Contralateral muscle activity and fatigue in the human first dorsal interosseous muscle

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Post M, Bayrak S, Kernell D, Zijdewind I. Contralateral muscle activity and fatigue in the human first dorsal interosseous muscle. J Appl Physiol 105: 70–82, 2008. First published May 2, 2008; doi:10.1152/japplphysiol.01298.2007.—During effortful unilateral contractions, muscle activation is not limited to the target muscles but activity is also observed in contralateral muscles. The amount of this associated activity is depressed in a fatigued muscle, even after correction for fatigue-related changes in maximal force. In the present experiments, we aimed to compare fatigue-related changes in associated activity vs. parameters that are used as markers for changes in central nervous system (CNS) excitability. Subjects performed brief maximal voluntary contractions (MVCs) with the index finger in abduction direction before and after fatiguing protocols. We followed changes in MVCs, associated activity, motor-evoked potentials (MEP; transcranial magnetic stimulation), maximal compound muscle potentials (M waves), and superimposed twitches (double pulse) for 20 min after the fatiguing protocols. During the fatiguing protocols, associated activity increased in contralateral muscles, whereas afterwards the associated force was reduced in the fatigued muscle. This force reduction was significantly larger than the decline in MVC. However, associated activity (force and electromyography) remained depressed for only 5–10 min, whereas the MVCs stayed depressed for over 20 min. These decreases were accompanied by a reduction in MEP. MVC electromyography activity, and voluntary activation in the fatigued muscle. According to these latter markers, the decrease in CNS motor excitability lasted much longer than the depression in associated activity. Differential effects of fatigue on (associated) submaximal vs. maximal contractions might contribute to these differences in postfatigue behavior. However, we cannot exclude differences in processes that are specific to either voluntary or to associated contractions.

associated activity; recovery; transcranial magnetic stimulation; electrical stimulation

Motor fatigue is characterized by a gradual decline in maximal force or by an increase in effort to maintain a constant submaximal contraction. To stress that the decline in force is due to fatigue-related changes in both the periphery (muscle and peripheral nervous system) and the central nervous system (CNS; Ref. 23), we use the term motor fatigue. Although several studies have followed time-related changes due to peripheral and central fatigue, only a few studies have looked at fatigue-related changes in contralateral muscles (3, 11, 30, 37, 40, 46, 53, 54).

During strong unilateral contractions, muscle activity is not restricted to the target muscle but activity is also observed in both ipsilateral and contralateral (nontarget) muscles (e.g., Refs. 16, 17, 40, 51, 53; see for reviews Refs. 1, 15, 18, 26). This activity is habitually irrelevant for movement execution or postural control. Generally, it occurs unintentionally and is commonly not even noticed by the subject. In 1874, Westphal (49) described for the first time contralateral movements of this kind and since then different names have been used for this activity (e.g., mirror movements, motor overflow, motor irradiation, and associated activity). In this study, we use the term associated activity to indicate the unintended activity in homologous muscles.

In adult subjects, associated activity in the homologous muscle is positively related to the strength of the target contractions (4, 5, 11, 18, 21, 40, 47, 53). Even though “mirror movements” is a term that is often used for this activity, the exact timing of the target and associated contraction is not similar (19, 53). Currently, there are two main classes of theories about the neural networks involved in associated activity: the “motor overflow” and the “default bilateral activation” theory. According to the first theory, voluntary muscle activation patterns tend to spill over to contralateral homologues muscles. The spilling over might exist on different levels of the CNS (e.g., supplementary motor cortex, via the corpus callosum at cortical levels, or via interneurons at spinal levels). The second theory implies that the default activation pattern actually comprises a bilateral motor program and that during unilateral contractions the activation of the nontarget muscles is actively inhibited. Although the exact central pathways by which associated activation in the contralateral muscle occurs are still under debate (see for reviews Refs. 1, 15, 17, 26), a recent experiment (51) demonstrated that the cortex contralateral to the muscle showing the associated activity plays a crucial role.

Although the associated force increases during a fatiguing contraction of the contralateral (target) muscle, the amount of associated force in an already fatigued muscle is depressed (53). Thus after a fatiguing contraction of the right first dorsal interosseus (FDI) a maximal voluntary contraction (MVC) of the left FDI is accompanied by significantly reduced levels of associated activity in the right FDI (53). This decline is still evident after correction for fatigue-related changes in maximal force. Understanding these fatigue-induced changes in associated activity and relating these changes to fatigue-induced excitability changes on central and peripheral levels might help in the understanding of the pathways underlying associated activity. Therefore, it is the aim of this study to describe 1) the increase in associated activity during a fatiguing task.
with the contralateral FDI muscle and 2) to compare the recovery of the associated activity with the recovery of fatigue-induced changes at central and peripheral levels. Since the amount of central fatigue and the time course of recovery from fatigue is affected by the duration of the fatiguing task (10, 27, 45), we used two kinds of fatigue tests: a short-lasting 2-min maximal contraction and a longer lasting submaximal contraction. By these means, we manipulated fatigue-related changes in the CNS and possibly also the amount of fatigue-related changes in associated activity.

