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Central adaptations during repetitive contractions assessed by the readiness potential

Abstract Physiological fatigue, a loss of maximal force producing capacity, may originate both from changes at the peripheral and at the central level. The readiness potential (RP) provides a measure to study adaptations to physiological fatigue at the motor cortex. We have studied the RP in the course of repetitive contractions at a high force level. Fourteen female healthy subjects made repetitive force grip contractions at 70% of their maximal voluntary contraction (MVC) for 30 min. Contractions were self-paced and inter-squeeze interval was about 7 s. During the repetitive contractions, the area under the curve of the RP almost doubled at electrode Cz and increased fourfold at electrodes C3′ and C4′. The onset of negativity moved forward from 1.5 to 1.9 s before force onset at Cz and from 1.0 to 1.6 s and 1.7 s before force onset at C3′ and C4′, respectively. EMG amplitude and median frequency did not change signifi-
cantly and MVC after the fatiguing exercise was 93% of MVC before, indicating relatively little physiological fatigue. The increase of the RP during the repetitive contractions is clearly in excess of the almost absent signs of peripheral fatigue. Because the increase of the RP does not lead to an increased force production, we propose that it is a central adaptation counteracting the decrease of cortical efficiency during repetitive contractions.

Keywords Motor-activity related cortical potential · Bereitschaftspotential · Electroencephalography · Repetitive voluntary contraction · Movement-related cortical potential

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Introduction

Physiological fatigue is usually defined as an exercise-induced decrease of maximal voluntary force producing capacity. It may originate from changes in the nervous system (central fatigue) and/or in the muscle tissue (peripheral fatigue). Both types of fatigue occur in healthy subjects (e.g. Bigland-Ritchie et al. 1978; Gandevia et al. 1996; Kent-Braun 1999; Schillings et al. 2003). Simultaneous changes take place along the whole neuraxis during fatigue and therefore, it is difficult to ascertain causal relations. Moreover, the central changes are often regarded as an adaptation or compensation for the high demands posed at the muscular level.

Central fatigue has been demonstrated using the method of twitch interpolation which involves stimulation of the peripheral nerve. To study fatigue more upstream in the nervous system, magnetic and electrical stimulation at supraspinal sites have been used (for reviews see Taylor et al. 2000; Gandevia 2001). These techniques give artificial input into the nervous system and measure the response at the output site by recording the force or the electrical muscle response. However, the interpretation of these data is cumbersome due to the fact that the output of the motor cortex during rest and

voluntary activation are different and the fact that the responses following magnetic stimulation are often submaximal. Therefore, the changes in the output can only be interpreted as a change in excitability of the motor cortex, which is of course not the same as the actual diminished voluntary drive. However, recent evidence indicates that magnetic stimulation can measure voluntary output at force levels of 50–100% (Todd et al. 2003, 2004)

Freude and Ullsperger (1987) have introduced the readiness potential (RP) in the study of fatigue. This negative movement-related cortical EEG potential appears over the human scalp about 1 s or more before a self-paced motor act. It is mainly generated by the supplementary motor area (SMA) and the primary motor cortex (MI) (for a review see Deecke 1996). In the absence of fatigue, its amplitude is related to the amount of voluntary force (Becker and Kristeva 1980; Freude and Ullsperger 1987) and perceived effort (Slobounov et al. 2004). It provides a measure to determine changes at the motor cortical level, which (1) does not require artificial input and (2) measures directly at the level of the motor cortex instead of at the output site (such as in the case of the twitch interpolation technique). It cannot be used during sustained contractions, but is an especially interesting tool for studying central changes during more natural repetitive contractions.

