

UC Irvine

UC Irvine Previously Published Works

Title

Motor cortex excitability in chronic fatigue syndrome

Permalink

<https://escholarship.org/uc/item/3fn1q5tx>

Journal

Clinical Neurophysiology, 111(11)

ISSN

1388-2457

Authors

Starr, A
Scalise, A
Gordon, R
[et al.](#)

Publication Date

2000-11-01

DOI

10.1016/s1388-2457(00)00444-2

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Motor cortex excitability in chronic fatigue syndrome[☆]

A. Starr^{a,*}, A. Scalise^{a,b}, R. Gordon^a, H.J. Michalewski^a, M.D. Caramia^{a,b}

^aDepartment of Neurology, University of California, Irvine, CA 92697-4290, USA

^bDepartment of Neurology II, University of Rome Tor Vergata, Rome, Italy

Accepted 21 August 2000

Abstract

Objective: To use transcranial magnetic stimulation (TMS) to define motor cortical excitability in chronic fatigue syndrome (CFS) subjects during a repetitive, bilateral finger movement task.

Methods: A total of 14 CFS patients were tested and compared with 14 age-matched healthy control subjects. TMS of the motor cortex (5% above threshold) was used to elicit motor evoked potentials (MEPs). Subjects performed regular (3–4/s) repetitive bilateral opening–closing movements of the index finger onto the thumb. MEPs of the first dorsal interosseus (FDI) were measured before, immediately following exercise periods of 30, 60 and 90 s, and after 15 min of rest.

Results: Performance, defined by rate of movement, was significantly slower in CFS subjects (3.5/s) than in controls (4.0/s) independent of the hand measured. The rate, however, was not significantly affected by the exercise duration for either group. The threshold of TMS to evoke MEPs from the FDI muscle was significantly higher in CFS than in control subjects, independent of the hemisphere tested. A transient post-exercise facilitation of MEP amplitudes immediately after the exercise periods was present in controls independent of the hemisphere tested, but was absent in CFS subjects. A delayed facilitation of MEPs after 15–30 min of rest was restricted to the non-dominant hemisphere in controls; delayed facilitation was absent in CFS subjects.

Conclusions: Individuals with CFS do not show the normal fluctuations of motor cortical excitability that accompany and follow non-fatiguing repetitive bimanual finger movements. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Transcranial magnetic stimulation; Non-fatiguing finger movements; Exercise; Hemisphere asymmetry; Post-exercise facilitation; Delayed facilitation

1. Introduction

Subjects with chronic fatigue syndrome (CFS) have complaints of persistent motor fatigue (Holmes et al., 1988), impaired memory (Marshall et al., 1997), disordered sleep (Fischler et al., 1997), depression (Johnson et al., 1996) and susceptibility to repeated infections (Buchwald et al., 1997). No laboratory or clinical tests specific for CFS are available, and thus, diagnosis is based on the presence of a constellation of clinical symptoms (Fukuda et al., 1994). A variety of abnormalities of brain function have been found in patients with CFS, including diminished cerebral blood flow (Ichise et al., 1992; Goldberg et al., 1997), abnormalities of white matter on MRIs (Natelson et al., 1993; Lange et al., 1999), and reduced amplitudes of premovement brain potentials (Gordon et al., 1999). However, none of these changes

are specific to CFS, as they can occur in a variety of other conditions.

Transcranial magnetic stimulation (TMS) has been recently used to try to define changes in motor cortical excitability that may be specific to CFS. Sacco et al. (1999) showed that CFS subjects have decreased amplitude of motor evoked potentials (MEPs) compared with normal subjects from TMS of the motor cortex during exercise, and that the diminished muscle force could be significantly restored in CFS subjects by a TMS induced muscle twitch. Samii et al. (1996) showed that CFS subjects fatigue faster than normal subjects during sustained contraction of the wrist, that they had less of an increase in motor cortical excitability during the exercise compared with normal subjects, and a larger depression of motor cortical excitability when fatigued (post-exercise depression). These studies document that motor fatigue in CFS was not due to changes of muscle, nerve or spinal cord functions, but rather, reflected an altered excitability of the motor cortex. However, some of these changes in the motor cortex were not specific to CFS, as similar alterations were found, for

[☆] Supported by National Institute of Allergy and Infectious Diseases, #RO1 AI-34250.

