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TMS-responses during anticipatory postural adjustment in bimanual unloading in humans

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Abstract

Transcranial magnetic brain stimulation (TMS) was used to assess the influence of the corticospinal system on motor output during forearm unloading in humans. Unloading was obtained either "passively" by the experimenter, or "actively" with the subjects' own contralateral arm. Anticipatory postural adjustments consisted of changes in the activity of a forearm flexor muscle prior to active unloading of the limb and acted to stabilize the forearm position. Motor evoked potentials (MEPs) were recorded in the forearm flexor at different times during active and passive unloading, static forearm loading, and during lifting of an equivalent weight by the contralateral arm while the ipsilateral forearm was statically loaded and held stationary. In active unloading, MEP amplitude decreased with the decrease of muscle activity. Passive unloading resulted in a similar decrease of MEP as with active unloading. During stationary forearm loading, the change in MEP corresponded to the degree of loading. If during static loading the contralateral arm has lifted a separate, equivalent weight, the amplitude of MEP decreased. A possible role of direct corticospinal volley and the motor command mediated by subcortical structures in anticipatory postural adjustments is discussed.

Keywords: Bimanual unloading; Anticipatory postural adjustment; Transcranial magnetic stimulation; Motor cortex

It is known that the variety of movements in humans and animals is anticipated by postural adjustments aimed to minimize the center of mass displacement and to decrease the predicted balance disturbances (see review [16]). The anticipatory postural adjustments (APA) were shown first on dogs in the pioneering work by Shumilina [23]. In humans the change of legs' muscle activity anticipating the upright arm movement during standing was shown first by Belen'kii et al. [4]. Later on this observation was confirmed and expanded in other experiments [1–3,22].

According to the traditional point of view, the posture is regulated by local and long-loop reflexes those are modulated by basal ganglia [14], cerebellum [15], reticulo-spinal system [9]. There are also data pointing to the role of premotor [8] and motor cortex [5,15,17] in posture control and learning of novel postural tasks. The pathways of the motor cortical influences on the postural adjustments are not yet clear. It was suggested by the group of Kasai [11] that the central command related to postural adjustment could be attributed to cortical influences. However, the evidences of corticospinal excitability changes during APA are still absent. If the pattern of the postural adjustment is characterized by changes of activity of few muscles only, one could suggest a direct pyramidal pathway involvement into such a "local" postural synergy. The task of voluntary bimanual unloading is a good example of a "local" synergy. If a subject unloads the forearm by his/her contralateral arm, the unloaded forearm maintains an almost stable position ("barman effect") due to the reduction of the biceps activity prior to the unloading [7,10,17]. The passive unloading by the experimenter is followed by an upward deflection of the forearm.

To evaluate the role of the motor cortex in the anticipatory postural adjustment to the forearm unloading we investigated the motor potentials (MEPs) evoked by transcranial magnetic

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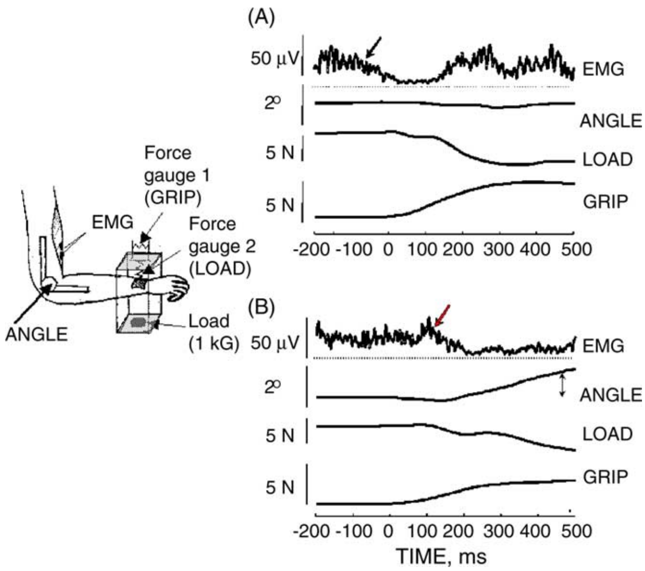

Fig. 1. Active (top) and passive (bottom) unloading. Left, schemes of the experiment. Right, time course of the EMG of m. biceps, elbow angle, load force, and handle grip force. In the time scale, zero corresponds to the touching of the handle. Note, that in the active unloading the EMG change precedes the onset of movement ($t = 0$) whereas in the passive unloading the EMG decreases after $t = 0$.

stimulation (TMS) in a forearm flexor at the time of bimanual unloading.

A group of eight healthy volunteers (23–52 years, three females and five males) participated in the study. All subjects were right-handed according to the Russian version of the Edinburgh Handedness Inventory test. The experimental procedures were approved by the Ethics Committee at the Institute of Higher Nervous Activity and Neurophysiology according to the Declaration of Helsinki.

