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Effort-induced mirror movements

A study of transcallosal inhibition in humans

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Abstract During sustained, fatiguing maximal voluntary contraction of muscles of one hand, muscles of the other hand gradually become activated also. Such effort-induced mirror movements indicate a decreased ability of the central nervous system (CNS) to selectively control individual muscles. We studied whether altered transcallosal inhibition (TCI) contributed to this phenomenon. TCI was determined in ten healthy subjects by measuring the ipsilateral silent period (iSP) and the contralateral silent period (cSP) during a sustained contraction of the abductor digiti minimi, induced by focal uni-hemispheric ipsilateral transcranial magnetic stimulation. Mirror movements occurred in all subjects in response to the effort. There was a bilateral increase in cSPs and a parallel increase in the iSP in the contralateral working muscle. In contrast, the iSP in the mirroring muscle remained unchanged, explained by a balance of increased crossed pyramidal inhibition (cSP) and decreased transcallosal inhibition. In finely tuned unimanual movements, mirroring activity of the contralateral hand is suppressed by TCI originating in the working hemisphere. During sustained, effortful contractions, the outflow of the contralateral hemisphere is increased due to reduced TCI. Effort-induced mirror contractions are thus the result of disinhibition of contralateral crossed projections rather than disinhibition of ipsilateral uncrossed pathways.

Keywords Transcallosal inhibition · Mirror movements · Effort · Fatigue · Human

Introduction

Mirror movements are unintended and unnecessary movements that accompany voluntary activity in homologous muscles on the opposite side of the body. They are observed in a variety of hereditary and acquired disorders, and may relate to heterogeneous pathophysiological mechanisms such as coactivation of the contralateral hemisphere (Schott and Wyke 1981; Nelles et al. 1998; Balbi et al. 2000), activation of ipsilateral (uncrossing) projections (Regli et al. 1967; Nirkko et al. 1997; Balbi et al. 2000), or bilateral branching of corticospinal neurons (Regli et al. 1967; Woods and Teuber 1978; Schott and Wyke 1981; Farmer et al. 1990; Carr et al. 1993; Nirkko et al. 1997; Nelles et al. 1998; Balbi et al. 2000). In healthy subjects, they occur during early childhood, but gradually disappear thereafter during the maturation of the central nervous system (CNS; Nass 1985; Heinen et al. 1998; Mayston et al. 1999). It is thought that in adults inhibitory connections between the hand areas of the two hemispheres exist to allow for independent hand movements (Geffen et al. 1994).

Mirror movements typically occur in healthy adults only during sustained effortful and fatiguing voluntary contractions (Cernacek 1961; Todor and Lazarus 1986; Dimitrijevic et al. 1992; Armatas et al. 1994). Such effort-induced mirror movements indicate a reduced ability of the CNS to selectively control individual muscles. The mechanisms causing this phenomenon are not clear, but effort-related facilitation or fatigue-induced disinhibition from one cortical hemisphere to the other via a callosal route has been suspected (Cernacek 1961; Nass 1985; Todor and Lazarus 1986). Well in line with this, we did not observe effort-induced mirror movements in a multiple sclerosis patient with marked callosal atrophy (K.M. Rösler, unpublished work).

Transcallosal inhibition (TCI) can be assessed by transcranial magnetic stimulation (TMS; Ferbert et al. 1992; Meyer et al. 1995; Rösler et al. 1995). When uni-hemispheric TMS is performed during an ongoing, tonic voluntary contraction, the activity is temporarily sup-

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pressed in muscles of the ipsilateral side of the body. This ipsilateral silent period (iSP) is not found in patients with lesions of the anterior part of the corpus callosum (Meyer et al. 1995), hence a transcallosal route is presumed to account for it. Using this method, absence of TCI has been demonstrated in young children with mirror movements (Heinen et al. 1998; Mayston et al. 1999). The present study was undertaken to analyze TCI during effort-induced mirror movements in healthy adults.

Materials and methods

Subjects

Ten healthy subjects (six men and four women, aged 28–63 years, mean 36 years) gave informed written consent to participate in the study, which was approved by the local ethics committee. All subjects were right-handed and none of them had a history of previous neurological disorders, implanted metal in the eye or in the brain, or a cardiac pacemaker. The subjects were informed that a magnetic stimulation study of central fatigue was performed. They were unaware of the fact that the activity of the contralateral hand (the mirror movement) was the focus of the analysis.