* Corresponding author. Tel.: +1-949-824-6088; fax: +1-949-824-2132.
E-mail address: astarr@uci.edu (A. Starr).

example, in depressed patients when motor performance was fatigued (Samii et al., 1996).

In the present study, we investigated the effects of repetitive bilateral finger motor task on motor cortical excitability of patients with CFS before fatigue occurred. The exercise, which was relatively forceless and of brief duration (90 s), was not accompanied by performance decrement. In controls, the exercise was accompanied by a transient facilitation of motor cortical excitability, and a later, delayed facilitation after 15 min of rest. CFS subjects, in contrast, showed a significant elevation of TMS thresholds at baseline before exercise and an absence of both post-exercise facilitation and delayed facilitation after rest. These results suggest that motor cortical excitability is abnormal in CFS, even in the absence of fatigue.

2. Subjects and methods

A group of 14 right-handed patients (age range, 28–59 years; 13 females and one male) diagnosed with CFS was tested. A group of 14 age-matched, right-handed normal controls (age range, 25–62 years; 7 females and 7 males) without a history of neurological problems or psychiatric illness was tested. All patients fulfilled the criteria for the diagnosis according to the CDC guidelines (Fukuda et al., 1994). Five patients were currently employed (4 part-time, one full-time) and two exercised regularly (one does daily water aerobics, and the other ‘works-out’ daily). The two subjects that ‘exercised’ did so at substantially reduced levels (less than 50%) compared with their pre-illness activity. The clinical and test scores for CFS and control subjects are summarized in Table 1. The 14 normal subjects were selected from a group of 21 healthy controls to match the age of the patients. In a previous study (Caramia et al., 2000), we reported no gender or age effects of MEPs in normal subjects using the same protocol described here.

Patients had experienced symptoms of fatigue for an average of 8.1 years (SD, 4.8). They had a mean score of 15.6 ± 5.5 on the Beck depression inventory (Beck et al., 1961), just below the score of 16 used to classify depression. Their mean score on the Krupp fatigue scale (Krupp et al., 1994) was 6.2 ± 1.9 (>4.0 indicates ‘fatigue’) and 5.0 on a subjective fatigue scale of 1–10, with 1 indicating ‘no fatigue’ and 10 indicating ‘most fatigue’.

Patients were given standard neuropsychological tests to quantify the speed of motor performance (trails A), and

both motor speed and cognitive speed (trails B). The times taken to complete trail A and B tests were significantly slower in CFS ($P < 0.05$; Table 1) compared with controls. Patient medications at the time of testing included antidepressants (4), thyroid and/or ovarian hormones (3), gamma-globulin (one) and anti-inflammatory medications (3). Two patients were drug-free and two did not complete the clinical questionnaire. One patient reported that, at the time of testing, he had been free from fatigue for over a month. He had experienced symptoms for 2 years, and we considered the month of improvement to be a remission. One patient and one control were identical twins. Signed informed consent forms were obtained from subjects following University guidelines for approved projects involving human subjects.

2.1. TMS

The right non-dominant hemisphere was tested in all 14 CFS and 14 control subjects. The excitability of the motor cortex in the left hemisphere was assessed in a subgroup of 6 CFS and 8 control subjects by repeating the experimental protocol. The interval between the two tests ranged from 1 h to 4 weeks. We tested the right hemisphere first and rescheduled subjects to return for testing the left hemisphere at their convenience. Eight CFS and 6 control subjects did not comply with the request to continue the investigation.