As far as we know, only two studies describe the change of the RP during a fatigue-inducing protocol. Freude and Ullsperger (1987) studied the RP during repetitive contractions at three different force levels, and Johnston et al. (2001) studied the RP during repetitive contractions at 70% of the maximal voluntary contraction (MVC). During repetitive voluntary contractions at a high force level (70–80% MVC) the RP increased, which was regarded as a way to compensate for peripheral fatigue (Johnston et al. 2001; Freude and Ullsperger 1987). However, an increase was present also during repetitive contractions at a low voluntary force level (Freude and Ullsperger 1987), when peripheral fatigue did probably not develop. From these studies it is impossible to deduce if the changes in BP (or part of it) reflect a central change in any case (thus independent of a compensation for fatigue-induced peripheral changes), as an expression of central changes in the areas responsible for the demanding and long-lasting repetitive motor behavior. In such a case we could speak of a central fatigue of (pre)motor cortex in itself.

The present study was developed to further investigate the behavior of the RP during repetitive contractions at a high force level. It presents EEG, EMG and force data of exercise that induces only little physiological fatigue. In order to avoid varying recovery times during the different stages of the experiment, we chose to use self-paced 7-s intervals, whereas Freude and Ullsperger (1987) instructed subjects to squeeze at self-paced irregular intervals of 4–10 s. The high force level studied by Freude and Ullsperger was 80% MVC, but not all subjects were able to perform the total series of contractions. Pilot experiments of our group showed that healthy subjects are able to repetitively produce 70% MVC for half an hour. This duration was needed to induce possible central changes and simultaneously enable reliable averaging of the EEG potential. It was the same force level as studied by Johnston et al. (2001). However, in their study contractions were sustained for 5 s, whereas they were short in our study. The shorter contractions lead to less physiological fatigue in our protocol. We hypothesize that it should be possible to set up a protocol that induces very little peripheral fatigue and at the same time, is highly demanding for the cortex areas responsible for motor functions, resulting in a clear BP increase.

Methods

Subjects

Fourteen female healthy volunteers without a history of neurological problems (age 26.6 ± 5.8, range 19–39) participated in this study. All subjects were right-handed, based on self-report. All subjects gave written informed consent. The protocol was approved by the local ethics committee; experiments were performed in accordance with the Declaration of Helsinki.

Experimental setup

Subjects sat on a chair with both forearms comfortably resting horizontally on a table. The right arm was stabilized by means of a vacuum pillow. Isometric handgrip force of the right, semi-supinated forearm was measured with a grip force dynamometer. EEG was continuously recorded from Ag/AgCl electrodes at Cz, C3′ (1 cm anterior to C3), C4′ (1 cm anterior to C4), Pz, and Fz, according to the international 10–20 system (Jasper 1958). In analyses, only Cz, C3′ and C4′ were used. Linked mastoids were used as references. Impedances were kept < 10 kΩ. Ag/AgCl electrodes positioned laterally to the right and left eye and directly above and below the left eye recorded bipolar horizontal EOG and vertical EOG, respectively. Surface EMG was recorded bipolarly from the muscle belly of the flexors and extensors of the fingers of the right hand, using NCS2000 disposable self-adhesive electrodes with 1 cm inter-electrode distance. Impedances of EOG and EMG were kept < 30 kΩ.

EEG, EOG and EMG were acquired with a multichannel bioelectric amplifier (Neurotop 32). Signals were band-pass filtered (EEG and EOG: 0.016–70 Hz, EMG: 10–70 Hz).

Data were sampled at 250 Hz and fed into a PC running Neuroscan 4.1 Acquire software. Force data were recorded both on the Neuroscan-PC and on a PC with custom-made force acquiring software.

Protocol

The experiment started with three initial MVCs, separated by 1-min rest periods. The strongest MVC was used for analysis. Then, the subjects' task was to make a 30-min series of repetitive handgrip contractions to 70% (powergrip) of the maximum MVC. Contractions were self-paced and had to be about 7 s apart. Subjects were instructed to relax immediately when the target force was reached. Before starting the trial, subjects had a short exercise period requiring low force levels in order to practice on interval timing. Directly at the end of the 30-min series, subjects made three final MVCs quickly following each other to prevent in between recovery. The strongest was used for analysis.

Real-time visual force feedback was provided by means of two adjacent columns of 16 leds each, which were vertically arranged and placed 1.5 m in front of the subjects. During the 30-min series, resolution of force presentation was 1.6% MVC per led. The 70% MVC level was indicated halfway by a horizontal bar beside the respective leds.