Magnetic stimulation

Transcranial magnetic stimulation was performed by a Magstim 200 stimulator (The Magstim Company, Spring Gardens, Whitland, UK), using a focal, figure-of-eight coil (outside diameter of each coil, 90 mm). For stimulation, the coil was positioned tangential to the skull, centered over the appropriate motor cortex, with the coil current in the intercept flowing anteroposteriorly. For each subject, the coil position for eliciting maximal contralateral responses was determined individually; it was, on average, 6 cm lateral to the vertex and 1 cm anterior to the interaural line.

Electrical and mechanical recordings

Bilateral EMG recordings were made from the abductor digiti minimi (ADM) muscle by surface electrodes attached in a belly-tendon arrangement. The EMG signal was amplified using a 1902 programmable signal conditioner (CED, Cambridge, UK) and sampled at 4 kHz by a stand-alone AD converter (MacLab, ADInstruments Pty, Castle Hill, NSW, Australia) connected to a personal computer (Macintosh, Apple Computer Cupertino, Calif., USA). The data were stored on hard disc for later offline analysis. The EMG signals from both ADM muscles were continuously displayed on a screen to monitor the on-going contraction. Fifty-hertz high-pass filtering was needed to eliminate low-frequency artifacts in the EMG traces. To record stimulation responses, epochs of 500 ms duration each were recorded, of which 100 ms preceded the stimulus.

The isometric voluntary contraction force of left little finger abduction was measured by placing the finger on a lever attached to a force transducer (Sensotec Columbus, Ohio, USA). The left forearm and hand were fastened with Velcro straps to the platform holding the force transducer. The force signal was DC-amplified using a Sedia amplifier (Sedia, Givisiez, Switzerland). During the experiments, the force signal was fed into an oscilloscope in front of the subject, to allow visual feedback of the exerted force and an estimate of fatigue.

Experimental protocol

In all experiments, the left ADM was the “working” muscle (i.e., the target muscle of the subjects' effort), and the right ADM was the “mirroring” muscle (consequently, in this paper, the right

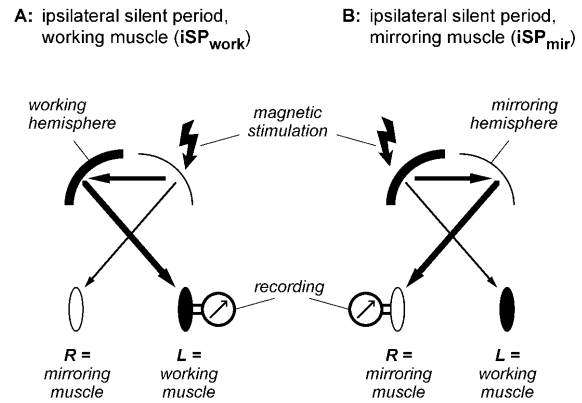


Fig. 1A, B Schematic view of the tested systems. *Thick arrows* depict the presumed path of the recorded inhibitory response

hemisphere is referred to as the working hemisphere, and the left hemisphere as the mirroring hemisphere). The left ADM was chosen as working muscle because mirror movements are usually greater with left-sided voluntary contractions than with contractions on the right (Todor and Lazarus 1986; Armatas et al. 1994; Liepert et al. 2001). The subjects sat on a chair, with the left hand fixed to the mechanical recording device. The fingers of the right, mirroring hand were taped together to allow isometric conditions as on the left side. The degree of mirror movements was clinically graded according to Nass (1985), using a scale of 1–4, as absent (0), slight (1), mild (2), moderate (3), and marked (4).

Stimulus thresholds were determined with the muscle at rest, defined as the intensity of stimulator output evoking a response in 50% of trials (Rothwell et al. 1999). For all subsequent stimulations, the stimulator output was increased to approximately 140% of the threshold. The maximal voluntary contraction force (MVC) was determined in 3 trials.

