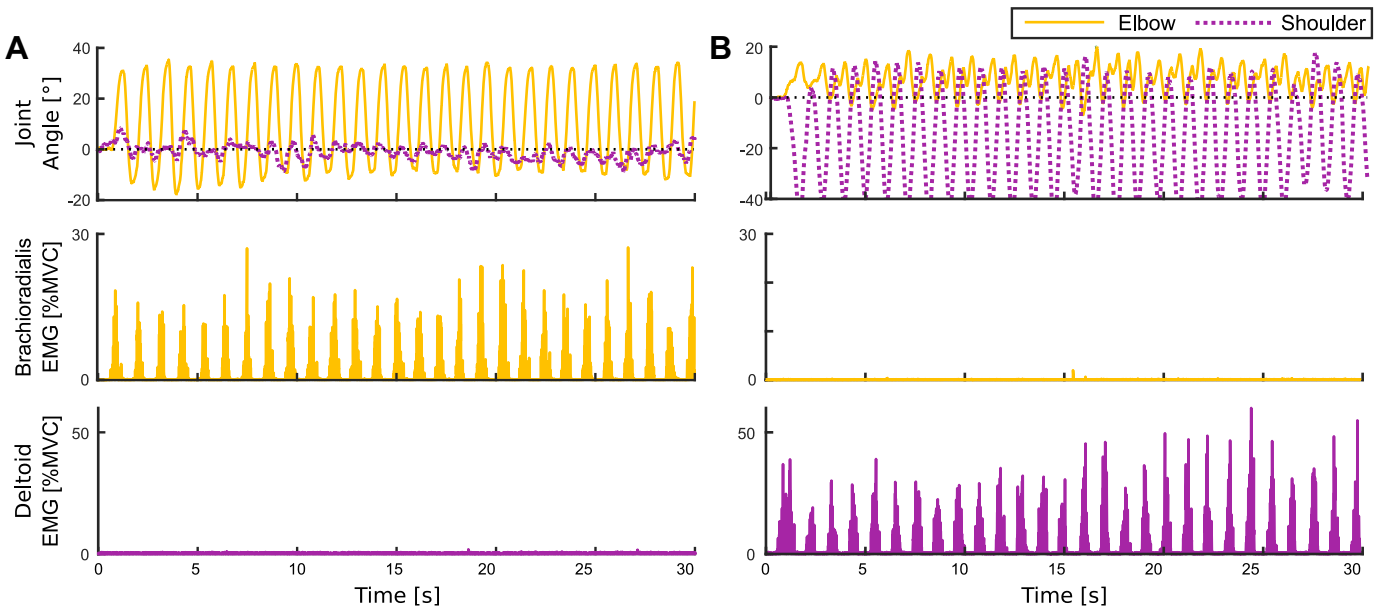

Figure 2. Quality of manipulandum-guided movement for 1 exemplary subject. Depending on the trial, the subject was guided to perform a rotation involving either the elbow (*A*) or the shoulder (*B*). The angles of the joints, as measured by goniometers, confirm that the 2 conditions could be clearly differentiated. The difference between the 2 conditions is also evident from the electromyogram (EMG) of the brachioradialis, which actuates the elbow, and the posterior deltoid, which actuates the shoulder. MVC, maximum voluntary contraction.

average peak EMG of 49 ± 20% MVC (SD) during shoulder movements. The hands of participants excited the elbow and shoulder rotations with peak forces of 19 ± 2 N and 22 ± 6 N (SD), respectively. This led to elbow rotations at 1.01 ± 0.04 Hz with peak velocities of 74 ± 8 cm s^{-1} and shoulder rotations at 1.00 ± 0.04 Hz with peak velocities of 72 ± 9 cm s^{-1} (SD), respectively. The movement frequency indicates that the participants had synchronized their movement with the countdown clock shown to them. In summary, the movements that triggered reflex modulation were strong, fast, and divisible into elbow and shoulder movement, as stated by the assumptions underlying the experiments.