Data analysis

The 30-min series of repetitive contractions were divided into five subsequent 6-min periods from which data are averaged. Accuracy of task performance during the 30-min series was checked by investigating handgrip forces and inter-squeeze intervals.

EEG, EOG and EMG epochs ranging from 3.0 s before to 1.0 s after force onset were collected, using Neuroscan 4.1 Acquisition software. Force onset was defined as the moment at which force exceeded 5% MVC. Baseline EEG and EOG was the average from 3.0 to 2.5 s before force onset. Automatic ocular artifact reduction was done (Semlitsch et al. 1986) and all epochs were visually inspected to remove major artifacts.

For every subject, mean epochs for the five subsequent periods of 6 min were low-pass filtered at 10 Hz, using Matlab 6.5 (The MathWorks). At electrodes C3', C4' and Cz the onset of the RP was determined visually after randomization of the trials. Earlier studies have recognized several potentials within the RP (e.g. Deecke et al. 1969; Shibasaki et al. 1980; Deecke 1996; Praamstra et al. 1996; Slobounov and Ray 1998). However, different authors have used different terms and the exact time intervals of these shorter potentials are not very consistent. Based on Freude and Ullsperger (1987), we chose to study four subsequent time intervals within the RP. Areas under the curve were automatically determined at the following intervals: 2.0–1.5 s, 1.5–1.0 s, 1.0–0.5 s and 0.5–0.0 s before force onset. Please notice that the term 'period' is used for the 6-min parts of the 30-min series of repetitive contractions; the term 'interval' is used for the 0.5-s parts of the RP. We studied areas under the curves instead of maximal amplitudes in order to reduce the influence of noise in the EEG data.

Median frequencies of the bipolar EMG of both flexors and extensors were determined from force onset to 1.0 s after force onset. Maximum amplitudes were determined from the rectified bipolar EMG.

Statistics

Statistical tests were performed with the Statistical Program for the Social Sciences (SPSS) 12.0. MVCs before and after exercise were compared with a paired samples t test. To investigate the changes over the five subsequent 6-min periods, linear regression was performed in Microsoft Excel 2000. One-sample t tests determined if slopes or areas deviated from zero. Pearson's correlations were determined between force and EEG slopes. Significance was set at $P \leq 0.05$.

Results

Force and EMG

The initial MVC was 363 ± 36 N. After the exercise period, MVC had declined significantly to 336 ± 46 N, which is $92.5 \pm 9.6\%$ of the initial value ($t = 2.93$, $P = 0.012$).

Subjects made repetitive handgrip contractions at mean force levels between 67.6 (4.0 SD)% and 76.1 (5.8)% of the initial MVC; group mean force level was 72.7%, mean SD 3.8%. Mean inter-squeeze intervals varied between 4.7 (0.7) s and 8.5 (1.9) s; group mean interval was 7.1 s, mean interval SD 1.0 s. Neither mean force (Fig. 1), nor variability of the mean force, mean inter-squeeze interval or its variability changed during the five subsequent 6-min periods. In the final 6-min period, produced force was 78.7 (6.8)% of the final MVC.

Maximum EMG amplitudes (Fig. 1 and Table 1) and median frequencies of both flexors and extensors (Table 1) showed no significant change over the five subsequent 6-min periods. EMG values are relatively low due to the 70 Hz low pass filtering, used to avoid aliasing by the sampling rate of 250 Hz.