The methods we used to evaluate cortical excitability during repetitive finger movements have been described previously (Caramia et al., 2000). TMS was performed using a round coil (90 mm) placed over the motor area of each hemisphere. The coil location was determined as the site that elicited the optimal MEP during muscle relaxation with the lowest threshold. This site, referred to as the ‘hot spot’ (Rossini et al., 1994), was marked on the scalp to ensure accurate coil positioning. The cortical motor threshold of the target muscle was defined by delivering stimuli in steps of progressively increasing intensity by 2% of the stimulator output until responses of about 100 μV were elicited in 50% of the trials (Rossini et al., 1994). For each condition (baseline, after exercise, after rest), TMS was tested at 5% above the threshold during a brief tonic contraction of the first dorsal interosseus (FDI) muscles. Subjects were instructed to perform the contraction of the index finger onto the thumb with ‘20% of their maximum force’. This level was chosen because TMS measures of

Table 1
Characteristics of CFS and control group^a

	Gender (F/M)	Age (years)	Subjective fatigue	Duration (years)	Beck	Krupp	Trails A (s)	Trails B (s)
CFS	13/1	44 (9)	5 (2)	8 (4)	16 (8)	6 (1)	34 (16)	76 (34)
Controls	7/7	41 (8)	NT	NT	NT	NT	23 (6) ^b	47 (9) ^b

^a Values are means with standard deviation in parentheses; NT, not tested.

^b $P < 0.05$. Controls faster than CFS.

post-exercise facilitation are relatively constant when tested at between 10 and 50% of the maximum force (Samii et al., 1996). Acoustic feedback from ongoing EMG activity of the target muscle, with a gain set at 100 μV /division, monitored the level of voluntary contraction for all subjects. TMS was delivered at an interval of 3 s for a total of 4 stimuli/condition. There were 3 main conditions: (1), baseline; (2), immediately after exercise of 30, 60 and 90 s; and (3), after rest (15 min after the last 90 s exercise period). The exercise involved bilateral repetitive opening–closing movements of the index finger towards the thumb with both digits extended in response to the instruction ‘make repetitive movements at about 3–4/s’. Subjects demonstrated their understanding of the instructions by practicing the movement for a few seconds. The coil was removed during the rest period and repositioned using the scalp markings for MEP testing. The threshold was again determined and was within $\pm 5\%$ of the original value.

At the conclusion of the 90 s exercise period, we asked whether subjects felt fatigue.

2.2. Rate of movement

Two procedures were used to evaluate the movement rate. First, the rate of contraction during each exercise period (30, 60 and 90 s) was determined in 10 subjects (5 controls, 5 CFS) during the TMS experiments by monitoring the acoustic output of the EMG from the tested FDI during exercise and tallying the total number of contractions. Second, in another 7 subjects (4 controls, 3 CFS), we recorded the EMG from both FDI muscles following the experimental protocol, but without TMS stimulation. The movement rate was defined (movements/s) for each hand by analyzing the last 10 s of movement in each epoch of exercise (30, 60 and 90 s). Also, a 10 s pre-exercise baseline epoch and a 10 s epoch after 15 min of rest was analyzed.

2.3. Data analysis

From the 4 transcranial stimuli delivered in each period of exercise (30, 60 and 90 s), the amplitudes of the largest two MEPs were averaged and this measure was used in the statistical analyses (Caramia et al., 2000). MEP amplitude was defined as the peak-to-peak excursion of the largest negative to positive deflection occurring after stimulus onset. MEP amplitudes were measured at baseline, immediately after each of the three exercise periods (30, 60 and 90 s), and after 15 min of rest.