**METHODS**

**Subjects**

The main experiment was performed on left and right hands of 15 healthy subjects [8 males and 7 females; mean age 29 ± 9 (SD) yr]. Twelve out of the 15 subjects received transcranial magnetic stimulation (TMS) of the cortex. In addition, 6 of the 12 subjects received peripheral ulnar nerve stimulation. In nine subjects, we repeated the experiments with direct stimulation of the muscle. Six of the 15 subjects received all stimulation protocols (i.e., TMS, electrical ulnar nerve stimulation, and stimulation of the FDI). All subjects performed two fatigue protocols on different days separated by at least 1 wk. In six subjects, additional experiments were performed concerning electromyography (EMG)-force relations in the FDI muscle (see Additional Experiments). All subjects gave their written informed consent before the study. Subjects were right-handed as confirmed by the Edinburgh Handedness Inventory (34) and free of neurological disorders. The local ethical committee of the University Hospital Groningen approved the research procedures.

**Experimental Setup**

The experimental setup has been described in detail in previous studies (53, 54). During the experiments, subjects were seated behind an experimental table with their forearms held midway between supination and pronation on the table. C-shaped clamps around the wrists stabilized the hands of the subjects. Digits 3–5 and thumbs (angle between index finger and thumb ~75°) of both hands were secured in such a way that only forces exerted by the index fingers were recorded. Both index fingers were held slightly abducted within a snugly fitting ring around the proximal inter-phalangeal joint. The ring was connected to an isometric force transducer measuring the abduction force of the FDI muscles (52). Surface EMGs of the FDI muscles of each hand were recorded with one electrode placed over the muscle belly and a second electrode placed at the metacarpophalangeal joint of the index fingers. A band-shaped earth electrode was strapped around the wrist.

Subjects received visual feedback of their force on an oscilloscope, and they were verbally encouraged during all contractions. Both EMG and force signals were amplified and recorded on a PC equipped with a data-acquisition interface (Cambridge Electronic Design, Cambridge, UK; CED 1401, sampling frequency: 2000 and 500 Hz for EMG and force recordings, respectively).

**Stimulation**

Responses were evoked by 1) TMS over the motor cortex contralateral to the test hand (n = 12, 8 males); 2) electrical stimulation of the ulnar nerve (n = 6, 3 males) in both forearms; and 3) electrical stimulation of the skin overlying the FDI (n = 9, 5 males) in both hands.

TMS. TMS was given with a flat circular coil (9-cm diameter) over the motor cortex. The coil was held with the handle pointing posterolaterally at ~45° to the midline and empirically positioned to obtain the largest motor-evoked potentials (MEPs) in the FDI. The coil of the TMS was fixed to an external frame and one of the investigators held both the coil and the subjects’ head. To maintain the exact position, the site was also marked on the skin to correct small deviations from the precise position.

The threshold of magnetic stimulation for evoking MEPs in the relaxed FDI muscle was determined as the minimum stimulus intensity needed to evoke visible MEPs in at least three out of five trials. The stimulus intensity during the experiment was set to 120% of this threshold.

Nerve stimulation. To correct for fatigue-related changes in the muscle, compound muscle action potentials (M waves) were evoked in the FDI muscles of both hands using electrical nerve stimulation. A stimulator (Digitimer D57) delivered single supramaximal electrical stimuli (200-μs duration, 35–90 mA, maximal intensity 400 V) via surface electrodes to the ulnar nerve that innervates the FDI muscle. Stimulation electrodes were placed 2 cm apart on the skin above the ulnar nerve just proximal to the wrist. The stimulus intensity was increased until the maximal M wave was evoked; during experiments, the stimulus intensity was set at 150% of this value. Stimuli were applied to both forearms, 2 s after the TMS stimulus and 2 s before the subject produced a MVC with the FDI.

Muscle stimulation. To follow changes in muscle activation, we used the "twitch interpolation" technique in nine subjects (2, 33). A stimulator (Digitimer D57) delivered pairs of electrical stimuli (1-μs duration, 40–100 mA, interstimulus interval of 10 ms, ~150% of intensity needed for maximal force response in the resting hand) via surface electrodes. The cathode was placed on the skin overlying the FDI muscle belly and the anode between the proximal parts of the first and second metacarpal bones.

To obtain control values, the FDI muscles were stimulated during the brief MVCs and shortly after the MVC when the muscle had relaxed. The force evoked by the twitch superimposed on the MVC was expressed as a percentage of the latter (potentiated) rest stimuli. Shortly after the fatiguing task the FDI muscles of both hands received two stimuli during rest to examine fatigue-related changes in the muscle. Hereafter, the recovery period started and for every second set of MVCs (see Recovery in Experimental Protocol) both FDI muscles received electrical stimuli during and shortly after the test contractions (Fig. 1D).

**Experimental Protocol**

MVCs. At the start of the experiment, subjects performed three sets of brief (4 s) MVCs in abduction direction (Fig. 1). Each set consisted of an MVC with the dominant index finger followed 30 s later by an MVC with the nondondominant index finger. Each set of contractions was followed by 30 s rest. The MVC with the highest peak force was designated the "control" MVC (cMVC). No instructions were given with regard to activity of the contralateral hand. During the initial MVCs, the amount of contralateral associated activity was measured and the FDI muscle that showed the largest amount of associated force was chosen as the test muscle. In eight subjects, the left FDI and in seven subjects the right FDI was selected as the test muscle.