EEG

Figure 1 shows grand averages of the five subsequent 6-min intervals from the electrodes covering the motor cortex (Cz, C3' and C4'). The onset of RP became significantly earlier in the course of the 30-min series at electrodes C3' and C4' and showed a trend at electrode Cz (C3': $t = 2.33$, $P = 0.037$; C4': $t = 2.36$, $P = 0.035$; Cz: $t = 1.94$, $P = 0.075$). At Cz the onset of negativity was 1.49 (0.80) s before force onset during the first and 1.86 (0.84) s before force onset during the last 6-min period. At electrodes C3' and C4' initially negativity onset was 1.00 (0.70) and 1.00 (0.82) before force onset; during the last 6-min period this was 1.62 (1.01) s and 1.70 (0.95) s before force onset, respectively.
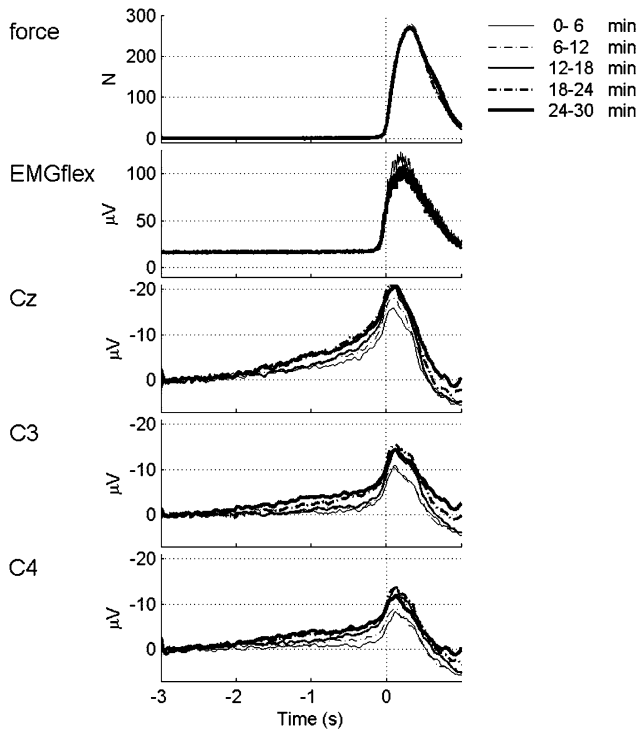
Fig. 1 Grand averages of force, rectified flexor EMG, and EEG epochs during a 30-min series of repetitive handgrip contractions at 70% MVC. Each panel shows the mean epochs from five subsequent 6-min periods. Within each panel, time 0 s indicates force onset; epochs range from 3 s before to 1 s after force onset. Force and EMG do not change significantly during the repetitive contractions. At the three EEG positions, the RP increases significantly during the 30 min

At Cz, C3′ and C4′ areas under the curve (2.0–0.0 s before force onset) increased significantly during the repetitive contractions (Cz: $t = 2.80$, $P = 0.015$; C3′: $t = 2.28$, $P = 0.040$; C4′: $t = 4.18$, $P = 0.001$). The area of Cz almost doubled from −6.7 (5.7) to −11.9 (9.2) mV ms; the areas of C3′ and C4′ increased fourfold from −1.8 (5.9) to −7.5 (8.1) mV ms and from −1.7 (6.1) to −7.3 (6.6) mV ms, respectively.

Figure 2 shows the areas under the curve for the four intervals of RP (2.0–1.5, 1.5–1.0, 1.0–0.5 and 0.5–0.0 s before force onset). Asterisks show areas that deviate significantly from zero. At Cz, the last three interval areas (Fig. 2, first row, three most right panels) showed a significant increase over the five 6-min periods ($t = 1.03$,

$P = 0.322$; $t = 2.36$, $P = 0.035$; $t = 2.84$, $P = 0.014$ and $t = 2.91$, $P = 0.012$, respectively). At C3′, the areas of the first three intervals (Fig. 2, second row, three most left panels) showed a significant increase over the five 6-min periods ($t = 2.16$, $P = 0.050$; $t = 2.48$, $P = 0.028$; $t = 2.16$, $P = 0.050$; $t = 1.95$, $P = 0.074$, respectively). At C4′, the areas of all intervals (Fig. 2, third row) increase significantly over the five 6-min periods ($t = 3.32$, $P = 0.006$; $t = 4.61$, $P < 0.001$; $t = 4.07$, $P = 0.001$; $t = 3.24$, $P = 0.006$, respectively).