The preexercise iSP was determined separately on both sides in 10 trials during contractions of 20% MVC of the left ADM (preexercise-iSP_{work}) and of the right ADM (preexercise-iSP_{mir}). Subjects were told to maintain the level of contraction some seconds after the stimulus had been given. The subjects were then asked to perform a sustained MVC with their left (working) ADM, for as long as possible, with visual feedback of the exerted force, and verbally encouraged by the examiner. When the exerted force had decreased to 50% of MVC, mirror movements in the right (mirroring) ADM were invariably present. At this point, exercise-iSP_{mir} was recorded after stimulation of the right (working) hemisphere (Fig. 1B). Ten trials were collected by stimulating every 3 s, while the subject continued with the contraction. The postexercise-iSP_{mir} was then measured in 10 trials some 1–5 min after the exercise, to avoid the immediate postexercise facilitation observed with ipsilateral (Brasil-Neto et al. 1999) and contralateral (Samii et al. 1996) brain stimulation. This measurement was done similarly to the preexercise measurement, hence the subjects were asked to maintain a muscle contraction of 20% MVC during the stimulus and during a few seconds after the stimulus. The subjects were then given some 5–10 min to recover. After that, the procedure was repeated with left-hemisphere stimulation, to determine the exercise- and postexercise-iSP in the working muscle (iSP_{work}; Fig. 1A).

Along with the iSPs, we also recorded the contralateral postexcitatory silent period (cSP) before, during, and after exercise. The cSP is considered an indicator of inhibitory mechanisms related to fatigue during a sustained contraction (McKay et al. 1996; Taylor et al. 1996; Sacco et al. 1997).

Data analysis

The EMG signals were rectified off-line and trials were averaged for each condition. The mean amplitude of the rectified EMG pre-

ceding the stimulus during 100 ms was defined as the EMG background activity. The iSPs were quantified by the period of relative EMG suppression after the stimulus, i.e., when the EMG activity dropped below the background activity. The onset latency of the iSP, its duration, and the mean amplitude reduction relative to the baseline (depth of inhibition) were measured. The duration of cSPs was similarly measured from individual trials and averaged

later. The depth of the cSP was not separately measured because activity was always reduced to zero (i.e., depth of inhibition = 100%). The Statview version 4.5 software package (1994; Abacus Concepts, Berkeley, Calif.) was employed for statistical analysis. Nonparametric tests were employed to compare values across conditions and between sides. The value of $P < 0.05$ was considered statistically significant.

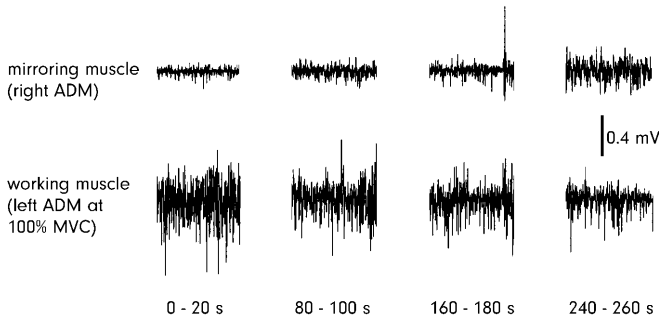


Fig. 2 Bilateral EMG recordings in the abductor digiti minimi (ADM) of one subject. Four epochs of 20 s each are shown. Amplification is the same on both sides (MVC maximal voluntary contraction force)

Results

In all subjects, the electromyographic activity in the working muscle declined gradually during the exercise, due to fatigue (Fig. 2). The exercise-iSP was determined when the force of the working muscle had decreased by 50%. At that time, the activity in the mirroring muscle had increased considerably (Fig. 2), reaching 3 or 4 on the clinical scale in all subjects, and a mean EMG activity of 49% of that on the working side (approximately 25% of MVC). Cocontractions of ipsilateral and contralateral heterologous arm muscles were also observed, but they were not as marked as the mirror movement (as observed by others: Todor and Lazarus 1986). Most sub-

