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Research report

Corticospinal control strategies underlying voluntary and involuntary wrist movements

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HIGHLIGHTS

- The corticospinal system sets spatial thresholds for proprioceptive reflexes.
- Voluntary motor actions are produced by resetting the spatial reflex thresholds.
- During involuntary actions descending systems maintain invariant values of reflex thresholds.
- Resetting of reflex thresholds solves the classical posture-movement problem.
- Corticospinal control is done without programming of EMG patterns and kinematics.

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ABSTRACT

The difference between voluntary and involuntary motor actions has been recognized since ancient times, but the nature of this difference remains unclear. We compared corticospinal influences at wrist positions established before and after voluntary motion with those established before and after involuntary motion elicited by sudden removal of a load (the unloading reflex). To minimize the effect of motoneuronal excitability on the evaluation of corticospinal influences, motor potentials from transcranial magnetic stimulation of the wrist motor cortex area were evoked during an EMG silent period produced by brief muscle shortening. The motoneuronal excitability was thus equalized at different wrist positions. Results showed that the unloading reflex was generated in the presence of a corticospinal drive, rather than autonomously by the spinal cord. Although the tonic EMG levels were substantially different, the corticospinal influences remained the same at the pre- and post-unloading wrist positions. These influences however changed when subjects voluntarily moved the wrist to another position. Previous studies showed that the corticospinal system sets the referent position (R) at which neuromuscular posture-stabilizing mechanisms begin to act. In self-initiated actions, the corticospinal system shifts the R to relay these mechanisms to a new posture, thus converting them from mechanisms resisting to those assisting motion. This solves the classical posture-movement problem. In contrast, by maintaining the R value constant, the corticospinal system relies on these posture-stabilizing mechanisms to allow involuntary responses to occur after unloading. Thus, central control strategies underlying the two types of motor actions are fundamentally different.

1. Introduction

The relationship between voluntary and involuntary motor actions has been a topic of public and scientific interest since ancient times [1–4]. Voluntary motor actions are self-initiated by subjects, unlike involuntary actions (usually called reflexes) that represent compulsory responses to unexpected external sensory or mechanical stimuli. A known example of an involuntary action is the unloading reflex demonstrated in a person who holds a heavy book on the palm of the hand by contracting elbow flexors and lets the arm go to another position when the book is suddenly lifted off the palm by a second person. To reproduce the response

Abbreviations: EC, efference copy; EMG, electromyogram; MNs, motoneurons; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; MEP, motor evoked potential; RMS, root mean square; SD, standard deviation; TMS, transcranial magnetic stimulation.

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in subsequent trials, it is usually sufficient to ask the subject to minimize voluntary interventions to the unloading [4] (for recent review see [5]).

Involuntary motor actions such as the stretch reflex and other proprioceptive reflexes have parameters (gains and thresholds) that are controlled by descending systems [6]. In other words, like voluntary motor actions, involuntary actions involve descending systems, rather than being generated autonomously by the spinal cord. The descending control strategies underlying the two types of actions are likely different but the essence of these strategies and differences between them remain unclear [6].

von Holst [2] emphasized that the control strategies in the two types of actions can be identified by solving the posture-movement problem, i.e. by answering the question of why self-initiated, voluntary movements of body segments from a stable posture are not impeded by posture-stabilizing reflexes [2,7–9]. A posture of one or more body segments is stabilized by intrinsic muscle properties and postural reflexes, including the stretch reflex, that generate position- and velocity-dependent resistance to deviations from this posture. Von Holst assumed that to prevent resistance of postural reflexes to self-initiated deviations from an initial posture, a copy of motor commands to muscle (called efference copy, EC) is used to compensate for the major source of this resistance – motion-related proprioceptive signals (reafference).

The EC notion conforms to the dominant view of pre-programming of motor output for actions, a view shared by several prominent scholars in the field [10–12]. There is, however, growing concern that this view might be incorrect [9,13–16]. In this controversial situation, it is important to re-examine the EC-based solution of the posture-movement problem to verify the physiological feasibility of this view. In von Holst's proposal, EC prevents resistance to self-initiated motion by suppressing reafference and thus postural reactions to deviations from the initial posture. In other words, the system destabilizes the initial posture to prevent resistance to the intentional movement. This proposal does not explain how stability of the final posture is regained. One can suggest that EC suppresses reafference only during motion and restores postural reflexes after that to stabilize the final posture. However, before the movement onset, postural reflexes were tuned to stabilize the initial posture and von Holst's proposal does not explain what prevents them from driving the body segments back to the initial posture.

Another problem of von Holst's proposal is that tonic EMG levels of arm muscles and thus ECs are often similar at different voluntarily established positions in isotonic conditions [7–9,16]. Therefore, in these cases, EC could only temporarily suppress postural reflexes. Again, restored postural reflexes should drive the body segments back to the initial position. This prediction of von Holst's proposal apparently conflicts with the absence of any tendency of body segments to return to the initial position after isotonic or other voluntary movements.

The posture-movement problem has been solved empirically, by identifying the central control strategies underlying the unloading reflex and voluntary changes in the elbow joint angle [4,5]. Specifically, by analyzing the unloading reflex, it has been found that with increasing amount of unloading, the arm displacement from the initial position increased, whereas the EMG activity of pre-loaded muscles decreased–a spring-like behavior described by a non-linear torque-angle characteristic resulting from intrinsic muscle properties and proprioceptive reflexes [4,5,17–20]. Thereby, the active muscle torque was reduced to zero at a specific, referent (R) elbow position. In the absence of co-activation of flexors and extensors, this position corresponds to the joint angle at which flexors and extensors reach their common activation threshold. More often, however, flexor and extensor thresholds are somewhat different being shifted in the opposite directions from R. Say, the flexor threshold is shifted to $R - R_f$ and the extensor threshold to $R + R_e$, thus surrounding the R with a *spatial zone* (between R_f and R_e) within which agonist and antagonist muscles are co-activated [5]. The level of muscle co-activation at position R is defined by the width of the spatial zone.