The subject was sitting comfortably in an armchair with eyes closed (Fig. 1) and with his/her head supported by the headrest, so the head has been relatively immobilized and possible head rotation did not exceed 1°. The subject's left upper arm held vertically along the chest and gently pushing backward against a support place above the elbow. The instruction to the subject was to hold the left forearm and the wrist horizontally in a semi-prone position with suspended basket loaded by 1.0 kg weight. Elbow angle was about 90°. The basket could be lifted using the handle fixed on it. In the "active unloading" (ACT) subject placed the index finger and thumb near the handle and closed his/her eyes. Upon command ("beep"), subject grasped the handle with his/her right index finger and thumb and lifted the basket. Subject was instructed to lift the basket by wrist and elbow movement. Elbow joint position of the right arm was practically stable during the task performance. In the "passive unloading" (PASS) the basket was lifted by the experimenter.

The elbow angle was measured by potentiometer-based goniometer. The handle on the basket was equipped with force sensor to measure the grip force (Fig. 1). Another sensor was placed between the basket and the forearm to measure the force acting on the forearm. Surface EMG was recorded from m. *biceps brachii* of the left forearm (BIC). The preamplified EMG signal was bandpass filtered (50 Hz–1 kHz) prior to sampling at 2 kHz. Force and angular signals were sampled at 500 Hz. EMG, force and angular signals were recorded in the interval 500 ms before and 2500 ms after the "beep".

TMS was delivered by a Mags1 (Schwarzer, Germany, maximum output: 2 T) using a 9 cm round coil. Fine adjustments of coil position were routinely made for individual subjects to identify the optimal location. The coil was placed tangentially to the scalp, with the handle pointing posterolaterally at a 30° angle from the midline. The coil was positioned over the vertex and the direction of the current was clockwise when viewed from above. Then, the coil was moved over the right hemisphere to determine the optimal position for eliciting MEP on TMS three to five times bigger than the left m. *biceps brachii* activity with the forearm unweighted and elbow at 90° flexion (RELAX). The stimulation intensity was set at 40–50% of maximum stimulator output and this intensity was used throughout the whole experiment. In order to stabilize the coil position during the experiment the coil was fixed to the chair by a brace and taped to an elastic swimming cap on the subject's head by scotch. MEP amplitude was verified repeatedly in RELAX condition throughout the experiment to ensure that the coil position remained steady.

In the active unloading task, the stimulus was triggered by the thumb and index finger touching the handle. The moment of the touch was obtained from the derivative of grip force sensor signal after 4 Hz filtering. The MEP amplitude was measured offline by calculating the peak-to-peak amplitude of EMG signal in the interval from 15 ms to 40 ms after the stimulus. For active unloading, TMS was delivered at the moment of the touch (ACT-0) and 20 ms (ACT-20), 40 ms (ACT-40) and 500 ms (ACT-500) after it.

In the passive unloading task, the muscle activity decreased after the weight was removed (Fig. 1B). The delay of this decrease was determined in five preliminary records for each subject and usually it was in range of 120–150 ms. Therefore, TMS was initiated after a delay that was characteristic for each subject (PASS-0) as well as 20 ms (PASS-20), 40 ms (PASS-40), and 500 ms (PASS-500) after the delay. Five-hundred microseconds delay was selected because the BIC activity gradually recovered to the initial level in the period of 200–300 ms after the grasp.

The active unloading is a coordinated bimanual task including postural preparation in the left arm as well as grasping and lifting by the right arm. To test the cortical influences on postural preparation itself modulation of MEP was studied in another bimanual task, that consisted of grasping and lifting of weight by the right arm without postural preparation in the left arm. In this task, the subject was instructed to keep the weight by the left arm and lifted a second, equivalent weight with the right hand ("contralateral" test, CONTRA). Such manipulation is associated with enhanced activity in the left motor cortex that could influence the excitability of the right motor cortex [24]. Thus, this test was used as additional control of the excitability of motor cortex during active unloading (ACT).

In summary, TMS was delivered in 11 tests incorporated into five different tasks: (1) active unloading (ACT-0, ACT-20, ACT-40, and ACT-500), (2) passive unloading (PASS-0, PASS-20, PASS-40, and PASS-500), (3) the stationary loaded arm (LOAD), (4) the relaxed arm (RELAX) and (5) the 'contralateral' test (CONTRA). All tests were executed in random sequence 10 times in each subject. So, each subjects was stimulated 110 times during the experiment. Duration of the whole experiment was 1 h 30 min.