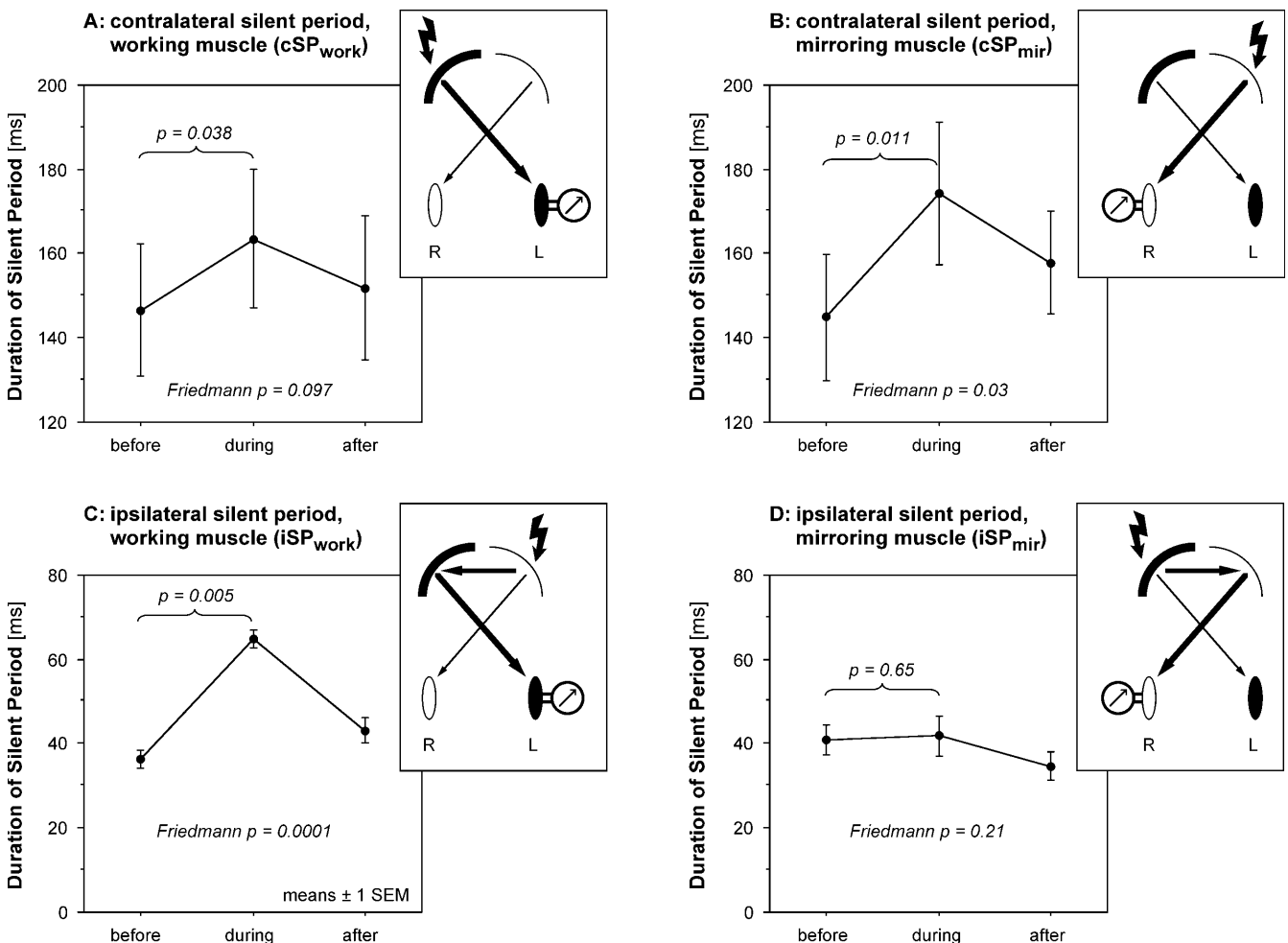


Fig. 3A–D Duration of contralateral and ipsilateral silent periods, before, during, and after exercise. Thick arrows depict the presumed path of the inhibitory response for: contralateral silent peri-

od in the working muscle (cSP_{work} in A), in the mirroring muscle (cSP_{mir} in B), ipsilateral silent period in the working muscle (iSP_{work} in C), and in the mirroring muscle (iSP_{mir} in D)

Table 1 Ipsilateral (*iSP*) and contralateral (*cSP*) silent period before, during, and after the exercise (mean \pm SD)

