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Research report

Subthreshold corticospinal control of anticipatory actions in humans

Samir G. Sangani [a,b], Helli A. Raptis [a,b], Anatol G. Feldman [a,b,*]

[a] Center for Interdisciplinary Research in Rehabilitation (CRIR), Montreal, PQ, Canada
[b] Department of Physiology, University of Montreal, Montreal, PQ, Canada

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ABSTRACT

Previous findings suggest that, by influencing the subthreshold state of motoneurons, the corticospinal pathways can set and reset the threshold position at which wrist muscle recruitment begins. Here we assumed that the corticospinal system can change the threshold position in a similar way before anticipated perturbation to *pre-determine* an appropriate emerging response to it. We first analyzed motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) applied to the wrist area of motor cortex *before unloading* of preloaded wrist flexors, i.e. before the subsequent involuntary wrist motion to another position (*natural unloading*). Subjects then learned to diminish the post-unloading movement extent without activating antagonist (extensor) muscles before unloading or making intentional movement corrections after unloading (*adjusted unloading*). Although activity levels of wrist muscles before unloading were similar, MEPs of extensor but not pre-loaded flexor muscles were higher before adjusted unloading. We also applied TMS in combination with a torque pulse that shortened extensor muscles such that the MEP occurred when the motoneuronal excitability was minimized. Although diminished following muscle shortening, MEPs before adjusted unloading were still higher than before natural unloading. Results suggest that the corticospinal system, possibly together with other descending systems participated in the tonic subthreshold facilitation of antagonist motoneurons before adjusted unloading, which appears sufficient in modifying motor commands and motion leading to adjusted unloading. This study reinforces previous findings that descending systems, in particular, the corticospinal system can employ threshold position control during and after learning a novel action.

1. Introduction

There is strong evidence in humans [1] that corticospinal influences on wrist motoneurons change a spatio-dimensional variable – the threshold angle (R) at which recruitment or de-recruitment of wrist muscles take place. This finding complements similar demonstrations of the ability of different descending and spinal systems in humans and animals to reset the threshold position at which activation of limb muscles is initiated [2–11]. Threshold position control also underlies intentional movement and isometric force generation [12]. It has several unique features.

First, threshold position control is possible due to the existence of position-dependent afferent feedback to motoneurons mediated by muscle, cutaneous and articular afferents [12]. It can be associated with central resetting of stretch reflex thresholds [2–6]. Once specified, the threshold position becomes the spatial threshold for all reflex or/and central sources of activation of the muscle [4].

Second, threshold position control is accomplished through facilitatory or inhibitory descending influences primarily responsible for subthreshold (pre- or/and post-synaptic) changes in the state of motoneurons [1]. As such, these changes can be made long before any observable changes in EMG activity, i.e. in a feed-forward way. Although subthreshold, these changes drastically influence the state of the motor system by shifting the equilibrium point to which the system is attracted [12]. As a result, muscle activity and forces are generated to bring the system to this point. Threshold position control thus releases the brain from the necessity of computation of EMG patterns (motor commands) for motor actions [13]. Instead, these patterns *automatically emerge* depending on the gap between the actual (Q) and the threshold (R) limb position as well as on the rate of change in this gap.

Third, the threshold position can be associated with the notion of spatial frames of reference in which the neuromuscular system operates. Each frame of reference represents a system of coordinates, the values of which are defined relative to a referent (origin) point as well as by the geometrical structure and metrics of the

Abbreviations: TMS, transcranial magnetic stimulation; M1, primary motor cortex; EP, equilibrium point; MEP, motor-evoked potential; MT, MEP threshold; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; SR, stretch response; EMG, electromyogram.

* Corresponding author at: Department of Physiology, University of Montreal, Neurological Science Research Centre, and CRIR, Rehabilitation Institute of Montreal, 6300 Darlington Avenue, Montreal, Quebec, Canada H3S 2J4. Tel.: +5143402111; fax: +1 5143402154.
E-mail address: feldman@med.umontreal.ca (A.G. Feldman).

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frame. The threshold position can be considered as the referent point of the spatial frame of reference in which muscles can be activated. Intentional control of motor actions is thus associated with shifts of this point, i.e. with shifts of the frame [1]. To emphasize this aspect of motor control, the threshold position is also called the *referent position*.

Empirical studies have shown that the nervous system takes advantage of the feed-forward nature of referent position control in learning to adapt motor actions to new external conditions [11,14,15]. In the present study we investigated the possibility that a similar control strategy allows the nervous system to *predetermine* an appropriate motor response to anticipated changes in the external forces (perturbation) by sending subthreshold tonic influences to motoneurons before these changes. No prediction of the onset of perturbation is required in this strategy. In addition, the strategy diminishes the necessity to modify the motor output after perturbation. We also addressed the question of whether or not the corticospinal system is involved in such subthreshold control of anticipatory actions.

In the present study, we first analyzed an involuntary flexion of the wrist joint to a stable position after sudden removal of the load (*natural unloading*, also called the unloading reflex [3,16–19]. The reflex is easily reproduced if subjects are instructed to abstain from intentional corrections of the unloading effects [3]. Subjects then learned to markedly diminish the post-unloading movement extent (*adjusted unloading*). Consider two possible control strategies of complying with the task demand.