The relative size of the final MVC did not correlate with the slope of the area under the total curve at any electrode position (Cz: $R = 0.097$, $P = 0.724$; C3′: $R = -0.413$, $P = 0.143$; C4′: $R = -0.175$, $P = 0.551$), nor with any slope of the areas under the curve of the separate 0.5 s-intervals.

Discussion

This study shows a clear increase of the RP in the presence of relatively small physiological fatigue during a 30-min series of repetitive handgrip contractions at 70% MVC. Although the 7.5% decline in MVC was significant, we regard it as relatively small. The change in MVC in the fatigue studies is very variable, but is typically in the range of 25–45% (Danion et al 2000; Hunter et al 2003). Moreover, according to the data of Siemionow et al. (2000), a change in the force of fresh muscle of about 7.5% increases the RP about 20%. In our results, the RP almost doubled at electrode Cz and increased fourfold at electrodes C3′ and C4′. During the first 6-min period, a significant negative deviation from baseline was only recognized at electrode Cz starting 1.5 s before force onset. In the course of the 30 min, negativity reaches significance also at electrodes C3′ and C4′ and its start becomes earlier.

Although a slight increase of the RP may be necessary to compensate for small (in the present study maximally 7.5%) peripheral changes (Freude and Ullsperger 1987; Johnston et al. 2001), the extent of RP increase suggests that MI and SMA compensate for additional, central, force-reducing factors. The fact that peripheral fatigue alone is not enough to explain the increase of the RP is confirmed by the absence of a correlation between the decrease of MVC and the increase of RP, and by the absence of significant changes in the (peripheral) EMG.

Table 1 EMG variables [means (SD)] during a 30-min series of repetitive handgrip contractions at 70% MVC

	0–6 min	6–12 min	12–8 min	18–24 min	24–0 min
Maximal amplitude flexors (μV)	159 (101)	143 (77)	143 (81)	142 (73)	140 (70)
Maximal amplitude extensors (μV)	170 (96)	166 (109)	157 (85)	155 (87)	153 (85)
Median frequency flexors (Hz)	53.4 (2.9)	53.1 (4.1)	53.4 (4.0)	53.8 (3.4)	53.8 (3.7)
Median frequency extensors (Hz)	51.4 (5.2)	51.2 (6.0)	50.1 (6.5)	51.6 (5.5)	52.2 (5.6)

Values do not change significantly

Fig. 2 Areas under four intervals of the RP curves during a 30-min series of repetitive handgrip contractions at 70% MVC. The *upper row* shows electrode Cz, the *middle row* electrode C3′, and the *lower row* electrode C4′. *Panels* at the *left* show the interval longest before force onset; *panels* at the *right* show the interval just before force onset. Within each panel, the indications 'p1' ... 'p5' at the *x*-axis indicate the five subsequent 6-min periods (0–6, 6–12, 12–18, 18–24, 24–30 min, respectively). *Error bars* show standard errors of the mean. *Asterisks* show values significantly deviating from zero. Notice the increase of the areas under the curve during the 30-min series
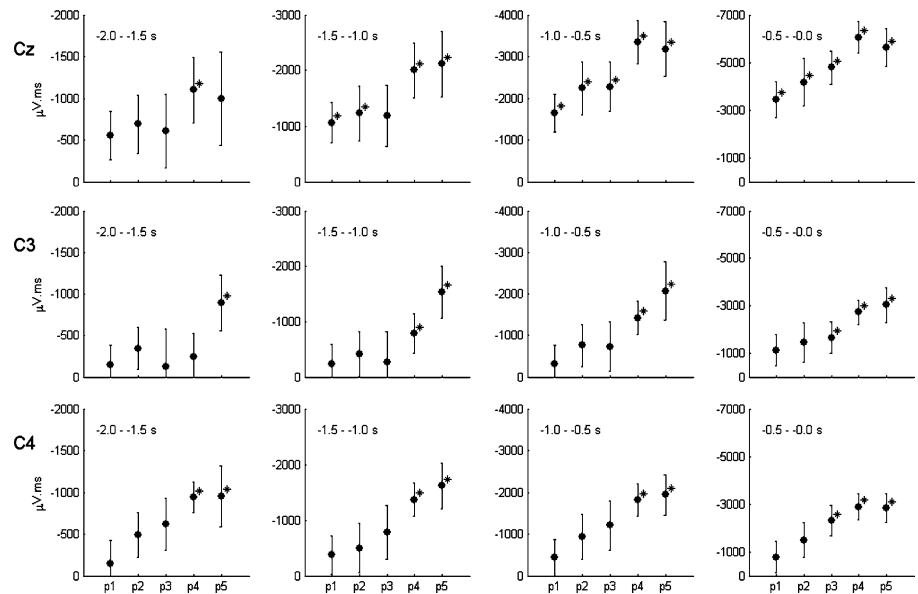
The large RP increase in comparison with only little physiological fatigue is in accordance with Freude and Ullsperger's (1987) findings during repetitive contractions at 20% MVC. They saw an increase of the RP in the supposed absence of peripheral fatigue, and suggested the influence of required concentration and attention for this low force level task as a possible explanation. However, our results contrast with Freude and Ullsperger's (1987) observation that RP was constant during repetitive contractions at 50% MVC.