In relation to the initial MVCs, the timing of magnetic and electrical stimuli was as follows: TMS was given during rest, 4 s before the MVC; electrical nerve stimulation was given 2 s before the MVC; and electrical muscle stimulation was given during and shortly after the MVC (Fig. 1A).

In the first session, subjects were randomly assigned to one of the two fatiguing protocols. During the second measurement, 7 or more days later, the subject performed the alternative fatigue protocol.

Fatigue protocols. PROTOCOL I: SUSTAINED MAXIMAL CONTRACTION. During this fatigue task subjects performed a sustained MVC for 2 min with the test hand (Fig. 1B).

PROTOCOL II: FATIGUING SUBMAXIMAL CONTRACTIONS. Subjects were instructed to maintain a force level of 30% cMVC for 26 s, followed by a 4 s MVC and 4 s rest. This combination of contractions and rest was repeated until subjects were unable to maintain the 30%
cMVC force for 5 s or more or when the force did not increase during the brief MVC (Fig. 1C).

**Recovery.** Both test protocols (protocols I and II) were followed by the same recovery protocol (Fig. 1D). Five seconds after the end of the fatiguing task, subjects performed two consecutive MVCs, first with test hand (fatigued) and then with the opposite hand (nonfatigued; with 4-s contractions and 4-s interval between the MVCs of the two hands). This pair of MVCs was repeated every 30 s during the first 5 min, thereafter every 60 s. For the recovery MVCs, the same magnetic and electrical stimulation procedures were used as for the initial MVCs (see above, Fig. 1D). We followed the recovery of fatigue-related changes in the various parameters for 20 min.

**Data Analysis**

The EMG and force recordings were analyzed offline with a personal computer equipped with Spike 2 for windows (version 5.16; Cambridge Electronic Design). The force peak and the root mean square (RMS) of the EMG (500 ms around this force peak) were measured for both the MVCs and the contralateral associated activity during the control and recovery condition. We expressed force and RMS EMG data as a percentage of the values during cMVCs. In addition, we calculated a ratio between EMG and force for the MVCs [RMS EMG (%cMVC-EMG)/force (%cMVC)].

The amplitude and area of the MEPs and maximal M waves were measured. The MEP data (12 subjects) were normalized to the mean M-wave data (obtained in 6 subjects) evoked at a nearby time. The M-wave data during the recovery was expressed as a percentage of the control M-wave data. The amplitude of the twitches elicited by the electrical stimulation in rest was measured and expressed as a percentage of the prefatigue control values. During the MVCs, the voluntary activation was calculated \[1 - (\text{amplitude of superimposed twitches/amplitude of rest twitch at nearby time}) \times 100].

For the test and non-test hand, force and EMG were measured during the fatiguing tasks and averaged for seven time periods (start and end of the contraction, and every 20% of the test; see Fig. 3).

In the text, we present data as means ± SD and in figures as means ± SE. Differences between hands or tasks in the short maximal contractions were tested with a paired t-test. Comparisons between

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**Fig. 1.** Experimental procedures: schematic display of forces and the timing of stimulation. Graphs illustrate contractions of the index finger in abduction direction. A: during initial brief maximal voluntary contractions (MVCs) with weaker contralateral associated contractions. B: during the sustained maximal protocol. C: during the fatiguing submaximal protocol. D: recovery protocol. Uninterrupted and straight arrows denote timing of transcranial magnetic stimulation (TMS; 4 s before the target contraction); twisted arrows denote timing of electrical ulnar nerve stimulation (2 s before the target contractions in both hands); and dashed arrows denote electrical first dorsal interosseus (FDI) muscle stimulation (during and shortly after the MVCs). R, right index finger; L, left index finger.
fatigue protocols were tested with a 2 (task) × 7 (time periods) repeated measures ANOVA. Effects of time in the recovery period for force, RMS EMG, and M-wave and MEP amplitudes, and areas were tested with a 2 (task) × 27 (time) repeated-measures ANOVA. For the twitches and voluntary activation, a 2 (task) × 14 (time) repeated-measures ANOVA was used. Time effects were tested post hoc with a paired t-test to investigate whether the recovery values were different from prefatigue values. We chose not to correct for repeated analysis because we aimed to describe the recovery process in much detail. If we correct for the number of statistical tests, this would imply that increasing the number of time points results in an increase in the threshold for significance. To stress that for the recovery data a significant time range is more important than individual significant data points, we identified in the graphs a significant time range with a line plus an asterisk. In case of significant interaction effects between tasks, a post hoc analysis was performed for the two tasks separately. Statistical significance was set at \( P < 0.05 \).

**Additional Experiments**

In six subjects additional experiments were performed to further investigate the changes in EMG-force relationships seen in the recovery period. After the cMVC was determined, subjects performed a set of five graded submaximal abductions at 5, 15, 30, 50, and 70% cMVC (10 s) with each index finger. These submaximal contractions were followed by a maximal contraction for 2-min (fatigue protocol I) with either the right (3 subjects) or the left FDI (3 subjects). In the recovery period, the subjects produced brief MVCs with their test hand (fatigued) followed by brief MVCs with their non-test hand (4-s rest between the 2 contractions). These pairs of contractions were repeated 10 times with an interval of 30 s. This timing was similar to the first 5 min in the recovery period of the main protocol; during this time the largest change in RMS EMG was seen after both fatigue protocols (see Fig. 4, C and D). After these MVCs, a similar set of five graded submaximal abductions (5, 15, 30, 50, and 70% fatigued MVC after 5 min) was performed with each index finger as was done in the prefatigue situation. Each set of submaximal abductions was followed by a brief MVC. The set of contractions started with the test hand and was then performed by the nonest hand. This procedure was repeated twice for each hand.