Topographically Precise Gain Scaling

As predicted, the brachioradialis and the deltoid showed a significantly enhanced short-latency reflex response after rotation of their respective actuated joint. Averaging over all subjects, the reflex response of the brachioradialis was higher after elbow than after shoulder rotation at $P = 1.0 \times 10^{-4}$ (Fig. 3*A*; linear mixed-effects model and 2-tailed t test: $df = 379$, $t = 3.8$). Conversely, the reflex response of the deltoid was higher after shoulder than after elbow rotation at $P = 1.77 \times 10^{-4}$ (Fig. 3*B*; $df = 338$, $t = 3.9$). Rotation conditions that caused a higher motoneuron excitability were thereby found to be associated with longer time delays between the end of the rotation and the excitability measurements, as shown in the Supplemental Results. Since this delay gave the underlying effect time to decay, it can be expected that the observed difference in motoneuron excitability was even more pronounced directly after a rotation than observed here.

When fitting the two linear mixed-effect models to the reflex recordings, the residuals were normally distributed (cf. Fig. 3, *C* and *D*). The predicted reflex behavior was also observed in individual subjects, as illustrated for an exemplary subject in Fig. 3, *E* and *F*. The individual reflexes were elicited by the manipulandum, which rapidly moved the subject's wrist. The response EMG occurred after a delay, which consisted of a mechanical delay until accelerometers detected the stretch onset at the perturbed joint and the