It has also been shown that the R and thus the torque-angle characteristic are shifted when the subject voluntary changes the initial arm position [4,5,17–20]. These shifts are accomplished by changing the sub-threshold state of α-motoneurons (MNs) [5,9,21] due to direct or indirect pre- and post-synaptic inputs to these MNs, via spinal interneurons and γ-MNs that innervate length- and velocity sensitive receptors–muscle spindles [22–24]. These sub-threshold signals that shift the R to elicit voluntary movement result in recruitment of agonist and de-recruitment of antagonist motor units. Therefore, the R is also called the reciprocal command, unlike the co-activation command (C) that specifies the width of the co-activation zone that surrounds the referent position. Thus, experimental data suggest that the nervous system actively controls reflexes in both actions but in involuntary action (unloading reflex), it maintains invariant values of the spatial thresholds at which proprioceptive reflexes are initiated, whereas in voluntary action, it shifts the spatial thresholds of reflexes. These empirical results underlie the equilibrium-point theory for motor actions [5].

Unlike all previous theoretical attempts to solve the posture-movement problem, referent position control represents an empirically-based solution of the problem [5,9]. Specifically, by resetting the R, the nervous system relays ("re-addresses") postural reflexes to a new position. In this case, the *initial arm position becomes deviated from the new R*. As a consequence, the same postural reflexes, instead of resisting motion, drive the arm toward a final posture at which muscle and external forces become balanced again. In other words, by shifting the referent position at which postural reflexes begin to act, the nervous system (1) converts these reflexes from a movement-resisting to a movement-producing mechanism and (2) relays stability to the final posture. The solution of the posture-movement problem remains valid even if a co-activation command is used: since the co-activation zone surrounds the R, this zone is shifted together with the R command when voluntary motion is made. Due to this hierarchy between the R and C commands and the spatial aspect of the latter, arm stiffness and damping responsible for an increase in arm stability due to the C command is relayed from the initial to the final arm posture. This shows that the C command subordinated to the R command in the context of threshold position control is a powerful tool in controlling action dynamics (movement speed in particular [5]) without any posture-movement problem.

The next step in the analysis of the relationship between voluntary and involuntary actions is to answer the question of which neural levels are involved in resetting or maintaining the referent position in the respective motor tasks. It has been shown that the referent position for activation of leg muscles in decerebrated cats can be set or reset by tonic electrical stimulation of different descending systems [23]. However, this method of changing the state of descending systems may not be considered as physiological.

In intact humans, it has recently been found that changes in corticospinal influences during intentional wrist movements are associated with resetting of the referent wrist position at which muscle recruitment is initiated [21,24]. Is it possible that the human motor cortex can also maintain identical corticospinal influences and thus maintain a constant *R*-value when motion to another wrist position is accomplished involuntarily, following unloading? The existing data are not sufficient to answer this question. One can argue that long-loop, transcortical reflexes [25–30] evoked by unloading could alter corticospinal influences when the wrist position changes due to unloading. This would imply that a different area of the brain is responsible for maintaining the same *R* value at

pre- and post-unloading positions. On the other hand, transcortical reflexes have been investigated by *stretching* of active muscles, whereas the unloading reflex primarily results from *shortening* of pre-activated muscles, while simultaneously stretched antagonists are less active if not silent. Unlike shortening, stretching of contracting muscles may be associated with triggered reactions that prevent active sarcomeres from being overstretched (e.g. [31,32]). In addition, transcortical reflexes are instruction-dependent as shown in animal experiments in which monkeys learned to oppose or assist the perturbation applied to their arm [26,27]. Compared to stretching, unloading of active muscles may not evoke modifications of corticospinal and other descending influences. However, the presence of such an invariant descending drive may be essential for stabilizing responses to unloading.

We tested the hypothesis that corticospinal influences are similar at pre- and post-unloading wrist positions but different at wrist positions established voluntarily.

2. Methods

2.1. Subjects

Nine healthy individuals participated in this study: 6 males, 3 females; right-hand dominant according to Edinburgh test [33]; mean age ± SD: 28.1 ± 4.2 years. All participants signed an informed consent form approved by the Institutional Ethics Committee (CRIR) in accordance with the 1964 Declaration of Helsinki. Since transcranial magnetic stimulation (TMS) was used in this study, subjects were excluded if they had a: history of a brain injury or seizures; family history of seizures; pregnancy; heart disease; cochlear or other implants; cardiac pacemaker; musculoskeletal injury of the upper extremities. Subjects were also excluded if they were taking medications (e.g. epileptic and psychoactive drugs) that could affect the excitability of the motor cortex. Participants were free to withdraw at any time during the study.

2.2. Apparatus

The experimental set-up has been described previously [21,24]. Briefly, subjects sat in a reclining dental chair with back support. The head and neck were stabilized with a cervical collar. The right forearm was placed on a table (elbow angle about 100°, horizontal shoulder abduction about 45°). The hand and forearm were placed in a neutral, semi-supinated position. Velcro straps were used to minimize the motion of the forearm. The hand with extended fingers was placed in a vertically oriented plastic splint attached to a horizontal manipulandum. The axis of wrist flexion-extension was aligned with the vertical axis of the manipulandum that could rotate freely. A torque motor (Parker iBE342G) connected to the axis of the manipulandum was used to load and unload wrist flexors and deliver brief perturbations at different wrist positions. In all tasks, subjects were instructed to abstain from flexing the fingers or pronating/supinating the wrist in the splint. Thus subjects had to minimize the involvement of degrees of freedom other than wrist flexion-extension.