Because EMG activity significantly changed during ACT and PASS, the background activity in these tasks was calculated as a mean value of the rectified EMG activity in the interval 5–15 ms after the stimulus for each trial [13]. The background activity in LOAD, RELAX and CONTRA was measured in 50 ms interval before stimulus for each trial.

In order to pool data across subjects for statistical analysis, the background activity in the LOAD series, averaged across all trials of each subject, was taken as 100%. The background activity in each of the other series was expressed as the percentage of this value. In order to compare the MEP response across subjects, the MEP amplitude averaged across all LOAD trials was considered as 100% and the response in other tests was expressed as the percentage to this value.

Two way ANOVA or paired *t*-test was used for statistical analysis. The level of statistical significance was set 0.05.

Fig. 1 shows a typical activity of BIC muscle during active (A) and passive (B) unloading of the forearm. A decrease of BIC EMG activity of the load-bearing arm during the active unloading preceded the onset of grasp by 20–50 ms. The unloading itself followed the onset of grasp by about 100 ms. A small change in angular position of the load-bearing arm occurred at 80–120 ms after handle touch. The BIC activity remained diminished for up to 100–200 ms after the onset of grasp.

TMS of the motor cortex evoked a biphasic MEP in m. biceps with a latency of 16–18 ms (Fig. 2). The amplitude of MEP changed drastically during the active unloading (Fig. 2). The averaged data across all subjects is shown in Fig. 3. The MEP amplitude had already decreased by the time of handle grasp (ACT-0) to 57 ± 27% of that in the LOAD condition and remained decreased in ACT-20 and ACT-40 at 50 ± 32% and 63 ± 33%, correspondingly. Fig. 2 shows that EMG activity at these times was also decreased. The average background activity at ACT-0 was 64 ± 34% of the background EMG during the LOAD condition, 55 ± 31%—at ACT-20 and 55 ± 33% at ACT-40. ANOVA shows that both MEP amplitude and background activity changed during active unloading ($p < 0.05$, $F(4, 28) = 14.48$). Post hoc testing revealed that MEP amplitude and background activity were smaller in ACT-0, ACT-20, and ACT-40 (Tukey's Honest significant Difference test, $p < 0.05$) than in ACT-500 and LOAD. ANOVA factor interaction did not find any difference in the changes of MEP amplitude and EMG activity during the process of active unloading ($F(4, 28) = 0.40$, $p > 0.80$). Statistical analysis of the ratio MEP/background also did not reveal any difference between ACT-0, ACT-20, ACT-40 and ACT-500 responses ($p > 0.31$, $F(4, 28) = 1.23$).

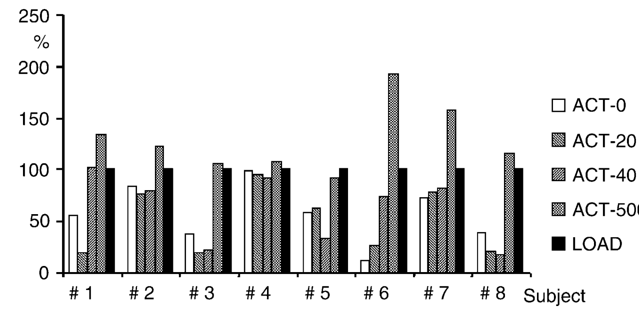

Fig. 3. Averaged amplitude of MEPs in all subjects at different moments of the active unloading. The MEPs amplitude during the load maintaining (LOAD) is 100%.

In the PASS condition, the MEP amplitude decreased with EMG background. MEP amplitude at PASS-0, PASS-20, and PASS-40 was 42 ± 23%, 60 ± 22%, 68 ± 31% of the MEP amplitude in LOAD, respectively. The average background activity at PASS-0 was 57 ± 40% of the background EMG in LOAD, 47 ± 27%—at PASS-20 and 55 ± 35% at PASS-40. At the end of unloading (PASS-500) MEP and EMG background had recovered to the control level with MEP at 98 ± 12% of the amplitude in LOAD, and EMG background at 99 ± 34%. Two way ANOVA with the factors: type of unloading (active, passive) and moment of stimulation (0, 20, 40, and 500 ms after start of unloading) did not find any difference in the changes of MEP and EMG background during active and passive unloading (ANOVA, $p > 0.52$, $F(1, 4) = 0.48$).