For the submaximal contractions, the mean RMS EMG and the mean force values were calculated over the total contraction time. For the MVCs, peak force and RMS EMG 500 ms around this peak were calculated. Before and after the fatigue task, a ratio between EMG and force was calculated [RMS EMG (%cMVC-EMG)/force (%cMVC)]. Differences in the EMG-force ratio before and after fatigue were tested with a paired t-test \( (P < 0.05) \) and difference between the submaximal and maximal contractions were tested with a two-sample t-test \( (P < 0.05) \).

**RESULTS**

**Brief Maximal Contractions**

No significant difference in control values of the MVCs or associated activity was observed between the subjects’ first and second experimental session. The mean MVC calculated over both experiments was 41.2 ± 8.9 N for the right hand and 43.1 ± 10.2 N for the left hand. In most subjects, contralateral associated EMG activity was evident in the FDI muscle (mean right: 9.1 ± 4.9% cMVC-EMG; left: 16.1 ± 22.3% cMVC-EMG) and in most subjects this activity resulted in overt movements. However, less associated force was shown compared with the RMS EMG values \( (P < 0.05) \); mean right: 7.2 ± 5.2% cMVC; left: 12.5 ± 13.3% cMVC). No significant differences were observed between the left and right hand with regard to MVC force or contralateral associated EMG activity.

**Fatiguing Protocol**

Figure 2 shows an example of the changes in force and EMG during the two fatigue protocols in the same subject.

**Voluntary contractions.** The mean endurance time of the submaximal protocol was 356.4 ± 115.6 s. During the “submaximal” part of protocol II, subjects maintained force around 30% cMVC while RMS EMG increased over time \( (F_{6,66} = 25.257; P < 0.001) \) from 42.1 ± 16.1 to 72.7 ± 14.3% cMVC-EMG \( (F_{3, A}) \). For both fatiguing protocols, the maximal force declined over time but a significant difference was revealed in the time course of the force decline \( (F_{6,66} = 12.797; P < 0.001) \); with the maximal protocol showing a faster decline in force than the submaximal protocol \( (F_{3, A}) \).

However, at the end of both fatiguing protocols, the force declined to similar values \( (protocol I: 42.2 ± 8.0% \text{ cMVC}; protocol II: 40.5 ± 6.7% \text{ cMVC}; paired t-test; \( P > 0.6) \). A difference between protocols was also seen for the time course of the RMS EMG \( (F_{6,66} = 2.841; P < 0.02; \text{ Fig. 3C}) \): no decline in RMS EMG occurred during the maximal protocol \( (\text{final value: } 81.3 ± 32.9\% \text{ cMVC-EMG}; F_{6,66} = 0.661; P > 0.6) \) whereas RMS EMG did decline during the submaximal protocol \( (\text{final value: } 73.2 ± 22.5\% \text{ cMVC-EMG}; F_{6,66} = 10.255; P < 0.001) \). When normalized to the first MVC in the recovery period, RMS EMG was 97.8 ± 35.1% \( (protocol I) \) and 84.0 ± 15.2% \( (protocol II) \), respectively.

**Associated contractions.** In the submaximal contractions \( (protocol II) \), an increase in the mean associated force and RMS EMG data was shown \( (force: \text{ to } 10.7 ± 8.7\% \text{ cMVC}; F_{6,66} = 10.038; P < 0.001 \text{ and } \text{ EMG: to } 16.4 ± 8.1\% \text{ cMVC-EMG}; F_{6,66} = 17.378; P < 0.001 \text{ respectively}; \text{ Fig. 3, C and D}) \). The increase in associated activity resembled the increase in RMS EMG seen in the test hand. During the MVCs, associated force and RMS EMG data increased during both fatiguing protocols \( (force: \text{ to } 28.3 ± 25.7\% \text{ cMVC}; F_{6,66} = 11.907; P < 0.001 \text{ and } \text{ EMG: to } 38.1 ± 24.2\% \text{ cMVC-EMG}; F_{6,66} = 10.196; P < 0.001 \text{ respectively}; \text{ Fig. 3, C and D}) \). The amount of associated activity was not significantly different between the two fatigue protocols for both the force and RMS EMG \( (F_{1,11} = 0.124; P > 0.7 \text{ and } F_{1,11} = 1.989; P > 0.1 \text{ respectively}) \).