2.3. Experimental procedures

Wrist flexors were pre-activated at the initial position by compensating an initial load (0.3 Nm) at 25 ± 5° (mean ± SD) of extension from the neutral position (0°). To establish and maintain the required position, subjects initially looked at a computer screen where the current and target wrist angles were displayed using vertical bars. Small unintentional co-activation of flexors and extensor muscles at the initial position was tolerated. However, 4 out of 9 subjects strongly co-activated flexors and extensors while compensating the load at the initial position. They were able to diminish extensor tonic activity to an acceptable low level (<20% of flexors' EMG at the same gain) after about 20 practice trials.

About 4 s after the initial position was established the load was suddenly removed. Subjects were instructed not to correct the wrist displacement elicited by unloading and let the wrist come naturally to a flexed position (unloading reflex). To facilitate this behavior, subjects closed their eyes as soon as the initial position was established. For all subjects, less than 4 trials were sufficient to comply with the instruction and stabilize the unloading response. In each trial, about 4 s after the post-unloading position had been reached, a computer-generated sound (tone) cued subjects to make an intentional movement by returning the wrist to the initial position in a self-paced way in the absence of a load; after that subjects opened their eyes. Thus, both tasks were performed in the absence of vision. By asking subjects to return the wrist from the post-unloading to the initial position, we ensured that the wrist displacements were similar in the two tasks. Corticospinal influences were evaluated at three steady-state positions established before unloading (position E), after unloading (position F), and after the intentional return movement to the initial position (position E^).

2.4. TMS conditioning technique

Corticospinal influences at positions E, F and E^ were evaluated by delivering single-pulse TMS to the wrist area of the motor cortex and by recording motor evoked potentials (MEPs) from wrist flexor and extensor muscles. MEPs depend not only on corticospinal influences but also on motoneuronal activity and excitability levels [21,34]. These levels are thus contaminating factors in evaluating corticospinal influences by TMS. To minimize this confounder, we delivered TMS during a brief muscle shortening at each of these positions (TMS conditioning technique [21]). Muscle shortening usually elicits a silent period in the tonic EMG activity [35–39] resulting from a pause in the discharges of muscle spindle afferents [38], possibly complemented by reciprocal inhibition of these MNs elicited by simultaneous stretch of antagonist muscles. The delay between the onset of the torque pulse and TMS (18–22 ms) was found empirically and individually for each subject such that the MEP occurred during an EMG silent period. Thereby TMS was delivered before afferent signals elicited by muscle shortening could reach the motor cortex (minimal latency 25 ms [40]). Shortening of flexor or extensor muscles was produced by a brief pulse generated by the torque motor. The pulse parameters (magnitude 0.45 Nm; duration 60 ms) were chosen based on the previous study [21] to bring MNs to their lowest excitability state at each position when MEPs occurred. The state of lowest motoneuronal excitability was confirmed by the observation that the MEP elicited by the same TMS pulse during the EMG silent period could not be further decreased by increasing the magnitude of the muscle shortening (a saturation effect) at the pre- and post-unloading wrist positions [21]. The saturating torque pulse was also helpful in minimizing the dependency of its mechanical efficiency on the background EMG level and wrist position.

Compared to [21], we further verified the TMS conditioning technique in three additional tests. First (4 subjects), we compared the EMG levels during EMG silent periods elicited by the muscle shortening pulse alone (no TMS) at wrist positions (E, F and E^) to see whether these EMG levels were actually equalized, as required by the TMS conditioning technique. In each trial, the torque pulse was applied at one of the three wrist positions chosen randomly (12 trials per position, 36 trials in total) and the root mean squares of EMG levels (in a window of 30 ms starting 25–30 ms after the onset of muscle shortening depending on the subject) during the EMG silent periods were computed at each of these wrist positions.

Second, we used H-reflexes (bipolar median nerve stimulation at the cubital fossa, single 0.2 ms pulse 18–20 ms after the onset of the muscle shortening torque pulse, depending on the subject) to see whether or not the excitability of MNs was equalized at different wrist positions following muscle shortening elicited by the torque pulse (no TMS was used in this test). Initially we focused on comparison of excitability of flexor MNs at pre- and post-unloading positions, E and F (3 subjects) but then extended the analysis to positions E, F and E^ (4 additional subjects). Both M- and H-reflex responses were quantified by measuring the individual peak-to-peak amplitudes. H-reflex responses for similar M-responses during muscle shortening were normalized by the maximal H-reflex obtained across different wrist positions, individually for each subject (36 trials; 7 subjects). Third, we applied TMS without the torque pulse at each of the three positions (1 position per trial; 36 trials in total, 9 subjects) to compare MEPs obtained by TMS alone with those previously obtained with TMS conditioned with the torque pulse. We thus tested whether or not the TMS conditioning technique made a difference in the evaluating corticospinal influences, especially at pre- and post-unloading positions that differed in terms of flexor tonic EMG levels.

When using TMS conditioning technique, single-pulse TMS preceded by the torque pulse was delivered at 1 of the 3 randomly chosen positions in each trial (1 pulse/trial; 12 trials for each of the three wrist positions and two torque pulse directions; 72 trials in total; about 30 s between trials). TMS during muscle shortening was delivered approximately in the middle of the period during which the respective position was maintained. This was done to ensure that MEPs elicited by TMS occurred during a period of steady-state (tonic) EMG activity at the respective wrist position and to give enough time (1.5–2 s) to recover from transient mechanical and neural effects of TMS between tasks. Such effects included a small muscle contraction (a jerk) sometimes resulting from MEP; transient changes in the EMG activity, and transient changes in the intra-cortical state elicited by TMS. Previous studies ([21,24] showed that 1 s was sufficient to recover from such mechanical, electromyographic and neural TMS effects. The time of delivery of each TMS pulse was varied within an interval of 500 ms to minimize anticipatory effects.

In most cases, MEPs exceeded the background EMG levels during muscle shortening and could be identified based on the latency and characteristic shape, but in all cases MEPs became apparent when MEPs were extracted by using the stimulus that triggered TMS for synchronized EMG averaging across 12 trials. This method is known to be efficient in increasing the signal to noise ratio such that MEPs were clearly visible and followed by a characteristic silent period.