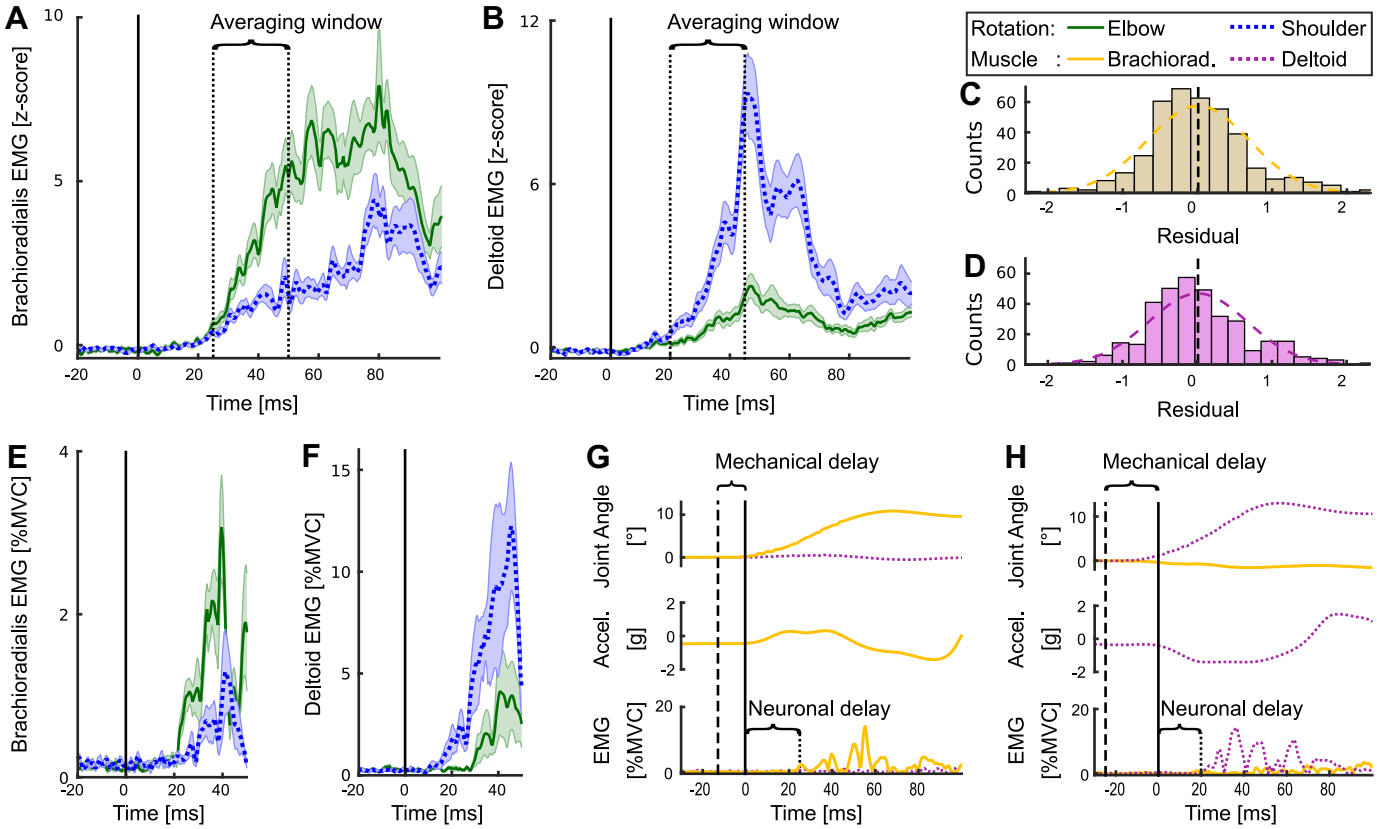

Figure 3. Short-latency reflex responses after movement of the shoulder or elbow joint. *A*: averaged over all 16 subjects, the right brachioradialis showed a higher short-latency electromyogram (EMG) response to stretching after rotating the right elbow ($n_e = 172$ trials) than after rotating the right shoulder ($n_s = 209$ trials). *B*: the opposite effect was observed for the right posterior deltoid ($n_e = 203$ and $n_s = 137$ trials). The origin of the time axis and the vertical solid lines indicate the perturbation onset. The shaded areas indicate the SEs in the EMG signals at each time step. Statistical significance was determined by fitting a linear mixed-effects model to the reflex response, averaged over the indicated window, of the respective muscle. *C* and *D*: as required for linear mixed-effects models, the residuals for both the brachioradialis (*C*) and the posterior deltoid (*D*) were well fitted by a normal distribution (dashed curves). *E* and *F*: reflex responses of the right brachioradialis (*E*) and the posterior deltoid (*F*) of an individual subject resembled the subject-averaged responses. MVC, maximum voluntary contraction. *G* and *H*: individual reflex responses in the brachioradialis (*G*) or the deltoid (*H*) were elicited by mechanically perturbing the subject's hand along the elbow or shoulder joint, respectively. After a mechanical delay, the perturbation accelerated the lower arm for the brachioradialis or the upper arm for the deltoid, as measured by accelerometers (*middle*). The angle of the other joint remained comparatively constant, as measured by goniometers (*top*). For the deltoid, the goniometer detects movement a few milliseconds earlier than the accelerometer, as the latter was attached to the soft biceps, resulting in a longer mechanical delay. After a neuronal transduction delay, the EMG electrodes recorded the short-latency reflex response in the perturbed muscle, while the other muscle remained silent (*bottom*).

neuronal transduction time (cf. Fig. 3, *G* and *H*). For the statistical analysis, the EMG responses were averaged over the time window from 25 ms to 50 ms after onset of the joint stretch for the brachioradialis and from 20 ms to 45 ms for the deltoid. These time windows are known to start after the respective neuronal transduction delays and to end before onset of the long-latency reflex responses (30, 34).

Serotonergic Neuromodulation as Potential Root Cause

The second experiment tested whether the observed change in motoneuronal gain may originate in serotonergic neuromodulation. For this, a new cohort of 16 human subjects received either a placebo or cyproheptadine, an antagonist to those serotonergic receptors that scale up motoneuronal gains following motion (16). As control condition, all participants performed the same trials as the last cohort in the morning. In the afternoon, eight of the participants subsequently took cyproheptadine and then repeated the trials. The other eight participants received a placebo instead of cyproheptadine in a double-blind manner. Cyproheptadine intake showed a topographically precise effect, but of opposite direction than predicted in Fig. 1, *H* and *J*: It made the brachioradialis reflex even more pronounced after elbow in contrast to shoulder movement, and vice versa for the deltoid. But placebo administration had the same effect, which was only slightly and nonsignificantly smaller, as detailed in the following.

To confirm that the measurements were correctly obtained, the statistical analysis initially reproduced two previously observed findings: First, the topographically diffuse functional effect of cyproheptadine discovered by Wei et al. (16) was confirmed with the measurements of the second subject cohort. In agreement with Wei et al., cyproheptadine diffusely decreased the postmotion reflex response of all muscles by $\beta_{12} = -0.25 \pm 0.09\%$ MVC at $P = 0.0082$ (SE; 3-way: $df = 2{,}231$, $t = -2.6$) compared to the placebo intake. Second, the results described in Fig. 3, *A* and *B*, from the first cohort that did not receive cyproheptadine at all were confirmed with the measurements obtained in the second subject cohort before drug or placebo administration. As expected, in the second cohort both the brachioradialis and the deltoid showed the same behavior before drug administration as in the first subject cohort: In the brachioradialis, the reflex response was larger by $\beta_{11} = +0.19 \pm 0.07\%$ MVC (SE; 2-way; $df = 1{,}144$) after rotation of the elbow than after rotation of the shoulder. In the deltoid, the reflex response was smaller by $\beta_{11} = -0.76 \pm 0.11\%$ MVC (SE; 2-way; $df = 1{,}087$) after elbow rotation than after shoulder rotation. Therefore, the initial statistical tests of the second subject cohort confirmed the findings of the initial study cohort.