**Recovery Protocol**

**Voluntary force and EMG: test hand.** At the start of the recovery protocol, MVCs were reduced to 57.1 ± 7.8% cMVC after the maximal protocol and to 53.9 ± 4.5% cMVC after the submaximal protocol. A partial recovery of the MVCs was seen after both protocols \( (\text{Fig. 4A}) \). However, a difference in the time course of the force recovery was found \( (F_{26,286} = 1.999; P < 0.01) \); after the submaximal protocol, force recovered slightly more rapidly than after the maximal protocol \( (\text{Fig. 4A}) \). Yet, in both fatiguing protocols MVCs failed to recover completely within the 20 min, but rather reached a plateau at ~70% cMVC. (MVC at 20 min, protocol I: 70.8 ± 12.6% cMVC-EMG and protocol II: 76.6 ± 11.9% cMVC-EMG).

The time course of the EMG demonstrated a different pattern. The RMS EMG almost attained cMVC values immediately after the fatigue protocols \( (protocol I: 86.6 ± 13.5\% \text{ cMVC-EMG and protocol II: 83.9 ± 20.7\% \text{ cMVC-EMG}) \) but then started to decline to below prefatigue values in the first 2 min \( (F_{26,286} = 20.453; P < 0.001; \text{ RMS EMG after 2 min, protocol I: 67.9 ±} \)
7.0% cMVC-EMG and protocol II: 67.7 ± 14.3% cMVC-EMG; Fig. 4E). No difference between the two protocols was found for the RMS EMG ($F_{1,11} = 0.447; P > 0.2$).

Shortly after either fatigue tasks, the EMG-to-force ratio had increased to 1.56 ± 0.38. Hereafter, however, the ratio decreased ($F_{26,286} = 21.391; P < 0.001$) to ratios lower thanprefatigue values (end recovery 0.86 ± 0.20; Fig. 4I).

Voluntary force and EMG: nontest hand. Statistical analysis revealed a significant effect of time for the MVC forces in the nontest hand ($F_{26,286} = 5.073; P < 0.001$; Fig. 4B). Although

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**Fig. 2.** Example of force and electromyography (EMG) [root mean square (RMS) EMG amplitude] recordings during the maximal (A; protocol I) and submaximal (B; protocol II) fatiguing protocol with the right index finger in the same subject. Note the increase in contralateral associated activity in the left index finger in force and EMG in both fatigue tasks. Arrows (B) point to an increase in associated activity while the subject tried to generate an MVC with the test muscle toward the end of the submaximal fatiguing protocol. Only a small increase in the force of the test finger was seen (subject already activated his or her muscle close to maximal) yet a larger increase in associated activity can be observed.
no fatiguing contractions were performed at this side, force had declined significantly (to 90.9 ± 5.0% cMVC). Interestingly, the time course of the RMS EMG in both the test and the nontest FDI showed a similar pattern. Immediately after the fatigue task RMS EMG values were close to control values (protocol I: 94.7 ± 21.8% cMVC-EMG and protocol II: 93.1 ± 18.4% cMVC-EMG) and then declined significantly during the first 5 min of the recovery (F26,286 = 29.064; P < 0.001; RMS EMG after 5 min, protocol I: 73.6 ± 13.6% cMVC-EMG and protocol II: 65.4 ± 6.9% cMVC-EMG; Fig. 4).

In contrast to the test FDI the EMG-to-force ratio had not changed immediately after the fatigue protocols (1.0 ± 0.2). However, also on the nontest side the ratio decreased during the recovery (F26,286 = 13.939; P < 0.001) to ratios lower than prefatigue values (end recovery 0.8 ± 0.2; Fig. 4).

Associated force and EMG: test hand. Both fatiguing protocols induced a similar decline in associated activity in the test muscle [fatigued muscle: force to 1.5 ± 2.1% cMVC and RMS EMG to 8.2 ± 9.4% cMVC-EMG (pooled data), no effect of task: F1,11 = 1.704; P > 0.2 and F1,11 = 3.182; P > 0.1, respectively]. The associated activity recovered over time (force to 8.1 ± 13.1% cMVC at the end of recovery, F26,286 = 4.324; P < 0.001 and RMS EMG to 15.0 ± 25.1% cMVC-EMG at end of recovery F26,286 = 2.633; P < 0.001; Fig. 4, C and G). Because the maximal force was affected by fatigue, we normalized the associated activity to the adjacent MVCs. Even after correction, the associated contractions were found to be depressed to 2.4 ± 3.8% MVC at nearby time directly after the fatigue protocol. This depression slowly recovered in about 10 min (F26,286 = 4.106; P < 0.001; Fig. 4F). We did not normalize the EMG values (see Additional Experiments).

Associated force and EMG, nontest hand. Interestingly, also for the nontest muscle (nonfatigued) a temporary decline in associated activity was found in both force (to 2.0 ± 2.2% MVC at nearby time) and RMS EMG values (to 3.8 ± 4.0% cMVC-EMG; Fig. 4, D and H). The postfatigue decline only became apparent 30 s after the fatiguing protocol and recovered within 2 min (force: F26,286 = 4.109; P < 0.001 and RMS EMG: F26,286 = 3.553; P < 0.001). After 2 min into the recovery a few data points showed a significant increase in the associated activity (Fig. 4, D and H). No differences between the two fatigue protocols were found (force: F1,11 = 1.068; P > 0.3 and RMS EMG: F1,11 = 0.70; P > 0.7).

M Waves

During sustained contractions, membrane properties of the muscle can be affected, e.g., by changes in the balance of intracellular ion concentrations and the activity of elec-
trogenic ion pumps. To correct for the effects of these changes in the muscle on the MEPs (see below), we recorded the maximal compound muscle action potentials (M waves) in six subjects. The data are presented in Fig. 5.