TMS was used to evoke MEPs in two wrist flexors (flexor carpi radialis, FCR; flexor carpi ulnaris, FCU) and two wrist extensors (extensor carpi radialis, ECR, long head; extensor carpi ulnaris, ECU). TMS was delivered via a figure-of-eight coil (70 mm outer size, 110° between the axes of each half of the coil) connected to a monophasic stimulator (Magstim 200, UK). The magnetic fields created by the

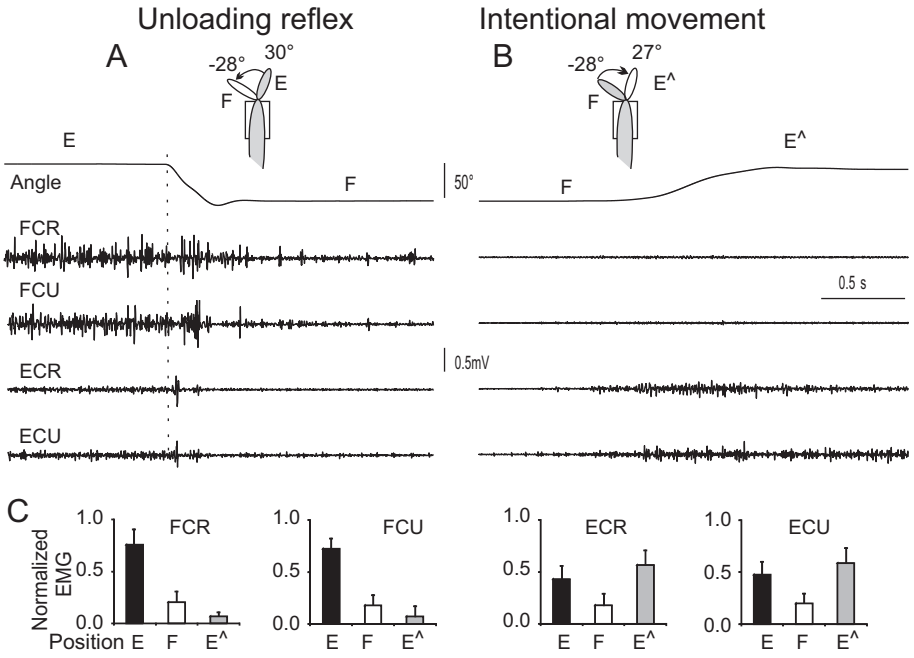

Fig. 1. Typical kinematics and EMG patterns during the wrist unloading reflex (A) and subsequent intentional return to the initial position in the absence of vision (B). (A) At the initial position (E), flexor muscles (FCR, FCU) were pre-activated by compensating a load acting in the extension direction. At this position, EMG activity of wrist extensors (ECR, ECU) was smaller than that of flexors. In response to sudden unloading, the wrist moved to position F. (B) From position F the subject intentionally returned the wrist, with a small error, to the initial position (E^). (C) Mean (±SD) EMG levels of muscles at the 3 positions for the group of 9 subjects. Flexor EMG levels were significantly different whereas only extensor EMG levels at position F differed from those at positions E and E^.

currents in the two halves of the coil resulted in a maximal stimulus at the intersection point [41,42]. The TMS coil was placed on the scalp surface above the area of the motor cortex projecting to the wrist muscles. The intersection of the coils was initially positioned approximately 2 cm anterior and 6 cm lateral to the left of the vertex corresponding to wrist area of motor cortex. To find an optimal position for eliciting MEPs in wrist muscles, the coil was moved medio-laterally around the initial position over the scalp in steps of ~0.5 cm. The optimal position of the coil was defined as the point at which the MEP remained stable in three consecutive trials when subjects actively maintained the wrist at the neutral position in the absence of the load. The stimulation intensity was then slowly decreased until the motor threshold (MT) was found. The MT was defined as the lowest stimulus capable of evoking at least 5 of 10 MEPs with the amplitude of at least 50 μV. The TMS intensity was then increased to 1.2 MT and kept unchanged during the experiment. The optimal point was marked with a felt pen on the scalp. Four additional marks on the scalp and perimeter of the coil served as a visual reference to maintain the coil position throughout the experiment.

2.5. Data recording and analysis

Experiments were run by custom made programs based on LabView software (National Instruments, USA). Wrist position was measured with an optical encoder coupled to the shaft of the torque motor of the manipulandum. Bipolar surface electrodes (inter-electrode distance ≈3 cm) were placed on the bellies of wrist flexor and extensor muscles (FCR, FCU, ECR, ECU) to record EMG activity and MEPs. EMG signals were amplified (telemetric system, Noraxon) and filtered (30–500 Hz). All signals were recorded at a sampling rate of 5000 Hz. The TMS trigger pulse was also recorded via a separate analog channel to indicate precisely when TMS was delivered during the trial. These data were stored on a PC and analyzed offline with MATLAB (Mathworks, USA) and Signal (Cambridge Electronic Design, UK) software specifically adapted to this project.

Each trial was analyzed individually to evaluate EMG activity, MEPs and wrist position. EMG signals were notch (60 Hz) and then band-pass filtered (35–400 Hz). For each muscle, we measured the root mean square (RMS) of EMG signals, in a 200 ms window before the TMS artifact. Previous analyses ([21,24] have shown that TMS has only transient kinematic and EMG effects that cease long before the onset of unloading (about 1.5–2 s later) or, in the cases when TMS was delivered at the post-unloading position, before the intentional return of the wrist to the initial position. EMG levels were also measured in 30 ms window during silent periods (not TMS) elicited by muscle shortening (see above).