Threshold differences between groups (CFS vs. controls) were tested using *t* tests. A repeated measures analysis of variance (ANOVA) was used to evaluate the MEP amplitude for the factors of time of testing (baseline, immediately after each of the exercises, and after rest), and group (CFS vs. control). A separate ANOVA was used to examine the additional factor of hemisphere (right vs. left) on a subset of subjects (6 CFS patients and 6 controls). Post-hoc tests

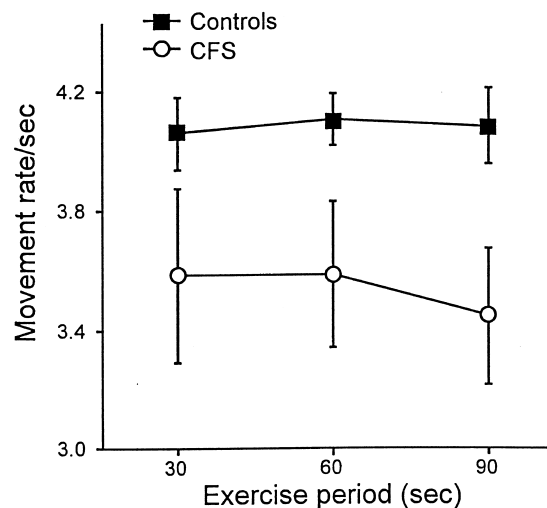


Fig. 1. Mean rates (bars indicate standard error) of repetitive finger movements during the three exercise periods in control and CFS subjects. CFS subjects perform significantly slower ($P < 0.05$) than controls, and neither group shows significant change as a function of exercise duration.

among the means were performed using *t* tests adjusted for the number of comparisons (Fisher's PLSD); differences at $P < 0.05$, or better, were considered significant. Wilcoxon signed rank tests were used to compare direction of change in MEP amplitude from baseline to after rest.

3. Results

3.1. Rate of movement

CFS subjects had a significantly slower movement rate than controls (3.5 vs. 4.0/s; $P < 0.05$) without a significant change of rate between the 3 exercise periods (Fig. 1), or any difference between the hands. The movement rate varied more in patients (2.2–4.5/s) than in controls (3.6–4.5/s). Approximately one-third of the CFS subjects (5 of 14) had movement rates that were slower than 3.5/s, the lowest rate found in the controls. All of the CFS subjects and half of the control subjects expressed feelings of ‘fati-

Table 2
MEPs and threshold from right hemisphere motor TMS^a

Time-course	Controls ($n = 14$)	CFS ($n = 14$)
Threshold (%)	52.9 \pm 8.2	62.0 \pm 10.3 ^b
Baseline (mV)	7.8 \pm 2.8	7.6 \pm 2.9
After 30 s of exercise (mV)	9.5 \pm 3.7 ^c	6.9 \pm 3.3
After 60 s of exercise (mV)	9.7 \pm 4.3 ^c	7.5 \pm 3.5
After 90 s of exercise (mV)	8.3 \pm 3.4	6.8 \pm 3.2
After rest (mV)	10.8 \pm 3.9 ^c	6.7 \pm 3.5 ^b

^a Mean values and SD.

^b $P < 0.05$ controls compared with CFS.

^c $P < 0.05$ condition (exercise or after rest) compared with baseline.

gue' at the end of the 90 s exercise period, although the movement rate did not slow significantly compared with the initial 30 s exercise period.

3.1.1. TMS

3.1.1.1. Non-dominant (right) hemisphere. The mean threshold intensity in CFS subjects was significantly higher than in controls (Table 2; $P < 0.05$). There was a significant interaction for MEP amplitudes between the factors of time of testing and group (time of testing \times group, $P < 0.001$). Fig. 2 shows representative MEP records from a control and a CFS subject. Post-hoc tests indicated a significant difference in MEP amplitudes only after rest ($P < 0.01$), with controls having larger MEPs than CFS subjects (10.8 vs. 6.7 mV, respectively; Table 2). The difference in MEP amplitudes immediately after 30 s of exercise approached significant levels (controls, 9.5 mV; CFS, 6.9 mV; $P = 0.06$).

