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Fatigued patients with multiple sclerosis have impaired central muscle activation

AK Andreasen, J Jakobsen, T Petersen and H Andersen

Background The pathogenesis of fatigue in multiple sclerosis (MS) is poorly understood.
Objective To elucidate the role of central motor activation we hypothesized that patients with primary fatigue have impaired central motor function and increased fatigability as compared to secondary fatigued and non-fatigued patients.
Methods Sixty patients with relapsing remitting MS and an Expanded Disability Status Scale score ≤ 3.5 were recruited and grouped as fatigued (Fatigue Severity Scale (FSS) ≥ 5.0) or non-fatigued (FSS ≤ 4.0). Nineteen patients were primary fatigued, 20 secondary fatigued and 21 non-fatigued. Maximal voluntary contraction, central activation and peripheral activation were determined by percutaneous twitch interpolation of the right quadriceps muscle.
Results Maximal voluntary contraction was similar between groups but did relate to scores of fatigue. Peripheral activation was similar in all groups. Central activation was impaired in both groups of fatigued patients compared to non-fatigued patients being 0.96(0.05) in primary fatigued and 0.96(0.04) in secondary fatigued versus 0.99(0.1) in non-fatigued patients. The impairment of central motor activation was related to degree of fatigue in all patients. During fatiguing exercise there was a similar loss of strength, without any time differences between the three groups.
Conclusion We conclude that impaired central motor activation is involved in MS-fatigue. *Multiple Sclerosis* 2009; **15:** 818–827. http://msj.sagepub.com

Key words: fatigability; fatigue; motor performance; multiple sclerosis; muscle fatigue; voluntary contraction

Introduction

Fatigue is a complaint in the majority of patients with multiple sclerosis (MS) [1]. It can be described as "a subjective lack of physical and/or mental energy" [2]. An obvious physiological explanation for muscle fatigue is dysfunction of the motor system or of its neural activation.

Physiological muscle fatigue is associated with an exercise-induced reduction of maximal voluntary strength. It arises due to altered properties within the muscle or because the central nervous system fails to drive the motor neurons sufficiently. When the central neuronal drive is suboptimal, activation of the muscle is incomplete and maximal voluntary strength remains smaller than true maximal muscle force evoked at direct muscle stimulation [3].

Patients with MS have reduced muscle performance [4–6], disuse being a characteristic finding in several studies of patients with a variety of physical disabilities [7–9]. In accordance with the pathophysiological mechanisms of MS, it is suggested that excessive physiological motor fatigue is of central origin rather than a consequence of intramuscular changes such as impaired contractile properties or metabolic dysregulation [10,11]. Impairment of central muscle activation has been shown in MS [12–14], and mechanisms underlying fatigue in MS have been related to impaired intracortical inhibition [15] and altered cortical activation during a motor task [16–18]. Hitherto, however, no studies have been able to establish an association between central muscle activation and subjective fatigue in MS [19,20].

Because development of effective treatment strategies against MS fatigue are warranted a better understanding of the underlying pathophysiology should be studied using quantifiable clinical,

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electrophysiological, and neuropsychological components [21]. Multiple etiologies of MS fatigue have been linked in a model encompassing both biological and psychological aspects. It suggests that the MS disease process with inflammation and demyelination is the primary trigger but also cognitive-behavioral variables such as anxiety, depressed mood, and reduced activity induces fatigue [22]. To investigate the relationship between fatigue and central muscle activation in MS, we conducted a study that takes several potentially fatigue inducing factors into account. A distinction was made between patients in whom nothing else than MS *per se* could explain the fatigue and patients who possibly were fatigued as a consequence of secondary factors such as poor sleep, depression, pain, and spasticity.

The hypothesis of the study was that in MS, central muscle activation and fatigability during exercise are more impaired in primary fatigued patients than in secondary and nonfatigued (NF) patients. The study included mildly and moderately disabled patients only. Fatigue was rated using the Fatigue Severity Scale (FSS) [23] and strength was measured at isometric dynamometry applying a percutaneous twitch interpolation technique [24,25].