Peak-to-peak MEP amplitudes were measured. For averaging and group statistics, MEPs were normalized by dividing each response by the maximal MEP values obtained at the three positions, individually for each muscle and subject. Two methods were used to normalize RMS amplitudes of EMG signals. First, as we did for MEPs, we divided each RMS value by the maximal RMS obtained at the three positions, individually for each muscle and subject. Second, at each of the three positions, we determined the maximal stretch reflex amplitude for each muscle in the trials in which the conditioning torque pulse shortened antagonist muscles. The mean of the three maximal values was taken as a normalizing coefficient for RMS, individually for each muscle and subject. A similar normalization procedure was used for comparison MEPs and other variables at the three wrist positions.

2.6. Statistical analysis

Peak-to-peak MEP amplitude and pre-TMS levels of EMG RMS obtained at each position were characterized by the mean and standard deviation (SD; error bars in histograms) for each muscle and subject. After verification of the variance similarity and distribution normality (Shapiro–Wilk test, $p < 0.05$), a one way ANOVA with Tukey post hoc tests (Statistica V8) was done to evaluate the difference in MEPs and EMG activity at positions E, F, and E^. Similar statistics were applied to MEPs and H-reflexes during EMG silent periods.

3. Results

3.1. Unloading reflex and intentional movement

Fig. 1 shows a typical example of wrist position and EMG activity in a representative subject in a trial in which a load (0.3 Nm) was initially balanced at an extension position (E) of 30°. The load acted in the extension direction and was compensated by wrist flexors (FCR, FCU). Compared to extensors (ECR, ECU), the pre-loaded flexors had relatively higher tonic EMG activity. In response to unloading, the wrist moved to a flexion position (F) of −28° (angular movement of 58°; range 50–65° for the group). The transition was initially associated with a silent period in the EMG activity of shortened flexors accompanied by EMG bursts of stretched extensors (Fig. 1A). When the post-unloading position (F) was reached, the tonic flexor activity was smaller compared to that before unloading and further decreased after the unloaded wrist was intentionally returned to an extension position (E^) of 27° (Fig. 1B). For each subject and for the group, the differences in the tonic flexor EMG activity at the three positions were significant (Fig. 1C; $F_{(2,24)} = 129$, $F_{(2,24)} = 208.9$, $p < 0.05$, for FCR and FCU respectively).

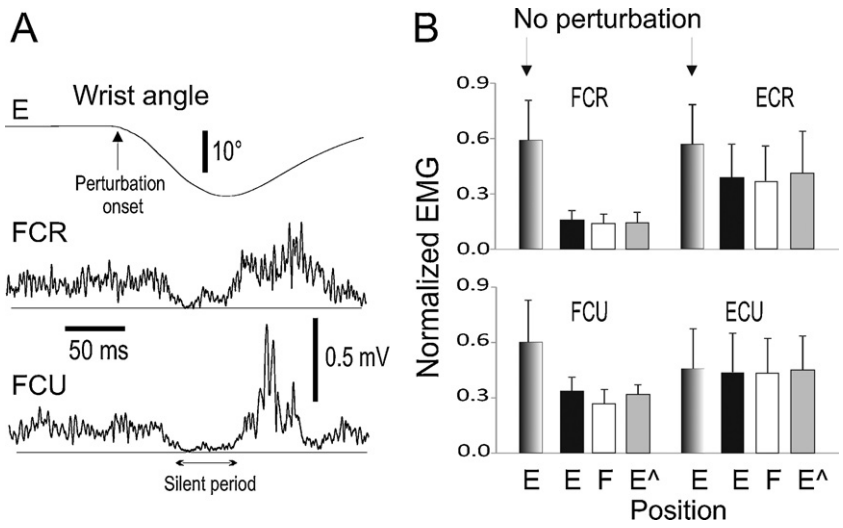

Fig. 2. EMG levels at different wrist positions during muscle sortening. (A) Examples of the changes in the mean flexor EMG activity elicited by muscle shortening in a representative subject. (B) Mean (±SD) EMG levels of muscles at the 3 positions for the group of 4 subjects. The first bar for each muscle shows the tonic EMG level at the initial position (E) in the absence of muscle shortening. The remaining bars show EMG levels at different wrist positions during EMG silent periods elicited by muscle shortening.

At position E, the tonic EMG activity of extensors was relatively low (Fig. 2A) and decreased to a near background noise level at position F. After subsequent intentional motion to position E^ (Fig. 1C), tonic extensor activity was higher than at position F. For the group, the differences in EMG levels at the three wrist positions were significant ($F_{(2,24)} = 21.1$, $F_{(2,24)} = 23.6$, $p < 0.05$, for ECR and ECU respectively).

3.2. Equalizing EMG levels and motoneuronal excitability at different wrist positions by muscle shortening

The differences in EMG levels at different wrist positions (Fig. 1) could result in misevaluations of corticospinal influences based on MEPs since the latter depend not only on these influences but also on the state of MNs (see Section 2). By eliciting a silent period in the tonic EMG activity by brief muscle shortening (Fig. 2A), it was possible to temporarily diminish and equalize EMG levels (one-way ANOVA; $p > 0.05$) at different wrist positions (E, F, E^) for flexors and extensors separately, as shown for the group of 4 subjects in Fig. 2B. Relatively small activity of extensors decreased to a background noise level when these muscles were shortened, at each of the three positions.

By testing H-reflexes of flexor muscles (FCR and FCU; Fig. 3A), we also found that the excitability of FCR MNs was equalized during silent periods at positions E and F in 7 subjects tested and at all three positions in 4 subjects tested (Fig. 3B). The same was the case for FCU MNs, except that in one subject (S7) the excitability at position E was somewhat higher than at positions F and E^ (Fig. 3B).

3.3. Responses to TMS conditioned by muscle shortening

To minimize the influence of the motoneuronal state on the evaluation of corticospinal influences at the three wrist positions, we used the TMS conditioning technique [22]. This was done by delivering TMS 18–22 ms after the onset a brief muscle shortening such that MEPs occurred during an EMG silent period when motoneurons were in a low state of excitability at positions E, F and E^ (for detail see Section 2).