Because weight bearing is a voluntary action presumably associated with motor cortex activation, MEP amplitude was compared for LOAD and RELAX. The ratio MEP/background did not significantly differ between RELAX and LOAD conditions ($p = 0.93$, paired *t*-test), indicating that MEP increased in proportion to the EMG-activity

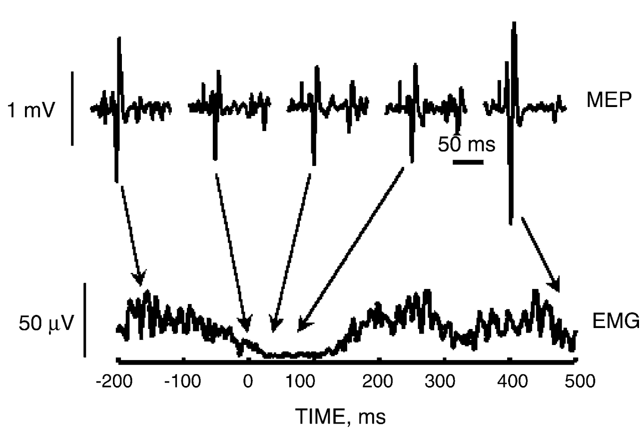

Fig. 2. Changes of MEPs in the active unloading. The upper row, MEPs at different moments (shown by arrows) of the active unloading. The lower curve, EMG of m. biceps during active unloading. Average of 10 trials.

associated with weight bearing. However, although the background EMG activity in CONTRA and LOAD tasks were equal, the amplitude of MEP in CONTRA was $30 \pm 13\%$ smaller than in LOAD conditions ($p < 0.05$, *t*-test). In comparison to ACT condition MEP in CONTRA was smaller $33 \pm 21\%$ ($p < 0.05$, *t*-test).

The main purpose of the present study has been to evaluate the role of motor cortex and the pyramidal system during APA in bimanual unloading task. Previous studies have reported that a supplementary motor area contralateral to the postural forearm, together with other premotor or motor areas, may select the circuits responsible for the postural adjustments [27]. In our previous study [12] we have shown that in animals the supplementary motor area contributes to bimanual coordination more than the primary motor cortex.

In our recent study [25] we observed that the TMS-evoked EMG responses in the soleus muscle increased considerable when balancing on the rocking platform. This observation seems to support the idea that postural instability might change the state and the role of the motor cortex in equilibrium maintenance.

Within the present study we have compared the MEP's in three different situations: unloading itself (passive unloading) and two bimanual coordinations, namely, active bimanual unloading (ACT) and holding the weight by one arm with simultaneous lifting another equivalent weight by the other arm (CONTRA). Only active unloading was preceded by the postural adjustment. However, during APA we have not found any specific changes of cortical excitability. Both in active and passive unloading, MEP amplitude decreased with the decrease of muscle activity similar to the stationary loaded arm, confirming numerous studies, those have shown that changes in MEP amplitude go in parallel to changes in background EMG [6,26]. The expected facilitation of motor responses in active unloading could be masked by the interhemispheric inhibition caused by the contralateral arm manipulation. During load lifting by the contralateral arm without unloading (CONTRA task) we have found that the decrease of the MEP occurred without changing of the background muscle activity. This indicates that corticospinal neurons of the motor cortex related to the "postural" arm are really inhibited by the motor cortex related to the "load lifting" arm. Interhemispheric inhibition was revealed by a number of experimental data [18,19,24]. One could suggest that the motor cortex activity in postural preparation might compensate this contralateral inhibition. The unchanged EMG level in the postural arm during inhibition of the appropriate motor cortex suggests also that the level of EMG during load maintenance can be determined not only by the direct corticospinal influence but also by the command mediated by basal ganglia and brain stem structures. This is compatible to the well known data about role of the motor cortex in control of distal musculature [13]. Thus, the decrease of MEP during the active unloading may be explained by decrease of the segmental excitability only. The question on subcortical generators of the APAs was not studied here. The comparison of TMS and transcranial electrical stimulation effect on APAs might give additional evidence for the APA origin. Although we have tried to exclude activation of the pectoral girdle of the right hand or neck muscles, the minor activity in these muscles might be occurred. In this case, not only contralateral but also ipsilateral motor cortex might be activated. It also could affect the modulation of MEP during APA. Thus, the result of the present study could not make clear whether the APAs are generated by the motor cortex. Particularly, stretch reflex from right hand muscles might influence the excitability of the motoneurones of the left side. However, the stimulus was triggered by touching the handle before the movement. One could suggest that only minor changes in MEP in our studies could be a result of spinal mechanisms.

It is interesting, that the arm stabilization in the active unloading is shown to appear at the age of 2–3 years [21]. According to the experimental data [17], this "natural" coordination is not specifically disturbed in patients with lesions of the motor cortex-pyramidal system, in contrast to an "artificial", learned coordination in which unloading is caused through a mechanical linkage by lifting another, equal load with the contralateral arm [20]. In such learned coordination, the postural adjustment (inhibition of flexor activity of the postural arm prior to the unloading) is specifically impaired in patients with lesions of the corticospinal system. These data suggest a predominant role of the motor cortex in learning a new pattern of postural adjustment but not in its performance in natural movements.

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