Subjects and methods

Subjects

During May 2006 – October 2007, patients who attended the MS outpatient clinic at Aarhus University Hospital or at the Hospital of Viborg County were recruited. Inclusion criteria were relapsing–remitting MS [26,27], age of 18–55 and an Kurtzke Expanded Disability Status Scale score (EDSS score) ≤3.5 [28]. Due to subsequent examinations, right handedness and normal function of the right arm were also required. Exclusion criteria were dementia, concomitant major medical illness, a clinical MS attack within the last 4 weeks, change of medical treatment within the last 3 weeks, magnetic resonance imaging contraindications, pregnancy, and living more than 65 km from the study site.

According to severity of fatigue, patients fulfilling the inclusion criteria were stratified into two groups. Fatigue was quantified with the MS-specific one-dimensional questionnaire (FSS), which contains nine items rated on a 7-point Likert scale. Patients with a FSS mean score ≥ 5.0 were considered fatigued, whereas patients with a FSS mean score ≤ 4.0 were characterized as NF. Patients with a FSS mean score between four and five were excluded [29–31]. Subsequently, fatigue was categorized as primary fatigue (PF) or secondary fatigue (SF). Primary fatigued patients were without any other fatigue-related complications or events. Fatigued patients who fulfilled one or more of the following items were categorized as secondary fatigued: *Poor sleep* (Pittsburgh sleep quality index > 5) [32], *poor well-being* (WHO-5, Well-Being Index score ≤ 9) [33,34], *depression* (Major Depression Inventory score (MDI) ≥ 26) [35], *pain* (two positive scores out of three; intensity (Visual Analog Scale (VAS) score ≥ 3), frequency (at least once a week) and at least moderate pain according to The North American Research Committee on Multiple Sclerosis (NARCOM's) pain questionnaire) [36], *infection* (symptomatic infection within three weeks, cystitis upon examination (leucocytes ≥ 10^5 or nitrite) and elevated CRP), *spasticity* (Modified Ashworth Scale score ≥ 3) [37], and *tiredness* due to pharmaceutical side effects.

The study was conducted in accordance with Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95). Monitoring of the study was performed by the GCP-Unit at Aarhus University Hospital. The regional scientific ethical committee, the Danish Medicines Agency, and the Danish Data Protection Agency approved the protocol. Data were collected from November 2006 to December 2007.

Study design

At attendance, the sequence of examinations was case story interview, EDSS assessment (Neurostatus by L. Kappos (version 03/2002)), neuropsychological examination, and isometric dynamometry of the right quadriceps muscle including twitch interpolation, followed by a six-minute walk test (6-MWT). After the examinations, patients at home answered and returned by mail the questionnaires concerning secondary fatigue and a validated Danish version of the Multidimensional Fatigue Inventory (MFI-20) [38]. MFI-20 is developed to measure fatigue among cancer patients and assesses five dimensions of fatigue (general, physical, and mental fatigues, reduced activity, and reduced motivation) [39]. According to the Neurostatus, symptoms of fatigue during motor activity or fatigue limits daily activities by more than 50% and adds to the EDSS. Therefore, fatigue was excluded from the pyramidal- and cerebral-functional system scores providing a corrected EDSS (Cor. EDSS). To distinguish fatigue from muscle weakness, spasticity and ataxia patients with a low degree of physical disability were recruited. EDSS scores were 3.5 or less, indicating that all patients had preserved walking performance. Walking distance was determined with the 6-MWT and performed in accordance with the guidelines of the American Thoracic Society [40].

Eventually, just before- and after-walking participants were asked to rate their current fatigue at a 10-point Borg Scale.