Stimulation site	Condition	Recording from ipsilateral muscle					Recording from contralateral muscle	
		Parameter	Onset latency (ms)	Duration (ms)	Depth (%)	Duration \times depth (%ms)	Parameter	Duration (ms)
Right hemisphere	Preexercise	iSP _{mir}	32.6 \pm 5.7	40.9 \pm 11.3	45 \pm 11	18.4 \pm 6.2	cSP _{mir}	144.9 \pm 44.9
Right hemisphere	Exercise	iSP _{mir}	36.6 \pm 5.4	41.8 \pm 15.1	42 \pm 16	17.3 \pm 8.4	cSP _{mir}	174.3 ^{*2} \pm 51.2
Right hemisphere	Postexercise	iSP _{mir}	36.0 \pm 4.7	34.6 \pm 10.3	49 \pm 13	17.1 \pm 6.6	cSP _{mir}	157.9 \pm 36.6
Left hemisphere	Preexercise	iSP _{work}	38.4 \pm 5.6	36.2 \pm 6.6	41 \pm 16	14.5 \pm 5.7	cSP _{work}	146.5 \pm 47.2
Left hemisphere	Exercise	iSP _{work}	39.3 \pm 8.5	65.0 ^{*3} \pm 6.7	60 ^{*3} \pm 12	39.7 ^{*3} \pm 10.2	cSP _{work}	163.4 ^{*4} \pm 49.1
Left hemisphere	Postexercise	iSP _{work}	35.0 \pm 5.7	43.1 ^{*2} \pm 5 \pm 9.6	56 ^{*2} \pm 15	24.7 ^{*2} \pm 4 \pm 9.1	cSP _{work}	151.8 \pm 51.6

*¹ $P < 0.05$; *² $P < 0.01$; *³ $P < 0.005$ (Wilcoxon; compared with preexercise); *⁴ $P < 0.01$; *⁵ $P < 0.005$ (Wilcoxon; compared with exercise)

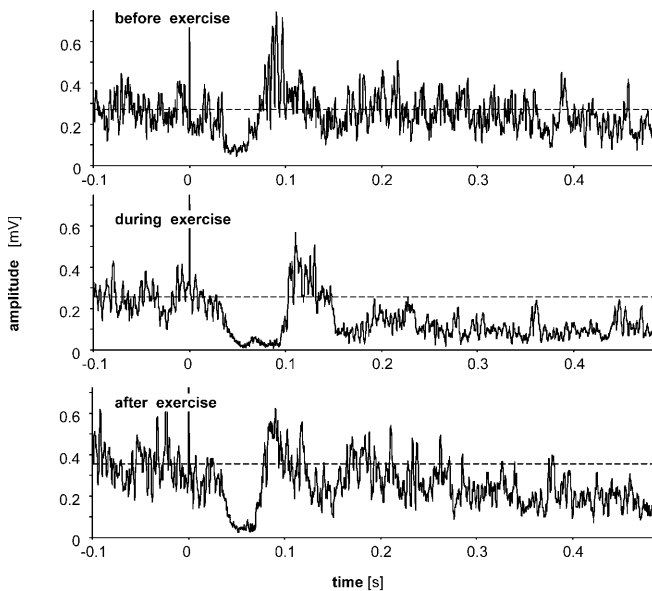


Fig. 4 Original recordings from the working abductor digiti minimi muscle in one subject. Each trace is the average of 10 trials. The mean prestimulus EMG level (background EMG) is given by the hatched lines. The ipsilateral silent periods are indicated by the hatched areas. Note the increase in duration and depth of the silent period during exercise, and the partial recovery to preexercise values after exercise

jects were not aware of the presence of mirror movements and cocontractions. Non of them knew that the unintended mirroring activity was the target of interest in the study.

Ipsilateral silent period

Before the exercise, the iSPs were similar in the mirroring and the working muscles (Table 1). During and after the exercise, the iSP_{mir} did not change, neither in time nor in depth (Fig. 3, Table 1). The iSP_{work} increased significantly in all subjects during exercise (Figs. 3, 4; Table 1); both depth of inhibition and duration increased (Table 1). This increase was observed in all subjects. After exercise, iSP_{work} recovered partially toward the

preexercise levels (Table 1, Figs. 3, 4). The background activity of the mirroring muscle during exercise-iSP measurement was considerably smaller than that in the working muscle during the exercise-iSP measurements. A relation between background EMG level and the duration or depth of the iSP (before, during, and after exercise; left and right side) was not found by linear regression analysis. Thus, the observed iSP changes were independent of background EMG levels.