**M waves: test index finger.** Immediately after the fatiguing protocols, the M-wave amplitude was significantly decreased to 85.6 ± 16.2% of control values, after which the amplitude recovered within a min (F26,130 = 3.787; P < 0.001; Fig. 5B). The area of the maximal M wave was significantly increased after the fatiguing protocols to 115.7 ± 17.5% of control values after protocol I and to 118.7 ± 22.8% after protocol II (F26,130 = 20.576; P < 0.001; Fig. 5B). We found no difference between the fatiguing protocols (amplitude: F1,5 = 1.773; P = 0.2 and area: F1,5 = 0.396; P = 0.5) or interaction effects with time (amplitude: F26,130 = 0.396; P = 0.9 and F26,130 = 0.974; P > 0.5).

**M waves: nontest index finger.** In the nontest FDI, the M-wave amplitude did not change significantly after the fatiguing protocols (98.9 ± 7.0% of prefatigue values; F26,130 = 1.332; P = 0.1; Fig. 5C). However, an interaction between task

Fig. 4. Maximal voluntary force (A and B) and RMS EMG (E and F) in the test (A and E) and the nontest (B and F) hand after protocol I (maximal: dashed line; squares) and protocol II (submaximal: uninterrupted line; circles). Associated force (C and D) and RMS EMG (G and H) seen in the test (C and G) and nontest (D and H) hand during maximal contractions with the opposite index finger. Associated force is expressed as a percentage of the MVC produced at a nearby time. The associated RMS EMG is expressed as a percentage of the cMVC (see RESULTS, Additional Experiment). RMS EMG-to-force ratios during the brief maximal contractions in the test (I) and the nontest (J) FDI muscle after protocol I (maximal: dashed line; squares) and protocol II (submaximal: uninterrupted line; circles). Values are means ± SE. Asterisks or horizontal lines with *P < 0.05 or better compared with control values (decrease); pluses or horizontal lines with #significant interaction between task and time (P < 0.05). In the case of significant interaction, post hoc analysis were performed for the two tasks separately (2 “asterisk lines” in E).
and time was found for the M-wave area \((F_{26,130} = 1.818; P < 0.02; \text{Fig. 5E})\). Post hoc contrast analysis revealed that after both fatiguing protocols the area was increased in the first 5 min (2 min after protocol I: 111.8 ± 10.2% of control values and after protocol II: 114.5 ± 7.1%). After the submaximal protocol, the M-wave area tended to be increased for 3 additional minutes (M-wave area after 8 min: 106.7 ± 6.7% of control values; \(P = 0.06\)).

**MEP**

In the FDI of the test hand, TMS evoked responses were recorded. To control for changes in the membrane properties in the muscle, we normalized changes in MEPs (obtained in 12 subjects; %control MEP) to the changes in the mean M wave (obtained in 6 subjects; %control M wave) at nearby times. We compared the normalized MEP data for the 6 subjects in whom we recorded both M wave and MEP to the normalized MEP data of the 12 subjects. In the 12 subjects, the data were normalized to the mean M wave (as obtained in 6 subjects), and in the 6 subjects the MEP data were normalized to their own M wave. The time course of the two MEP data sets was similar, and because of the enhanced statistical power with 12 subjects we decided to present the larger data set.

MEP amplitude and area were larger after the submaximal protocol than after the maximal protocol \((F_{1,11} = 9.756; P = 0.01\) and \(F_{1,11} = 10.766; P < 0.01\), respectively; \(\text{Fig. 6}\)). However, after both fatigue protocols MEPs had declined after 2 min (amplitude: protocol I: to 33.0 ± 24.2% control; \(F_{26,268} = 3.828; P < 0.001\) and protocol II: to 40.7 ± 37.6% control; \(F_{26,268} = 1.620; P < 0.04\) and area: protocol I: to 29.4 ± 23.2% control, \(F_{26,268} = 2.456; P < 0.001\) and protocol II: to 36.4 ± 30.7% control, \(F_{26,268} = 2.005; P < 0.005\)), although the decline was more pronounced and seemed more persistent after the maximal protocol. This was confirmed by post hoc analysis, revealing that MEP area was depressed almost throughout the whole recovery period after the maximal protocol and for only about 5 min after the submaximal protocol (\(\text{Fig. 6}\)).

**Muscle Stimulation**

**Rest twitches: test hand.** Immediately after both fatiguing protocols, a decline in the rest twitch was apparent (to 33.9 ± 16.4% of the control twitch). This decline was similar after both fatiguing protocols \((F_{1,8} = 2.006; P > 0.1)\). During the recovery period, the time course of the rest twitch resembled the time course of the MVCs; a recovery to 70% of control values during the first 5 min followed by a plateau \((F_{14,112} = 34.403; P < 0.001; \text{Fig. 7A})\).

**Rest twitches: nontest hand.** The rest twitch also declined in the nontest FDI (i.e., nonfatigued FDI; to 80.4 ± 10.2% of the control twitch) and no effect of the fatiguing protocol was observed \((F_{8,1} = 0.001; P > 0.9)\). In the first minute, the twitch recovered to control values followed by a small decline during the latter part of the recovery period \((F_{14,112} = 7.036; P < 0.001; \text{Fig. 7B})\).