Analyses within each group showed that MEP amplitudes were significantly affected as a function of time of testing for controls, but not for CFS subjects (Fig. 3). MEPs in controls increased in amplitude relative to baseline immediately following both the 30 and 60 s time periods ($P < 0.05$), but not following the 90 s exercise period. For controls, the MEP amplitudes after rest also showed a significant delayed facilitation ($P < 0.01$). In CFS, in contrast, MEP amplitudes did not change significantly compared with baseline values following any of the exercise periods, or after rest. Fig. 4 is a plot of the amplitude difference of MEPs in the post-rest period minus the baseline period for each CFS and control subject. There was a

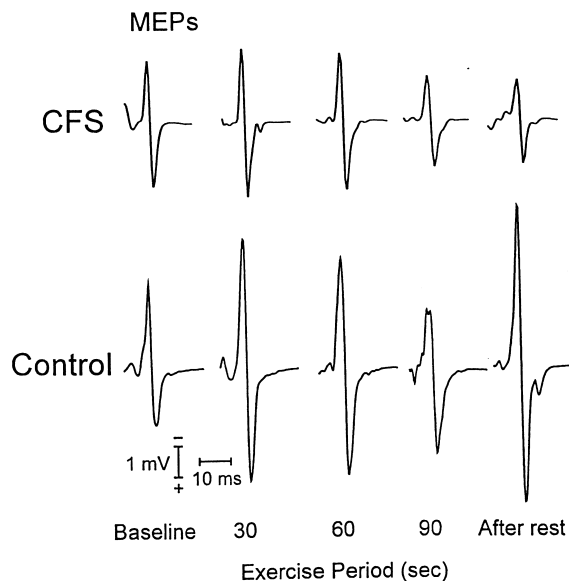


Fig. 2. Single trial recordings of MEPs from both a CFS and a control subject at baseline, during exercise and after rest. Note the MEP amplitude change for the 30, 60 and 90 s periods, and the post-exercise facilitation in the control; none of these changes were evident for the CFS subject.

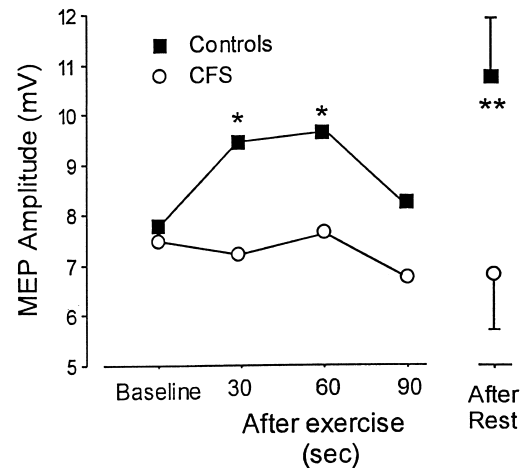


Fig. 3. MEP amplitudes elicited from the FDI muscle from CFS and controls tested at different times during and following exercise. MEPs were evoked by stimulating the right motor cortex. Note the significant increments of MEPs during the 30 and 60 s exercise periods (post-exercise facilitation) and rest period (delayed facilitation) in controls, but not in CFS subjects. Standard error bars are shown for after the rest condition.

clear separation of values for most CFS subjects from the controls. All controls showed an increased MEP amplitude ($P < 0.001$) after rest, whereas all but two CFS showed decreased MEPs after rest ($P < 0.05$).

3.1.1.2. Dominant and non-dominant hemispheres. We evaluated motor cortical excitability from both hemispheres in a subset of the study population: CFS ($n = 6$) and controls ($n = 8$). The threshold of TMS was

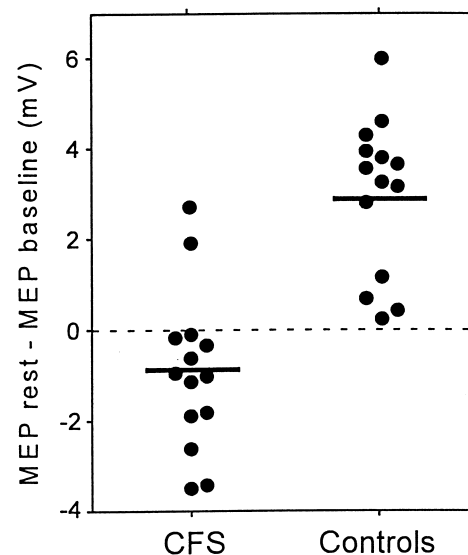


Fig. 4. MEP amplitudes from the FDI muscle of 28 individual subjects (14 CFS, 14 controls) in the rest period after exercise was defined as the difference between MEP amplitudes at baseline and MEP amplitude after 15 min of rest. There was a facilitation of MEP amplitude in all but two controls, whereas only two CFS subjects showed such a facilitation.