Next, the statistical analysis tested whether cyproheptadine may also provide precise neuromodulation and is responsible for the joint-specific reflex modulation observed in Fig. 3, *A* and *B*. After cyproheptadine administration, the joint specificity of the brachioradialis was increased compared to the measurements before drug intake, as predicted in Fig. 1, *G* and *H*, and demonstrated in Fig. 4, *A* and *B*: Before cyproheptadine administration, the brachioradialis showed a short-latency response that was larger after elbow than after shoulder movement by $\beta_{11} = +0.19 \pm 0.07\%$ MVC (see value above). This metric β_{11} is illustrated by the gray area in Fig. 1*G* and the gray line in Fig. 1*H*. Cyproheptadine further increased this metric β_{11} for joint precision by $\beta_2 = +0.28 \pm 0.09\%$ MVC (SE; 2-way; $df = 1{,}144$), illustrated by the arrow in Fig. 1*H*. Also for the deltoid, the joint specificity was more pronounced after cyproheptadine administration,

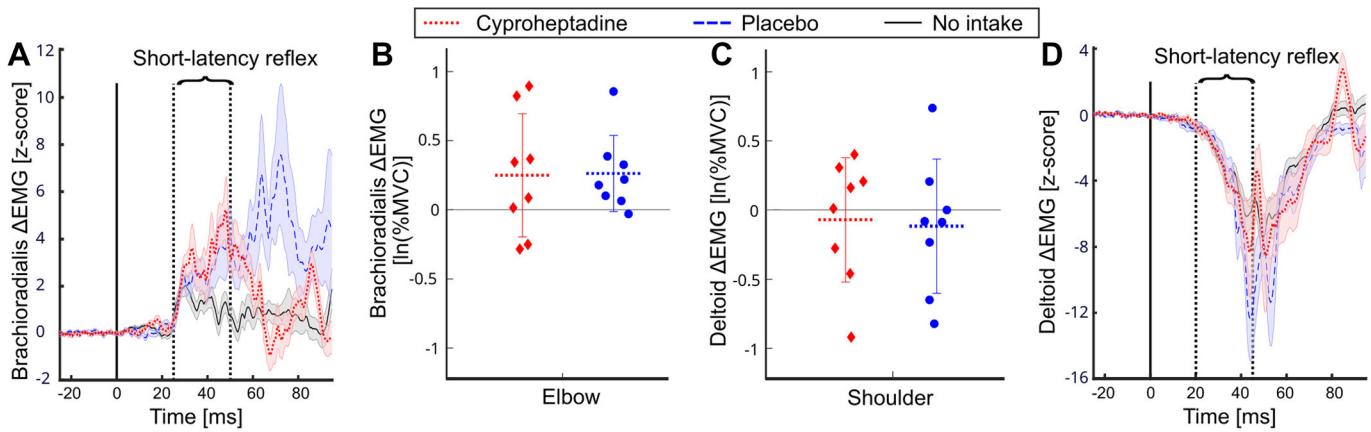

Figure 4. Effect of a serotonergic antagonist on the topographically precise scaling of motoneuronal gains. The curves show the average reflex response of the brachioradialis (*A*; 1,150 trials) and deltoid muscle (*D*; 1,093 trials) following rotation of the elbow, subtracted by the average reflex following rotation of the shoulder (more detailed trial breakdown in MATERIALS AND METHODS). They thus quantify the strength of the topographically precise scaling of motoneuronal gains, where a higher amplitude implies a larger effect size. The measurements were obtained before participants took any pill (black curve), after intake of the serotonin antagonist cyproheptadine (red curve), or after intake of a placebo (blue curve). *A*: for the brachioradialis, the effect is substantially higher after cyproheptadine intake than without any intake during the short-latency reflex window. This is the opposite effect than predicted in Fig. 1*H*. But the blue placebo curve shows the same effect and effect size as cyproheptadine. *D*: for the deltoid, both the cyproheptadine and the placebo had little to no effect on the topographical precision of gain scaling. Note that the signal has a negative value here as the deltoid reflex following elbow rotation was smaller than after shoulder rotation, as already shown in Fig. 3. *B*: on the level of the 16 individual subjects, we see a larger spread of the effect size in the elbow after cyproheptadine intake than after placebo intake. For each data point, the red curve shown in *A* is averaged over the short-latency reflex windows for all trials for a specific subject and the average of the black curve is subtracted. The more a point deviates from zero, the stronger the medication effect. The horizontal line visualizes the average and SE over all trials of all subjects within a specific group. MVC, maximum voluntary contraction. *C*: for the deltoid, the same metric shows that the cyproheptadine and placebo groups show a similar spread of effect strengths.