**Voluntary activation: test hand.** After both fatigue protocols, voluntary activation slowly decreased \((F_{13,65} = 4.552; P < 0.001; \text{Fig. 7C})\) and reached lower values than before fatigue (voluntary activation at end of recovery period: 70.8 ± 20.4%).

A similar pattern was seen after both fatigue protocols \((F_{5,1} = 0.162; P > 0.7)\).

**Voluntary activation: non test hand.** In the nontest hand, the time course of the change in voluntary activation was different after the maximal vs. submaximal protocol \((F_{13,65} = 1.964; P < 0.05)\). After the maximal protocol, subjects showed a decrease in voluntary activation over time (voluntary activation at end of recovery period: 78.9 ± 14.1%; \(\text{Fig. 7D})\). However, after the submaximal protocol, no significant decline in voluntary activation was demonstrated (voluntary activation at end of recovery period: 87.9 ± 8.1%).

**Additional Experiment**

In six subjects, we performed an additional experiment to investigate changes in EMG-force relationships in the recovery period. Therefore, we calculated mean RMS EMG and mean force values for the (complete) submaximal contractions. The EMG-force values obtained during the submaximal contractions in the control and recovery condition after both the left and right index finger task showed significant linear relations between EMG and force (for all subjects: \(j^2 \geq 0.91)\). In the prefatigue situation, the mean RMS EMG-to-force ratio for all submaximal contractions equaled 1.26 ± 0.32. However, in the
recovery period similar force levels (relative to the fatigued MVC) were accompanied by higher RMS EMG values. The RMS EMG-to-force ratio (%cMVC) was therefore higher (1.58/H11006 0.47; \(P/H11021 \leq 0.001\)). Surprisingly, this ratio had also increased during contractions of the nontest index finger (1.52/H11006 0.50; \(P/H11021 \leq 0.05\)). No significant differences were observed across the different force levels. However, during the brief MVCs the RMS EMG-to-force ratio decreased to 0.93/H11006 0.11 in the test and to 0.92/H11006 0.06 in the nontest index finger. This value was significantly different from the ratio obtained during the control submaximal contractions (both \(P \leq 0.001\)). Thus in the submaximal contraction the RMS EMG values for a given force had increased, whereas in the MVCs the RMS EMG values had decreased. This result suggests that the changes that induced this EMG decline are different for the submaximal and maximal contractions. Therefore we expressed the “submaximal” associated EMG data as a percentage of the cMVC values instead of the fatigued MVC values.

**DISCUSSION**

Our results demonstrated an increase in associated activity of the first dorsal interosseus during a fatiguing task performed by the contralateral muscle and a transient post-fatigue depression (lasting 5–10 min; Fig. 4, C and G) in the fatigued muscle, which differed in time course from other more persistent signs of a postfatigue decline in CNS excitability (MEP decline, see Fig. 6; decline of maximal voluntary drive, see Fig. 7C). The decline in associated activity was restricted to the test muscle, suggesting that the decline was not due to an overall depression but rather to fatigue-related changes associated with the fatigued state of the muscle. Furthermore, our results indicate that pathways and or neuronal processes involved in associated contractions are affected differentially by fatigue than those involved in voluntary contractions. Besides, the relevance of weak vs. strong force levels, differences in possible pathways will be further considered in the text below.

Associated Contractions During Fatiguing Protocol

Most subjects showed clear associated contractions in the contralateral FDI muscle during short maximal contractions, although there was a large between-subject variability (see also Ref. 53). The mean level of associated contractions seen in the FDI muscle was comparable with earlier studies using index finger abduction (40, 53). As expected from other studies (18, 21, 40, 53), the amount of associated activity progressively increased during both fatiguing protocols. Thus an increase in contralateral activity was observed even during the sustained MVC and the brief MVCs generated in protocol II; the increase of associated activity during the MVCs was similar for the two protocols.

In the light of the theories underlying associated activity (motor irradiation or default bilateral activation), this observation suggests that during the fatigue protocols the central activation increases despite a progressive decrease in MVC force. Several MEP studies indeed showed a steady increase in cortical excitability during fatigue protocols involving either
Changes in Associated Activity and Cortical Excitability After Fatiguing Protocols

After the fatiguing protocol, contralateral associated contractions were depressed (see also Ref. 53). The postfatigue depression of associated contractions was seen in both force and EMG recordings and was still evident after correction for fatigue-related changes in the MVC. The present study focused on the recovery of associated activity in relation to that of other fatigue-related changes. We found that the fatiguing protocols induced a decline in MEPs elicited with TMS directed at the motor cortex contralateral to the test FDI. At the same time, the compound muscle potential increased (M-wave area). This result is consistent with earlier studies (13, 25, 32, 39, 50) that examined MEP changes after fatigue during rest. It is unlikely that the prolonged decline in MEPs is caused by events exclusively at the motoneuron level. Experiments testing motoneuron excitability with measurements of H reflexes and F waves showed no clear effects after fatigue (Refs. 13, 25, 29, 50; however, also see Ref. 32). Nevertheless, a depression in the muscle response evoked by stimulation of the corticospinal tract that lasted about 2 min was seen after a 2-min maximal contraction (25).