Table 3
Motor evoked potentials from TMS of dominant and non-dominant hemispheres^a

	Controls (<i>n</i> = 8)		CFS (<i>n</i> = 6)	
	DH	NDH	DH	NDH
Threshold (%)	48.2 ± 7.8 ^b	55.3 ± 8.5 ^c	63.1 ± 10.4	66.5 ± 11.2
Baseline (mV)	11.1 ± 2.9	8.2 ± 2.9	6.6 ± 2.6	7.4 ± 1.7
After 30 s of exercise (mV)	11.9 ± 3.7	10.8 ± 3.9 ^d	6.5 ± 2.7	7.8 ± 2.9
After 60 s of exercise (mV)	11.8 ± 3.0	11.0 ± 4.5 ^d	6.0 ± 3.1	7.6 ± 1.6
After 90 s of exercise (mV)	11.6 ± 2.8	9.5 ± 3.7	5.9 ± 3.6	7.0 ± 3.7
After rest (mV)	10.3 ± 2.6	12.6 ± 4.4 ^d	6.7 ± 1.6	6.5 ± 1.4 ^b

^a Mean values and SDs. DH, dominant hemispheres; NDH, non-dominant hemispheres.

^b $P < 0.01$ DH for controls to CFS.

^c $P < 0.05$ NDH for controls compared to CFS.

^d $P < 0.01$ for controls, condition (exercise or after rest) compared to baseline.

lower for controls compared with CFS in both the left ($P < 0.001$) and right ($P < 0.05$) hemispheres (Table 3). MEP amplitudes (controls vs. CFS) were significantly different for the left hemisphere ($P < 0.01$), independent of the test time, with amplitudes in CFS being less than those in controls (11.1 mV for controls vs. 6.2 mV for CFS). For the right hemisphere, there was a significant interaction ($P < 0.001$) between group and time of testing, with MEP amplitudes being significantly smaller between CFS and controls only after the rest period (CFS, 6.5 mV; controls, 12.6 mV).

4. Discussion

The major finding in the present study was the absence of normal changes in motor cortex excitability in CFS compared with controls during and after exercise. The MEPs in controls increased in amplitude immediately after exercise (post-exercise facilitation) and again after rest (delayed facilitation). In normal subjects, the mechanisms for facilitation are intracortical within the motor structures. For post-exercise facilitation, the mechanism is thought to be due to increased excitability in the motor cortex (Sacco et al., 1999). For delayed facilitation, the mechanism is likely to be different, reflecting intracortical synaptic reorganization underlying short-term potentiation (Butefisch et al., 2000). Moreover, delayed facilitation in normal subjects was limited to the non-dominant hemisphere, indicating differences of motor cortical organization in the two hemispheres. In contrast, there were no significant amplitude changes encountered in CFS subjects either during exercise or after rest in either hemisphere. These findings differ from other studies that report larger MEP amplitude changes in CFS subjects both during and after exercise (Sacco et al., 1999; Samii et al., 1996). However, the exercises used in these latter studies (Sacco et al., 1999; Samii et al., 1996) involved effortful, sustained exercise of the wrist or elbow muscles to the point of

‘exhaustion’. The exercise used in the present study consisted of repetitive and ‘forceless’ distal movements of the index finger. The duration of the movements in the present study was relatively brief (30, 60 and 90 s) and there were no significant decrements of movement rates in either CFS or controls. While all CFS subjects and 50% of the controls reported a sense of ‘fatigue’ at the end of the last (90 s) exercise, all but two CFS subjects indicated that they could have continued the movements if requested. The finding that subjective ‘fatigue’ can be experienced prior to objective changes in movement rate is compatible with early involvement of the central motor system in the experience of fatigue.