as predicted in Fig. 1, *I* and *J*, and demonstrated in Fig. 4, *C* and *D*: Before administration, the reflex response was smaller after elbow than after shoulder movement by $\beta_{11} = -0.76 \pm 0.119\%$ MVC (see value above; illustrated by the gray area in Fig. 1*I* and the gray line in Fig. 1*J*). Cyproheptadine pushed this metric β_{11} further into the negative realm by $\beta_2 = -0.038 \pm 0.109\%$ MVC (SE; 2-way; $df = 1{,}087$; illustrated by the arrow in Fig. 1*J*). Cyproheptadine thus decreased the β_{11} for the deltoid ($\beta_2 < 0$; Fig. 4*D*) and increased it for the brachioradialis ($\beta_2 > 0$; Fig. 4*A*), leading to an effect strength β_2 of cyproheptadine on these muscles that differed significantly by $\beta_3 = -0.34 \pm 0.15\%$ MVC at $P = 0.02$ (SE.; 3-way; $df = 2{,}231$, $t = -2.3$) from the measurement obtained in the morning before drug administration.

However, the placebo cohort suggests that there are complementary or alternative root causes for the joint-specific reflex modulation besides the serotonergic effects blocked by cyproheptadine. Although cyproheptadine enhanced the joint-level specificity by $\beta_3 = -0.34 \pm 0.15\%$ MVC (see above), the placebo also enhanced it by $\beta_3 = -0.28 \pm 0.15\%$ MVC (SE; 3-way; $P = 0.065$, $df = 2{,}231$, $t = -1.8$) compared with measurements obtained before any administration. Comparing cyproheptadine directly against the placebo, the effect size β_3 of cyproheptadine was only slightly more pronounced than that of the placebo by $\beta_3 = -0.06 \pm 0.17\%$ MVC and was nonsignificant (SE; 3-way; $P = 0.72$, $df = 2231$, $t = -0.36$).

To conclude, as in the first cohort, subjects of the second cohort showed an increased reflex of the brachioradialis after elbow movement compared with after shoulder movement, and vice versa for the deltoid. The second cohort showed that cyproheptadine at least diffusely decreased the gain adaptation of short-latency reflexes across both joints following movement, significantly more than a placebo. Nevertheless, cyproheptadine and the placebo affected the joint specificity similarly compared to the administration-free control trials: the brachioradialis reflex was even more pronounced after elbow than after shoulder movement (Fig. 4*A*), and the deltoid reflex was even more pronounced after shoulder than after elbow movement (Fig. 4*D*).

DISCUSSION

The present study shows that the CNS scales motoneuronal gains of muscles driving individual joints independently from each other to adjust movements to changing mechanical conditions. This gain adaptation happens quickly within a few tens of seconds of movement and outlasts the movement and muscle activity that triggered it by at least several hundreds of milliseconds. The motoneuron excitability was specifically increased for motor pools that dominantly innervate a moving joint, compared with movements of other joints. A serotonin blocker reduced the overall excitability of all motor pools after movement, but the joint-specific effect of movement on motor pool excitability showed no difference after serotonin blocker administration compared with after placebo administration. To obtain these findings, human subjects performed strong and fast periodic rotations primarily moving either their elbow or their shoulder joint. After repeated rotations, a short-latency stretch reflex was elicited and its EMG response quantified the motoneuron excitability. The experiments were repeated under administration of either a serotonin antagonist or a placebo. The results confirm that serotonin adapts the short-latency gain of all muscles in a merely diffuse manner (16), but they also show that this serotonergic motor feedback must be enhanced by a complementary mechanism that, combined, allows adaptation of the motoneuronal gains fast, persistently, and with joint-specific precision to ongoing movement.