An ipsilateral motor-evoked potential was never recorded (i.e., an excitatory phenomenon preceding the TCI, stemming from uncrossed monosynaptic or oligosynaptic corticospinal input).

Contralateral silent period

During exercise, the cSP increased significantly in duration on both sides (the working side and the mirroring side; Table 1, Fig. 3). After exercise, the duration decreased again (Table 1, Fig. 3). In all trials, contralateral motor-evoked potentials preceded the cSP. These responses were not further analyzed.

Discussion

Effort-induced mirror movements are a highly reproducible phenomenon and were observed in all of our subjects. When the EMG of the target muscle had decreased to 50% due to fatigue (increasing the perceived effort to sustain the contraction), the contralateral mirroring contraction was clinically always graded moderate to marked. In parallel, the mirroring muscle's EMG reached 25% of MVC (or approximately 50% of that of the working muscle) on average (Fig. 2). Our hypothesis was that this type of unintended (and usually unnoticed) activity was associated with a decrease in transcallosal inhibition from the working to the opposite hemisphere. We used fatiguing contractions of the left ADM because previous studies had indicated that left-sided voluntary contractions would produce stronger mirror movements than contractions on the right side (Todor and Lazarus 1986; Armatas et al. 1994; Liepert et al. 2001). We ap-

plied the paradigm of measuring the ipsilateral silent period (iSP) in response to TMS to quantify TCI. The presence of iSPs after unihemispheric transcranial magnetic brain stimulation has been linked previously to transcallosal connections in healthy subjects and patients (Ferbort et al. 1992; Meyer et al. 1995). Thus, we expected the iSP to decrease in the mirroring muscle (iSP_{mir}; Fig. 1B).

Our results are well in line with our hypothesis. During exercise, inhibition within the crossed pyramidal path increased bilaterally, as demonstrated by increases in cSP_{mir} and cSP_{work} (Table 1, Fig. 3A, B). Yet, despite this increase, the iSP_{mir} remained unchanged during exercise (Table 1, Fig. 3D). The final path of the iSP measurement is the crossed pyramidal pathway. Our finding of an unchanged iSP_{mir} is thus explained by a balance between *increased* crossed pyramidal inhibition and *decreased* transcallosal inhibition. By the same token, the parallel increase in the iSP_{work} and cSP_{work} (Fig. 3A, C) suggests unchanged transcallosal activity originating from the mirroring hemisphere. It is noteworthy that measurements of iSP_{work} were always performed after those of iSP_{mir}. Nevertheless, pre- and postexercise results were similar in the two sets of measurements (Fig. 3), arguing against a sequence effect caused by insufficient recovery from fatigue. Moreover, persisting fatigue would have resulted in a reduction of iSP_{work}, which was not observed. Summarized, our results conform with our hypothesis of a side-specific reduction of TCI from the working to the opposite (mirroring) hemisphere, which occurs in association with the presence of effort-induced mirror movements.

It should be noted that ipsilateral excitatory responses (ipsilateral MEPs) were not observed here. They could arise from uncrossed corticoreticulospinal or corticoproprio-spinal projections (Ziemann et al. 1999), or from uncrossed, fast-conducting corticomotoneuronal paths (Nirkko et al. 1997). In patients, the presence of such paths is associated with mirror movements (Nirkko et al. 1997), and “unmasking” of uncrossed paths was previously suggested to account for effort-induced mirror movements in healthy subjects (Zülch and Müller 1969; Nass 1985). If, during unimanual tasks, TCI were to account for the suppression of uncrossed paths, then the appearance of mirror movements during effort would imply a reduction of TCI from the nonworking to the working hemisphere. This was not observed in the present study (Fig. 3C). Hence, our data do not support a role for uncrossed pathways in effort-induced mirror movements.