In our protocol, changes in the central nervous system seem to reduce central efficiency during repetitive contractions. In order to still produce the required force level, motor cortical activity is increased. It can only be speculated as to which specific processes hinder force production. The reduction of the level of force output relative to the amount of motor cortex activity may be due to a reduced motoneuron response to cortical drive, possibly as a result of inhibiting afferent feedback. It may also be caused by a decreasing efficiency of the motor cortex itself during the repetitive contractions. Besides, activity of other cortex areas influencing motor output might be involved. In this context it is interesting to note that the RP also became evident over more electrodes in the course of the task. A recent PET study that measured regional cerebral blood flow after sustained contractions revealed a gradual increase of activity with the level and duration of muscle contraction in the contralateral MI, primary and secondary somatosensory areas, somatosensory association area, and the temporal areas AA and AI; SMA and cingula activity increased bilaterally (Korotkov et al. 2005). In addition, fMRI showed increasing activity of both the ipsilateral and contralateral primary sensorimotor areas, the SMA, prefrontal cortex, cingulate gyrus and cerebellum during both repetitive and sustained submaximal contractions (Liu et al. 2003).

We decided to measure at Cz, C3′ and C4′, because these positions are situated above the SMA and left and right MI, respectively (Praamstra et al 1996). The later onset of negativity at C3′ and C4′ (1.00 s before force onset) in comparison with Cz (1.49 s before force onset) in the first 6-min period is in accordance with the finding that activity of the SMA precedes activity of MI (for a review see Deecke 1996). The change of onset of negativity in C3′ during the 30-min series suggests that activity of the contralateral MI starts to develop earlier to prevent central fatigue. This change in activity was also found at C4'. Bilateral occurrence of the RP is widely recognized (e.g. Deecke 1996), but this finding suggests that also the ipsilateral cortex increases activity during repetitive contractions. The results of Johnston et al. (2001) showed the same pattern. Indeed, an increase of ipsilateral cortical activity with fatiguing exercise is reported in SMA (Korotkov et al. 2005) and the primary motor cortex (Liu et al. 2003). The idea is also supported by the data of Zijdewind and Kernell (2001) who measured increasing EMG activity in the contralateral homologous muscle during fatiguing contractions. However, it is difficult to explain why the negativity at C4′ had about the same size as the negativity at C3′. Brunia et al. (2004) suggest that subcortical sources cause bilateral activity. Though, we cannot exclude that volume conduction of electric fields originating from the SMA contributes to the signals measured at C3′ and C4′. The techniques to determine which sources are responsible for the changing RP unfortunately need a different experimental design and registrations from more electrode positions (Praamstra et al. 1996).

To conclude, our study shows a clearly increasing RP in the presence of only small physiological fatigue during repetitive contractions at a high force level. The RP seems to represent a special kind of central fatigue in healthy subjects during exercise relatively unrelated to

peripheral fatigue. The protocol provides an interesting tool to study the decrease of central efficiency and offers prospects for studies in patients with diminished central activation.

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