Previously it had been thought that short-latency spinal stretch reflexes simply showed gain scaling based on motoneuron drive (7) and were only modifiable with long-term training protocols (11). However, recent work has shown two conditions in which these short-latency feedback loops can be changed at least momentarily: First, during early learning on novel tasks, where it appears that changes in gamma motor neuron drive can tune the stretch reflex responses, making them more linear with respect to errors which might improve motor learning (37) and second, changes in the posture of the wrist joint have been shown to elicit different short-latency stretch responses, potentially through selective gating of heteronymous reflex loops via spinal interneurons (14) and through presynaptic inhibition (15, 38, 39). Both of these effects were suppressed by the protocol of the present study: First, the muscles were at rest before perturbation, and the trials under the different conditions were equally distributed over time. Second, the perturbation parameters, such as the initial position as well as the stretch duration and distance, were kept constant. Our findings thus suggest a third mechanism for modifying the gain of the spinal stretch reflexes, which is persistent enough to accumulate information throughout a movement cycle and is still fast enough to react to mechanical changes.

Wei et al. (16) have previously shown that reflex modulation observed several hundreds of milliseconds after strong proprioceptive input can be diffusely scaled up and down by serotonin agonists and antagonists, respectively. In the ventral region, this spinal neuromodulation is 90% due to the raphe nucleus obscurus and pallidus (18), which receive proprioceptive input (17, 40, 41) and accordingly release serotonin onto spinal motoneurons (18, 42), where it activates 5-HT_2 receptors that scale up the motoneuronal gain (16, 19, 43). The present experiments confirm that this serotonergic gain modulating affects muscles diffusely across joints, but they also expose a complementary mechanism that can adjust this fast, persistent modulation with joint-specific topographic precision. This joint-specific complementary effect itself was even increased after administration of the serotonin antagonist, but only by the same extent as after administration of the placebo. It is thus likely that the enhanced joint specificity was due to an uncontrolled third factor. The third factor is likely linked to the fact that experiments without treatment were always conducted first in the morning and experiments after placebo or antagonist administration in the afternoon. This sequence was necessary because of two effects: First, the EMG electrodes had to stay attached throughout all experiments to ensure comparability, which prevented spreading the trials across several days. Second, the slow degradation of the serotonin antagonist prevented conducting experiments without antagonistic effect later on the same day. Although serotonin thus set the overall gain of the reflexes across joints after movement, the joint-specific complementary effect that differently adjusted

the gain for individual joints was likely of nonserotonergic origin.

A potential root cause for the joint-specific gain modulation is reciprocal inhibition, as we have previously elaborated in a review (23). Serotonergic neuromodulation is known to increase motoneuronal gains by inducing persistent inward currents, which can be terminated by synaptic inhibition (44). It is thus possible that the periodic movements have triggered serotonergic neuromodulation that set an overall gain for all muscles. Precise reflexive or descending synaptic inhibition may have fine-tuned the neuromodulatory effect for the different muscles. Besides tuning the relative strength of different muscles, the quick effect of synaptic inhibition could also have tuned the reflex gain separately at different stages of the periodic movement cycle (38), which was not the focus of the present study. Meanwhile, the long time constant of serotonergic neuromodulation would have allowed accumulation of information across the whole movement. Future investigations should test this theory and should examine active and passive movements to determine whether the joint-specific modulation is primarily driven by feedback from proprioceptive afferents or descending motor commands from the motor cortex.

The evolutionary advantage of topographically precise gain scaling is revealed in the robotic control algorithm that predicted it (45). If the CNS amplifies the motoneuronal gain of muscles that show a larger movement amplitude, the resulting gains will amplify the motor signals along the optimal, local, linear approximation of the resonance mode of the mechanical system in a least-squared sense (22). Experiments in biomimetic robots demonstrated the functional advantages of this phenomenon: It exploits the compliant properties of a locomotor system. Under mechanical conditions that are typical for biological motions, such as nonlinear dynamics, physical noise, and damping (26), the energy efficiency of the resulting motion matches the performance achieved by computationally intense optimal controllers. The gain scaling observed here can modify CNS motor commands, for example, as a runner steps from a stiff to a compliant ground. To counteract the decreasing ground stiffness, runners intuitively increase their leg stiffness and thereby straighten their knees (46). The CNS achieves this effect by scaling up the activation of ankle muscles relative to that of the knee muscles (47). For this, the gain scaling adaptation observed here acts sufficiently slowly to adjust motoneuronal gains to information accumulated across full movement cycles, while it decays quickly enough to react to changing environments (23, 45).