MEPs elicited during EMG silent periods were substantially smaller than MEPs elicited by TMS alone but still detectible based on latency and characteristic shape, especially after averaging across 12 trials synchronized by the pulse that also triggered TMS. MEPs were clearly visible and followed by a characteristic silent period (e.g. [42,43]), as illustrated in Fig. 4A. ANOVA showed a positional effect on MEPs ($F_{(2,24)} = 8.2$, $F_{(2,24)} = 5.5$, $F_{(2,24)} = 15.1$, $F_{(2,24)} = 3.4$, $p < 0.05$, respectively for FCR, FCU, ECR and ECU). However, post hoc testing showed that when the positional differences in the EMG activity and motoneuronal excitability were minimized by muscle shortening initiated before TMS, MEPs at the pre-and post-unloading positions *became indistinguishable*, for each muscle (Fig. 4B). In contrast, when subjects made a voluntary extension by returning the wrist to the initial position after unloading, flexor MEP amplitudes significantly decreased whereas extensor MEPs increased (reciprocal pattern of changes in MEPs; Fig. 4C).

This analysis shows that corticospinal influences were similar at the pre- and post- unloading wrist positions. In contrast, there were

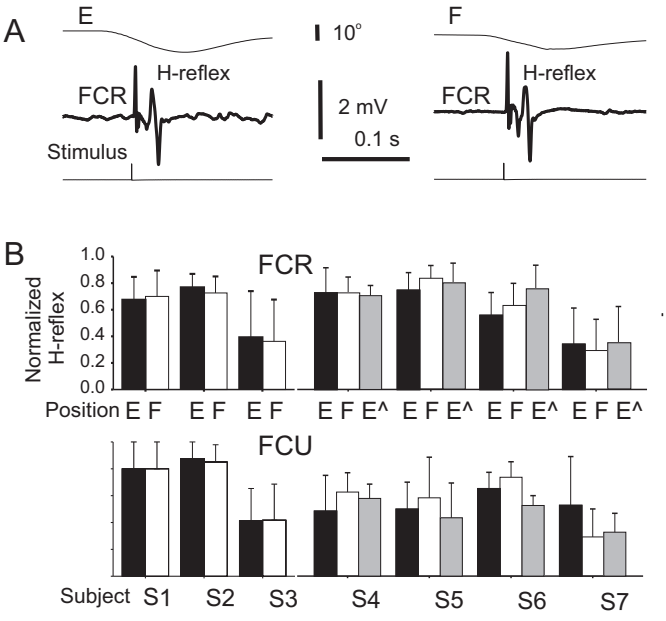

Fig. 3. Testing the excitability of motoneurons with H-reflex during a silent period elicited by a brief shortening pulse in flexor (FCR). (A) Raw examples of H-reflex during muscle shortening. (B) Means and standard deviations of normalized H-reflex in 2 flexors (FCR and FCU) at different wrist positions for 7 subjects.

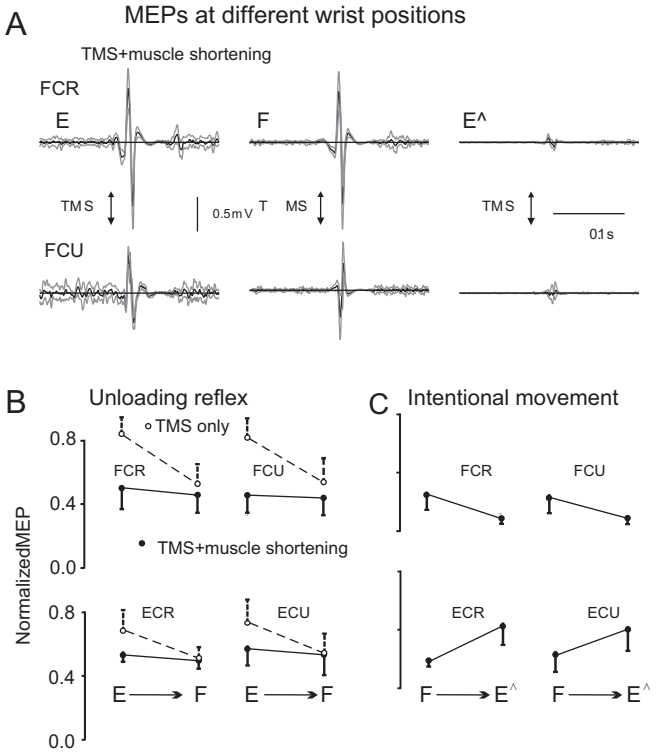

Fig. 4. Corticospinal influences on flexor and extensor motoneurons at different wrist positions in the unloading and intentional movement tasks, evaluated by the TMS conditioning technique (TMS+ muscle shortening). (A) An example of flexor MEPs (mean ± SD) at 3 wrist positions (E, F and E^) in one representative subject (same as in Fig. 2A). (B) Group means (±SDs) of flexor and extensor MEPs, elicited by TMS alone (opened dots, dashed lines) or during a silent period in the activity of flexors or extensors (filled dots, solid lines); left dots refer to MEPs obtained before unloading (position E) and right dots refer to MEPs obtained after unloading (position F). Note that MEPs obtained with TMS conditioning technique show that corticospinal influences before and after unloading were similar for motoneurons of each muscle. (C) Group means and standard deviations of flexor and extensor MEPs in TMS conditioning experiment showing reciprocal changes in corticospinal influences on flexor and extensor motoneurons in intentional movement from position F to E^.

reciprocal changes in the corticospinal influences on wrist flexor and extensor MNs when subjects intentionally changed the wrist position from F to E^. Note that in this case corticospinal facilitation of stretched flexors became smaller whereas that of shortening extensors became larger. This reciprocal pattern was thus *opposite to the pattern of activation of muscles during the stretch reflex* when the activity of lengthening muscles increases but that of shortening muscles decreases.