There were significant differences in movement rates between CFS and controls on this simple task. Controls moved on average at 4.0/s, whereas CFS subjects moved at 3.5/s with some CFS subjects making repetitive movements as slowly as 2.5/s. The movement rate was determined by the subjects themselves in response to the request to ‘make repetitive finger movements at a regular rate of 3 to 4/s’. Motor performance has been shown to be impaired in CFS in other tasks, including those requiring sustained effort (Sacco et al., 1999; Samii et al., 1996) and reaction times indicating signal detection (Gordon et al., 1999; Prasher et al., 1990; Scheffers et al., 1992). These performance changes are accompanied by a reduction in premovement readiness potentials and have been interpreted as representing impaired central drive to the motor cortex in CFS (Gordon et al., 1999).

CFS subjects have normal pyramidal motor tract speed and sensory nerve conduction times (Brouwer and Packer, 1994). Moreover, when CFS subjects are ‘fatigued’, the motor force can be significantly restored by a TMS of the motor cortex (Sacco et al., 1999). The finding in the present study of a slight, but significant elevation of the TMS threshold in CFS compared with controls at baseline could also be accounted for by an altered motor cortical excitability. Other authors (Sacco et al., 1999; Thomas 1987) have not reported a significant difference in threshold between CFS and normal subjects.

The movement rate was significantly slowed by about 15% in patients compared with controls. This reduced movement rate may be the result of altered cortical excitability. Alternatively, the reduced movement rate in CFS patients may have been a factor contributing to the changes of cortical excitability in CFS. We do not favor the latter explanation as motor cortical excitability was also depressed in the 5 CFS patients with the fastest movement rates (mean, 3.8/s; SD, 0.35).

There are several limitations in the experimental design used. First, the factor of gender was not balanced between the control and CFS groups. All but one of the CFS subjects were female, whereas the male/female ratio was balanced (7/7) in the control group. However, in control subjects, motor cortical excitability changes were independent of gender, reducing the possibility that the differences we found between CFS and control subjects were gender based. Second, the force of contraction was not measured, and thus, might have been unequal between the two groups. However, the EMG amplitude during TMS could not be distinguished between patients and controls, suggesting that the level of target muscle activation was comparable between the two groups. Third, CFS patients were taking a variety of medications and were unwilling to discontinue them for the experiments. It is possible that the medications had a common effect in depressing motor cortical excitability, but we did not find evidence from the TMS literature to support this assumption. Antidepressants used by some of the patients can cause an enhancement of neural excitability in animals, a finding opposite to what occurred in the CFS subjects (Sugiyama, 1995; Yeung et al., 1999).

Due to the small sample size (14 subjects with CFS), we were unable to address which of the many factors (e.g. gender, specific medication, etc.) comprising the clinical picture of CFS were significantly related to the altered pattern of motor cortical excitability. Our study also did not address the question of specificity of altered motor cortical excitability to CFS, since we did not include other patients with 'fatigue', such as those with diagnoses of depression, multiple sclerosis or generalized systemic illness. We tested two subjects with 'fatigue' who did not fulfill the criteria of CFS because of significant preexisting psychiatric histories (one with obsessive compulsive disorder, the other with depression). Both had normal motor cortical excitability changes before, during, and after the exercise. Additional patients with fatigue, but not with CFS, need to be studied to define the specificity of these changes in motor cortex excitability.

In summary, the present study demonstrates abnormal cortical motor excitability in CFS during and following repetitive finger movement. These results are compatible with a reduction or alteration in the normal pattern of short-term potentiation in the motor cortex as an effect of repetitive exercises. Moreover, these excitability changes in the motor cortex in CFS can occur before motor performance becomes significantly compromised.