One limitation of our study is that the reflex modulation was only investigated when the muscles were relaxed and the arm was completely still. Although this study design does not prove the observed reflex modulations to be present during movements, the design was necessary to avoid the influence of other factors such as gain scaling (9, 10, 48) or posture (14). Moreover, as short-latency reflexes exhibit the lowest feedback gain when the muscles are relaxed, we would expect even stronger effects when the muscles are active. A second potential issue is that it is inherently impossible to perfectly isolate the movement of one joint, such that always muscles in both joints must have been active during the experiments. However, we could show that the brachioradialis was primarily active during the elbow rotation and the deltoid during the shoulder rotation, respectively (cf. Fig. 2). The goniometer measurements confirmed that little to no motion occurred in the shoulder during the elbow rotation and vice versa, and an activation of muscles in the resting joint, or slight movement of this resting joint, would likely have only decreased the observed effect size. It is thus likely that with perfect isolation of individual muscle activation during the movements, the observed effect would be even stronger. A third potential issue is the absence of a background load in the muscles before the perturbation. It has been shown that small differences in participant instructions such as to resist or relax to the perturbation can produce modulation in the short-latency reflex (49). Later work showing different preparatory activity in the motor cortex (18, 50, 51) has raised questions about whether this activity might reflect differences in the subthreshold activity of the motor neuron pools that could affect the reflex gains (9, 31, 32). However, recently this idea has been challenged, with evidence that this might reflect different gamma motor neuron drive setting up feedforward changes in the feedback gain (12, 33). Moreover, this work has argued that background loads might hide differences in modulation of the short-latency stretch reflexes (33). Although we argue that the absence of a background load is critical in our work, and supported by recent studies (12, 33), we cannot completely rule out the possible influence of small differences in the motor neuron pool activation level below threshold that could have a role in these results. However, this is unlikely to contribute in this case, as the specific direction of the perturbation was unknown and randomly applied, unlike the resist or relax instructions. As a last point, further exploratory research is necessary to analyze the characteristics and the origin of the joint-specific, persistent gain scaling mechanisms discovered here. Possible characteristics of interest include how quickly it builds up during movement, how it evolves after movement cessation, and which other tasks besides periodic movement may trigger it. A potential root cause for the joint-specific gain modulation is reciprocal inhibition, as described above, but further research is necessary to truly uncover the mechanisms in the CNS that underlie our novel motoneuron gain modulation effect.

Overall, the results of this study demonstrate that the CNS can specifically change the fastest short-latency reflex gains of individual muscles. By virtue of its unprecedented topographic and temporal precision, the gain scaling mechanism observed here provides unique and important characteristics to adapt human motor control to match the performance of an energy-optimal controller under sudden mechanical changes of the musculoskeletal system or the environment. As elaborated in an accompanying patent (52), this novel gain scaling mechanism can be mimicked by exoskeletons to improve the motor performance of patients suffering from movement impairments, e.g., after spinal cord injuries.

DATA AVAILABILITY

The data are available at https://doi.org/10.6084/m9.figshare.20931226. A separate folder is provided for *study 1*, which

functionally investigated gain scaling of motoneurons, and *study 2*, which tested the influence of serotonin on gain scaling. One data folder is provided per subject, including the preliminary recordings and the main experimental recordings, as described in MATERIALS AND METHODS.

SUPPLEMENTAL MATERIAL

Supplemental Material is available at https://doi.org/10.6084/m9.figshare.20931226. It provides additional details on the methods, supporting results, and the raw data for researchers wishing to reproduce the statistical analysis.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.S., A.S., H.H., P.v.d.S., T.M., D.W.F., and A.A.-S. conceived and designed research; P.S. and A.S. performed experiments; P.S. and A.S. analyzed data; P.S., A.S., H.H., P.v.d.S., D.W.F., and A.A.-S. interpreted results of experiments; P.S. and A.S. prepared figures; P.S., A.S., and D.W.F. drafted manuscript; P.S., A.S., H.H., P.v.d.S., T.M., D.W.F., and A.A.-S. edited and revised manuscript; P.S., A.S., H.H., P.v.d.S., T.M., D.W.F., and A.A.-S. approved final version of manuscript.

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