3.4. Responses to TMS alone

The MEP elicited by single-pulse TMS in flexors decreased with the transition from E to F that was reached after unloading and further decreased with the intentional motion to position E^ (Fig. 4B, dashed lines). Like tonic EMG levels (Fig. 1C), MEPs elicited by TMS alone significantly differed at different wrist positions, in each muscle (for the group, $F_{(2,24)} = 49.9$, $F_{(2,24)} = 38.6$, $F_{(2,24)} = 10.8$, $F_{(2,24)} = 8.0$, $p < 0.05$, for FCR, FCU, ECR and ECU respectively). Tukey post hoc tests showed that flexor MEPs significantly decreased with transition from position E to F (dashed lines in Fig. 4B) and from position F to E^. Extensor MEPs decreased with the transition from position E to F but increased with the transition to position E^. Extensor MEPs at the pre-unloading position did not differ from those after the wrist was returned to the initial position. This analysis showed that unlike MEPs resulting from TMS conditioned by muscle shortening, MEPs resulting from TMS alone were correlated with EMG levels, especially for positions E and F (Fig. 4B).

4. Discussion

4.1. Control of voluntary and involuntary wrist movements

In our paradigm, using appropriate timing and magnitude of muscle shortening before delivering TMS, the activity and excitability of MNs was equalized at the three wrist positions (Figs. 2 and 3; [21]). The TMS conditioning technique revealed that MEPs at the pre- and post-unloading positions (E and F) were similar, both for flexors and extensors, suggesting that corticospinal influences were also similar at these positions.

The MEPs at the two wrist positions could not be similar if the influences of other descending systems on flexor and extensor MNs (transmitted either directly to α-motoneurons or indirectly via interneurons and/or γ-MNs) were different at these positions. Therefore, not only the cortical but also other descending systems maintained similar influences on wrist MNs at these wrist positions. Thus, under constant descending influences established before unloading, afferent feedback was able to bring the wrist to another position after unloading.

It has previously been shown that rather than motor commands to muscles, descending systems specify the referent position, R, at which motor commands emerge, both in animals [23] and humans [24]. Therefore, the similarity of descending influences at the pre- and post-unloading positions revealed in the present study also suggests a similarity in *R* values at these positions. This conclusion was confirmed by computer modeling in which an invariant value of *R* was sufficient to simulate the EMG and kinematic patterns of the unloading reflex [44]. Thus, both experimental and modeling studies corroborate the hypothesis that the involuntary changes in the wrist position elicited by unloading are accomplished under descending influences that maintain the same referent position at which postural reflexes are initiated.

The TMS conditioning technique showed that in contrast to unloading reflexes, voluntary motion from position F to E^ in the absence of a load was associated with changes in the corticospinal influences on flexor and extensor MNs. These changes were reciprocal for flexor and extensor muscles: with intentional wrist extension, corticospinal facilitation of stretched flexors became smaller whereas that of shortening extensors became larger. Thus, the motor cortex is able to control flexor and extensor muscles in a coordinated way. The corticospinal system is also flexible enough to control in a task-specific way flexor and extensor muscles not only in combination but also in isolation [21].

The reciprocal pattern of corticospinal influences on flexor and extensor MNs observed in the present study was opposite to the pattern of activation of muscles during the stretch reflex when the activity of lengthening muscles increases but that of shortening muscles decreases. In a previous study [24], we showed that the reciprocal pattern of corticospinal influences on agonist and antagonist MNs associated with voluntary wrist repositioning was also inverted relative to the pattern of stretch reflexes. In that study, unlike the present study, TMS pulses were not conditioned by muscle shortening, but instead the tonic EMG levels and the excitability of MNs at different wrist positions were equalized by compensating the passive resistance of wrist muscles at different positions with a torque motor. This showed that the changes in the corticospinal influences associated with voluntary wrist repositioning were accomplished *independently of* motor commands, i.e. in an open-loop way. The independency ("decorrelation") of corticospinal influences on motor commands to muscles was also apparent from the analysis of unloading

responses in the present study since these influences were similar whereas the tonic EMG levels were different at the pre- and post-unloading wrist positions.

One limitation of our analysis is that corticospinal influences were evaluated at the pre- and post-unloading positions but not during motion from one position to another. The possibility remains that descending influences were *transiently* modulated during motion elicited by unloading, for example, due to transcortical reflexes resulting from unloading (see Section 1). Transcortical effects of unloading when subjects were instructed not to intervene have not been investigated systematically. However, when monkeys were trained to oppose deviations from an initial position of the arm against a load, cells in the primary motor cortex reacted to unloading much less than to loading of the arm (see Fig. 3A and B in [45]).

Another limitation of our analysis is related to the conditioning technique employing a brief muscle shortening initiated 18–22 ms before TMS. Afferent signals elicited by muscle stretching arrive at the motor cortex after a 25 ms delay [40]. Although TMS in our study was delivered 3–7 ms earlier than this delay, some transcortical effects of brief muscle shortening before TMS could not been ruled out. However, H-reflex testing (Fig. 3) revealed that the excitability of MNs during silent periods appeared to be similar at the pre- and post-unloading positions, which might not be the case if tonic transcortical effects were different at these positions. Our analysis of intentional changes in the wrist position also showed that the TMS conditioning technique does not conceal the existing differences in the corticospinal influences on wrist MNs at different voluntarily established wrist positions (Fig. 4; see also [21]).

4.2. Further implications

The differences in the control strategies underlying the two types of motor actions can be explained in the following way. During the unloading reflex, descending systems rely on the ability of spinal reflexes to provide a spring-like response to the external perturbation and bring the arm to a stable final posture. This behavior, however, is not provided autonomously by spinal reflexes but it is under continuous supervision of descending systems: in involuntary actions, descending systems establish and maintain the referent position at which reflexes begin to act. This does not mean that descending systems are always indifferent to external perturbations. Indeed, the referent position can be changed if the anticipated response to perturbation is not satisfactory. Continuous supervision of reflexes by descending systems is accomplished even during full muscle relaxation when corticospinal influences specify a referent position that prevents muscle activation in response to passive movements in the entire biomechanical range of motion of body segments [24]. In self-initiated movements, the corticospinal system, possibly together with other descending systems, resets the referent position at which reflexes begin to act, thus (1) solving the posture-movement problem (see Section1); (2) maintaining dynamic stability of motion and (3) stabilizing the final posture.