Acknowledgements

This research was partially supported by grants from the National Institute of Allergy and Infectious Diseases (NIAID, #34250) and from the Italian 'Consiglio Nazionale delle Ricerche' (CNR). The authors would like to thank Professor Giorgio Bernardi for his support and encouragement.

References

- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:53–63.
- Brouwer B, Packer T. Corticospinal excitability in patients diagnosed with chronic fatigue syndrome. *Muscle Nerve* 1994;17:1210–1212.
- Buchwald D, Wener MH, Pearlman T, et al. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J Rheumatol* 1997;4:372–376.
- Butefisch CM, Davis BC, Wise SP, et al. Mechanisms of use-dependent plasticity in the human motor cortex. *Proc Natl Acad Sci USA* 2000;97:3661–3665.
- Caramia MD, Scalise A, Gordon R, Michalewski HJ, Starr A. Delayed facilitation of motor cortical excitability following repetitive finger movements. *Clin Neurophysiol* 2000;111:1654–1660.
- Fischler B, Le Bon O, Hoffmann G, et al. Sleep abnormalities in the chronic fatigue syndrome: a comorbidity study. *Neuropsychobiology* 1997;35:115–122.
- Fukuda K, Strauss SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953–959.
- Goldberg MJ, Mena I, Darcourt J. NeuroSpect findings in children with chronic fatigue syndrome. *J Chronic Fatigue Syndrome* 1997;3:61–68.
- Gordon R, Michalewski HJ, Nguyen T, Gupta S, Starr A. Cortical motor potential alterations in chronic fatigue syndrome. *Int J Mol Med* 1999;4:493–499.
- Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 1988;108:387–389.
- Ichise M, Salit IE, Abbey SE, et al. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun* 1992;13:767–772.
- Johnson SK, DeLuca J, Natelson BH. Depression in fatiguing illness: comparing patients with chronic fatigue syndrome, multiple sclerosis and depression. *J Affect Disord* 1996;39:21–30.
- Krupp LB, Sliwinski M, Masur DM, Friedberg F, Coyle PK. Cognitive function and depression in patients with chronic fatigue syndrome and multiple sclerosis. *Arch Neurol* 1994;51:705–710.
- Lange G, DeLuca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. *J Neurosci* 1999;17:1:3–7.
- Marshall PS, Forstot M, Callies A, Peterson PK, Schenck C. Cognitive slowing and working memory difficulties in chronic fatigue syndrome. *Psychol Med* 1997;29:58–66.
- Natelson BH, Cohen JM, Brassloff I, Lee H. A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. *J Neurosci* 1993;12:213–217.
- Prasher D, Smith A, Findley L. Sensory and cognitive event related potentials in myalgic encephalomyelitis. *J Neurol Neurosurg Psychiatry* 1990;53:247–253.
- Rossini PM, Barker AT, Berardelli A, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroenceph clin Neurophysiol* 1994;91:79–92.
- Sacco P, Hope PAJ, Thickbroom GW, Byrnes ML, Mastaglia FL. Cortico-

- motor excitability and perception of effort during sustained exercise in the chronic fatigue syndrome. *Clin Neurophysiol* 1999;110:1883–1891.
- Samii A, Wassermann EM, Ikoma K, et al. Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. *Neurology* 1996;47:1410–1414.
- Scheffers MK, Johnson R, Grafman J, Dale JK, Strauss SE. Attention and short-term memory in chronic fatigue syndrome patients: an event-related potential analysis. *Neurology* 1992;42:1667–1676.
- Sugiyama T. Effect of monoamines and antidepressant drugs on calcium-dependent current generating the after hyperpolarization of hippocampal pyramidal cells abstract. *Nihon Shinkei Seishin Yakurigaku Zasshi* 1995;15:135–145.
- Thomas PK. Postviral fatigue syndrome. *Lancet* 1987;2:218–224.
- Yeung SY, Millar JA, et al. Inhibition of neuronal KV potassium currents by the antidepressant drug, fluoxetine. *Br J Pharmacol* 1999;128:1609–1615.