Lack of transcallosal inhibition from the working to the mirroring hemisphere was previously assumed to account for the physiological mirror movements of young children. In preschool children, TMS yields no iSP (Heinen et al. 1998). In these children, bilateral activation of both motor cortices occurs during unimanual tasks, as shown by bilateral activation of transcortical, cutaneous-muscular long-loop reflexes (LLRs; Mayston et al. 1999). Both the appearance of iSP and reduction of LLRs are paralleled by the disappearance of mirror movements

during maturation (Heinen et al. 1998; Mayston et al. 1999). Thus, in preschool children, mirror movements probably arise from lack of transcallosal inhibition from the working to the mirroring hemisphere; resulting in bilateral activation of the crossed pyramidal tract. Our present data suggest a similar mechanism in adult effort-induced mirror movements. During unimanual movements, neuroimaging studies demonstrate bilateral activation of supplementary motor areas (premotor cortex and supplementary motor area; Nirkko et al. 2001). Such bilateral activation would result in mirror movements, but during effortless finely tuned hand movements, mirroring by the contralateral hemisphere is suppressed by TCI to allow for manual side independence (Geffen et al. 1994). Transcallosal inhibition was demonstrated by TMS (Ferbort et al. 1992; Meyer et al. 1995; Rösler et al. 1995) and is also suggested by neuroimaging studies, where the primary motor area of the mirroring hemisphere is deactivated (Dettmers et al. 1996; Allison et al. 2000; Nirkko et al. 2001). When the effort of the unimanual movement increases (e.g., by the wish to overcome the fatigue-induced loss of force), TCI decreases – as shown here – and side independence is lost, resulting in mirror movements. The decrease in TCI is well in line with previous studies demonstrating an enhancement of excitability of the nonworking motor cortex during unimanual, high-force (at least 50% of MVC) tonic muscle contractions by use of cortical paired-pulse stimulation (Muellbacher et al. 2000; Liepert et al. 2001). In further accordance with this, an increase in regional cerebral blood flow in the ipsilateral hemisphere was observed with increasingly forceful contractions in one positron emission tomography study (Dettmers et al. 1996).

The increased duration of the cSP_{work} during an effortful fatiguing contraction was an expected finding, since it has been demonstrated previously (McKay et al. 1996; Taylor et al. 1996, 2000; Sacco et al. 1997; Taylor and Gandevia 2001). Here, we observed an effort-related increase in the cSP also in the mirroring muscle (Table 1, Fig. 3B). Theoretically, two mechanisms could account for this increased contralateral crossed inhibition: First, inhibitory activity from the working hemisphere could be mediated via a callosal route to the mirroring hemisphere. This is unlikely given our result of a decrease in TCI from the working to the mirroring hemisphere. Second, inhibition could be a consequence of the sustained muscle contraction of the mirroring muscle, either by refractoriness or fatigue of the involved cells, or through enhanced supraspinal inhibition by a reflex mechanism. The present data allow no judgement about these possibilities. Nevertheless, while inhibitory segmental reflexes have been demonstrated during fatigue (Bigland-Ritchie et al. 1986), inhibitory transcortical LLRs have not been described during fatigue. On the contrary, excitatory LLRs increase during fatigue of small hand muscles (Duchateau and Hainaut 1993). Thus, a passive central phenomenon (refractoriness or fatigue of descending systems) in response to the sustained muscle contraction is possibly involved.

The presence of bilateral inhibition of the cortical motor outflow during an effortful and fatiguing contraction is interesting in the light of activation of the supplementary motor areas, as suggested here and in neuroimaging studies (Dettmers et al. 1995, 1996; Nirkko et al. 2001). It is unclear at which level of the motor hierarchy the inhibitory mechanism accounting for the cSP acts. A supraspinal mechanism is suggested by the observations that the latter part of the cSP is not accompanied by a depression of spinal reflexes (Fuhr et al. 1991) and because the cSP is longer than the SP after peripheral nerve stimulation (Wilson et al. 1993). It has previously been proposed that muscle fatigue is associated with both increased excitation and increased inhibition within the motor cortex (Taylor et al. 1996). Enhanced descending supraspinal drive could compensate for the loss of excitation (or the increase in inhibition) during fatiguing contractions (Duchateau and Hainaut 1993). Our present results are in line with this notion.

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