The independence of descending influences on ascending proprioceptive signals and motor commands is not absolute: task-specific changes in the thresholds can be made based on all previous sensory information arriving to the brain, but once a decision is made the central changes in the thresholds are accomplished in an open-loop way. Thereby, the motor cortex is likely always ready to change these thresholds if sensory signals go beyond certain limits (e.g., due to perturbations). A more general idea is that by specifying spatial thresholds of reflexes, descending systems only indicate the boundaries (spatial frame of reference) within which neuromuscular elements can work. In this sense, these commands are not "motor" per se. Motor commands to muscles, i.e., the output of MNs emerge within these boundaries depending on the gap between the actual position of body segments and the threshold positions, as well as on the rate of change in this gap [5]. Thus, the corticospinal system specifies where, in space, MNs should work, rather than how they should work in terms of motor commands. While monitoring the emerging dynamics of motor action, control levels may decide whether or not to prolong, shorten or change the pattern of shifts in the referent position if movement corrections or a transition to another motor action are necessary.

4.3. Constraining the choices between different theories of motor control

The empirical notion of the referent position control is a core of the equilibrium-point theory [5]. Results of this study clearly show that claims that this theory has no physiological basis are unfounded (see also [8]). Moreover, this theory has been advanced by offering physiologically feasible solutions not only to the posture-movement problem but also problems of redundancy in multi-muscle and multi-joint control of motor actions, including locomotion [5]. In addition, the existence of the referent position control integrated into the theory substantially constrains the choice between different theories of motor control.

For example, it is usually assumed that the brain pre-computes a prototype of motor commands to muscles, i.e. EC, with the help of hypothetical neural structures–internal models of the neuromuscular plant interacting with the environment (for recent review see [46]). Unable to solve the posture-movement problem, EC-based formulations cannot be considered as physiologically feasible (see Section 1). Another limitation of these formulations is that they implicitly presume that *MNs are linear devices* such that the motor commands that represent *the output of MNs* can also represent, via an inverse scaling factor, the input to MNs from descending systems. However, electrical thresholds make MNs fundamentally non-linear devices in which the output of MNs, i.e. motor commands, cannot be inverted to represent the motoneuronal input. The previous [21,23] and present study, confirm this suggestion: corticospinal influences can be de-correlated from EMG levels, i.e. motor commands to reveal that these influences (inputs to MNs) are actually *independent of* the output of MNs, both in involuntary and voluntary actions. These results as well as the known rule that correlations do not imply causality also show that observations of correlations of neural activity in the motor cortex and other brain areas with variables describing the motor output (e.g. [47]) are not sufficient to derive conclusions on the function of these areas or on the existence of internal models.

The referent position control also questions a departure point of internal model approaches that the nervous system directly pre-plans movement trajectories of body segments. Instead, by using referent position resetting as a tool for action production, the brain allows movement trajectories to emerge following the natural tendency of the nervous system to minimize, in the limits of biomechanical and neural constraints, the difference between the referent and actual position of body segments. This minimization principle (not available in internal model formulations) is valid for voluntary and involuntary movements or isometric torque productions [5].

In more recent internal model formulations, it is proposed that, rather than motor commands to muscles, the brain anticipates sensory consequences of motor actions and sends proprioceptive predictions to MNs. The latter are activated or not depending on the prediction error, i.e. the mismatch between the predicted and actual proprioceptive feedback [48]. An obvious problem of such proposals is that both corticospinal and proprioceptive influences are predominantly facilitatory and add together at the level of MNs, whereas the proprioceptive error can only be identified based on

the difference between these influences. Such a difference could be evaluated following the existence of corticospinal projections to spinal interneurons that presynaptically inhibit Ia afferent inputs to MNs [6]. However, presynaptic inhibition is usually *attenuated* when agonist MNs are facilitated by descending systems [49], thus strengthening, rather than opposing, proprioceptive feedback to MNs. Therefore, the hypothesis of pre-programming of proprioceptive feedback, like that of motor commands, seems inconsistent with experimental data, not to mention that it does not solve the posture-movement problem.

Is it possible to reconcile internal model formulations with the notion of referent position control in some kind of a hybrid theory? In particular, one can assume that the brain uses internal models to pre-compute the referent positions for actions. One should take into account that shifts in referent positions that delivered to motoneuronal inputs are simultaneously outputs of pre-motor (e.g., corticospinal) neurons. Like MNs, these neurons also have electrical thresholds and therefore are fundamentally non-linear devices that cannot receive computed referent positions and reproduce these positions at the neural outputs. This limitation is similar to that of MNs that receive signals that are independent of the motoneuronal output (see above). Thus, while strongly supporting the equilibrium point theory, the fundamental non-linearities of neurons as well as results of the present and previous studies [16,21,24] conflict with theories of motor control in which motor commands, EC, proprioceptive feedback or shifts in referent positions are pre-computed by internal models (see also [49,50]).

5. Conclusions

Our analysis shows that descending systems are actively involved in both voluntary and involuntary changes in the wrist position but in fundamentally different ways. Descending systems reset the spatial thresholds of reflexes when voluntary changes in position are made, but maintain these thresholds when positional changes are produced involuntarily, following external perturbations. The differences in the control strategies are related to the necessity to reset spatial reflex thresholds to a new posture and thus convert the posture-stabilizing mechanisms from those resisting to those assisting self-initiated motion. In contrast, descending systems may rely on these mechanisms to generate involuntary responses to perturbations by maintaining the same spatial thresholds of reflexes. These results substantially constrain the choice between different theories of motor control.

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