It has been suggested that part of the depression in the above described muscle response is caused by decreased corticospinal-motoneuronal synaptic efficiency (35). This decrease was most evident at rest or during submaximal contractions, whereas the depression could be overcome by an increasing voluntary drive during maximal contractions. A decrease in synaptic transmission that affected weak contractions but had a less significant effect during strong contractions can partly explain our decline in associated activity: a more pronounced decline in force during the “submaximal” associated activity than in the MVC. Yet, the decline in contralateral associated activity exceeded the time course of the depression after stimulation of the corticospinal tract (25), suggesting that other probably supraspinal changes might play a role (24, 44).

An interesting observation in this respect is that during brief maximal contractions after a fatiguing submaximal contraction with the FDI fMRI data demonstrated a decline in brain activation in the supplementary motor area (SMA; Ref. 48, see also Ref. 8). This observation is attractive because SMA is an area that is often considered to be important for bilateral movements (6, 14, 38, 41). If associated activation is the resultant of bilateral activation of the primary motor cortex, the SMA is an relay area that could be of interest (see Ref. 6). Hence, the decline in SMA activity after a fatiguing contraction could underlie the decline in associated activity.

Similar to the muscle response elicited by corticospinal stimulation (35), a MEP elicited by motor cortex stimulation after fatigue has been shown to be declined during rest (13, 25, 29, 50) but not during a maximal contraction (43, 44). This observation emphasizes the differential effects of fatigue on muscle responses evoked by supraspinal stimulation during rest or during maximal activation. Hence, similar effects of fatigue on synaptic efficacy as have been shown on spinal motoneurons might also be important for cortical motor cells. Therefore, this observation could be important for explaining the found fatigue-related differences between associated and maximal contractions.

In the test hand, the time course of the MEP depression was comparable with the time course of the reduction in voluntary RMS EMG and the superimposed twitches. That is, directly after the fatiguing protocols, these parameters were relatively well maintained but started to deteriorate during the first 3–4 min (22) and showed no or only a slow recovery, especially after the maximal contraction protocol. Both the decline in voluntary activation and voluntary RMS EMG together with the reduced MEPs suggest postfatigue excitability decreases in the CNS motor pathways. These relatively long-lasting effects of fatigue on the MEPs were described earlier, but their relation to changes in the voluntary drive has not been described explicitly. Alternatively, the changes in voluntary activation and voluntary RMS EMG could be enhanced by our recovery protocol (brief MVCs with short rest periods), but it seems unlikely that in the test hand the effects of these short lasting MVCs were more pronounced than the 2-min maximal contraction.

Differences Between the Fatiguing Protocols

Several studies found that the amount of fatigue-induced changes in the CNS dependent on the duration of the task (Refs 10, 27; see for review Ref. 45). We used either a 2-min maximal contraction or a longer-lasting series of submaximal contractions to fatigue the FDI. Contrary to our expectations, we found a slightly faster recovery of MVC force and MEPs after the submaximal protocol. Nevertheless, these differences were small and also not accompanied by similar differences in associated activity.

Contralateral Muscle

Besides a decline in associated contractions in the test muscle, this study revealed that after the fatigue tasks the associated contractions in the non-test finger were also suppressed for 0.5–1.5 min into the recovery. Furthermore, during the recovery small and inconsistent changes in the non-test muscle occurred in the voluntary activation, whereas the MVC force and RMS EMG were declined during the complete recovery period. These changes in the contralateral muscle could be due to long-lasting central effects spreading to the contralateral side (see Refs. 7, 12, 30, 37; however, also see Refs. 46, 54). Alternatively, the repeated brief MVCs during the recovery period could have induced additional fatigue as was also suggested by the reduced rest twitch.

Fatigue-Related Change in EMG-to-Force Ratio

We found that the EMG-force relationship changed in the recovery period in both the fatigued and nonfatigued muscles, as was indicated by a decrease in the RMS EMG-to-force ratio during the MVCs. In the submaximal contractions (see Additional Experiment), however, an increase in this ratio was found. During the submaximal contractions this increase in RMS EMG-to-force ratio for a given force was expected for the test muscle. Due to muscle fatigue more motor units have
to be recruited, and consequently neural drive has to be increased. The nontest muscle showed only little evidence of muscle fatigue (a small decline in MVC force and rest twitch), and hence we did not expect such a large increase in neural drive. In our main experiment, however, we found that the M-wave area showed a small but significant increase in both 

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were involved in strong voluntary movement. In the fatigued muscle, even after correcting for fatigue-related changes in the maximal force, a decline in associated activity was observed. In addition, the time course of the recovery of the associated activity differed from the recovery of several indicators of excitability of the CNS (voluntary force, EMG, MEPs, and superimposed twitch). Hence, the decline in associated activity after the fatiguing protocols can only partly be explained by changes in pathways involved in strong voluntary contractions but also needs changes that are limited to the associated contractions (e.g., increased intracortical inhibition, SMA activity) or changes that are more pronounced during submaximal than maximal contractions (e.g., decreased synaptic efficacy at low-rate activation). Furthermore, we cannot exclude postfatigue changes that are specific to either voluntary or to associated contractions.

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