First, to produce adjusted unloading, the nervous system could re-program the EMG patterns produced during natural unloading. In particular, after unloading, the system could activate antagonist (extensor) muscles earlier to start movement deceleration beforehand, thus terminating the wrist flexion after a smaller excursion. This strategy would be consistent with the traditional view that the nervous system directly pre-programs EMG patterns required for motor action, possibly by pre-computing them by using an internal model of the neuromuscular system interacting with the environment.

Second, to diminish post-unloading wrist displacement, it would be sufficient to shift the antagonist threshold of antagonist muscles closer to the initial wrist position while waiting for unloading. To achieve this, descending systems could increase tonic subthreshold facilitation of antagonist motoneurons without recruiting them prior to unloading. Following wrist flexion resulting from unloading, antagonist muscles would be stretched and reach the adjusted threshold sooner than in natural unloading. Because of earlier activation of antagonist muscles, the extent of wrist motion would be reduced.

Although the two control strategies may result in similar EMG patterns in adjusted unloading, these strategies are quite different. According to the first strategy, the system deals directly with EMG patterns by modifying them at specific kinematic phases to adjust the movement extent resulting from unloading. In contrast, a qualitative analysis described in Appendix A as well as a computer simulation of the unloading reflex [20] show that shifting the spatial threshold for recruitment of antagonist muscles prior to unloading would be sufficient to elicit changes in the variables characterizing the motor output (EMG patterns, muscle forces and kinematics) required for diminishing the post-unloading movement extent without pre- or re-programming of the motor output.

We tested the prediction of the threshold position control strategy that descending systems can diminish the post-unloading wrist displacement by increasing, in a subthreshold way, the tonic facilitation of antagonist (extensor) motoneurons prior to unloading. In terms of EMG activity, the initial states of the system before natural and adjusted unloading will be similar: flexor muscles will generate similar tonic activity required to counterbalance the load whereas extensor muscles will have minimal activity in both tasks. However, the intrinsic states of the system in these two tasks before unloading will be substantially different: the descending facilitation and thus excitability of extensor but not flexor motoneurons before adjusted unloading will be higher than before natural unloading. Results appeared to be critical for several theories of motor control, including the referent position control theory itself.

Although several descending systems can accomplish the predicted subthreshold adjustment of the state of extensor motoneurons before unloading, we additionally verified, using transcranial magnetic stimulation (TMS), whether or not corticospinal pathways are involved in such an adjustment. Some results of this study were preliminarily published in abstract form [21].

2. Methods

Ten healthy subjects (5 males and 5 females; mean age and standard deviation, 28.3 ± 6.5 years) were recruited for our study after signing an informed consent form approved by the Institutional Ethics Committee (CRIR) in accordance with the 1964 Declaration of Helsinki. All subjects were right-handed (Edinburgh's test [22]). They had no history of neurological diseases, personal or family history of seizures (e.g. epilepsy). They did not have pacemakers, metallic implants (except dental implants) or physical deficits of the upper extremities. Subjects were excluded from the study if they took medications that could affect cortical excitability (e.g. psychoactive pills). Women did not participate if they were pregnant.

2.1. Apparatus

The experimental set-up has been described previously [1]. Briefly, subjects sat in a dental chair having 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 in a neutral, semi-supinate position. Velcro straps were used to minimize the motion of the forearm placed on the table. 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. The subjects were instructed to compensate for an initial load (0.3 N m acting in the extension direction) without tending to flex the fingers or pronate/supinate the wrist in the splint, thus minimizing the involvement of degrees of freedom other than wrist flexion-extension. 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 the pre-unloading position.

2.2. TMS

A mono-phasic single-pulse stimulator (Magstim 200, UK) was used for TMS applied via a butterfly-shaped coil (110° between the two wings, 70 mm outer diameter of each wing) placed on the head such that the electric currents induced by magnetic fields from the two wings of the coil summated at an intersection point in the motor cortex. To diminish the pressure of the coil on the head, the coil was attached to the double-joint manipulandum of the dental chair. The coil induced a posterior-anterior electrical current flow in the cortex. TMS was delivered to the wrist area of the left motor cortex and the hotspot was found by moving the coil to a position where the threshold for eliciting motor-evoked potentials (MEPs) in wrist muscles was minimal at the neutral wrist position actively maintained with minimal EMG activity in the absence of the load. EMG activity and MEPs were recorded from 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). The two wrist flexors may act as antagonists during wrist abduction (FCR) and adduction (FCU). They may also assist in elbow flexion. Similarly, the wrist extensors may act as antagonists during wrist abduction (ECR) and adduction (ECU) but as synergists with FCU and FCR in assisting elbow flexion [23].

The TMS spot was defined as optimal if TMS elicited an MEP of more than 50 μV in the ECR (6 subjects) or FCR (4 subjects) at a minimal TMS intensity (active motor threshold, MT) in at least 5 out of 10 sequential trials. 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. To allow subjects to rest, the coil was removed and placed again from time to time but only between different experiments.

2.3. Experimental procedures

The neutral wrist position was defined as 0°; wrist flexion positions were considered as negative and extension positions as positive. In experiment 1, at the initial position (~10° of extension) shown on a computer display, wrist flexors were pre-activated by compensating an initial load of 0.3 N m. About 4 s after the initial