Isometric dynamometry with percutaneous twitch interpolation

Isometric dynamometry with percutaneous twitch interpolation of the right quadriceps muscle was performed using a Biodex System 3 PRO® (Biodex Medical Systems, Inc., Shirley, NY, USA). The back chair was positioned at 85 degrees from the horizontal plane. The center of rotation was through the lateral femoral condyle, the arm of the dynamometer being fixed just proximal to the malleoli. The test position was at 90-degree flexion at the knee joint, and straps were placed to stabilize the trunk, pelvis, thigh, and shin. Electrical stimulations were applied with two surface electrodes (8 × 12 cm). They were placed transversely to a line between the anterior superior iliac spine and the proximal edge of the patella bone at the intersections of the upper and middle parts and at the middle and lower parts of the right thigh.

Electrical conduction was improved with a power-leading gel and surface electrodes were fastened with tape and bandaged. Familiarization to the isometric tests served as warm-up, patients being instructed to perform consistent maximal voluntary contractions (MVCs) lasting 4 s with abrupt relaxation leading to a marked plateau. The stimulus intensity was determined carefully for each participant. During the tests, standardized verbal instructions were provided and the force trace depicted on the computer monitor served as visual feedback [41,42].

Initially, it was attempted to investigate the right tibialis anterior muscle but a pilot setup showed that the Biodex System 3 PRO® was not suitable for the twitch interpolation method applied for that muscle, probably due to inertia of the system. Instead, the quadriceps muscle was tested twitch recordings being optimized by positioning the knee at 90 degree of flexion.

Twitch

Stimuli were given with increasing current until a maximal twitch torque was obtained from the resting muscle (pretwitch). During the isometric tests, supramaximal stimuli were applied using 110% of the pretwitch current. An external Stimulator Digitimer® model DS7 (Digitimer Ldt, Welwyn Garden City, UK) with a 400-volt output delivered paired stimuli separated by 10 ms intervals at a stimulus duration of 200 μs.

Baseline motor testing

Baseline motor testing consisted of four MVCs, each lasting 4 s separated by rest intervals of 120 s. A single MVC is shown in Figure 1. At the end of each contraction, a supramaximal stimulus was imposed giving rise to a superimposed twitch. As soon as the force fell to baseline values, a posttwitch was elicited. MVC was compared to a large pool of data from 150 healthy subjects collected in our laboratory using a test position at 70 degrees of flexion at the knee joint. The MVC was corrected for age, weight, height, and gender, relative MVC being the ratio MVC: MVC-expected.

Central activation and peripheral activation

Central activation (CA) was defined as 1 – (superimposed twitch: posttwitch ratio) × 100, indicating that a small superimposed twitch reflects a high CA. Peripheral activation (PA) is the posttwitch: pretwitch ratio, indicating that a small posttwitch reflects a small PA. The maximal value of each patient was used for statistical analysis.

Fatiguing exercise tests

To investigate MVC, CA, and PA as a function of time changes during repetitive contractions over a fixed time interval were recorded. The exercise regimen was composed of eight MVCs each of 4 s duration with a 2 s of rest interval between contractions, followed by a sustained 15 s MVC (Figure 2). Superimposed and posttwitch stimuli followed 4th and

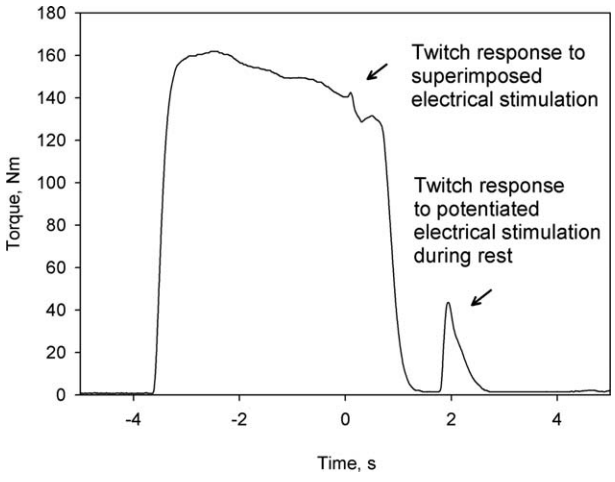

Figure 1 An illustrative example of a baseline maximal voluntary contraction with superimposed percutaneous twitch interpolation. Time zero corresponds to the time for superimposed paired stimulation.

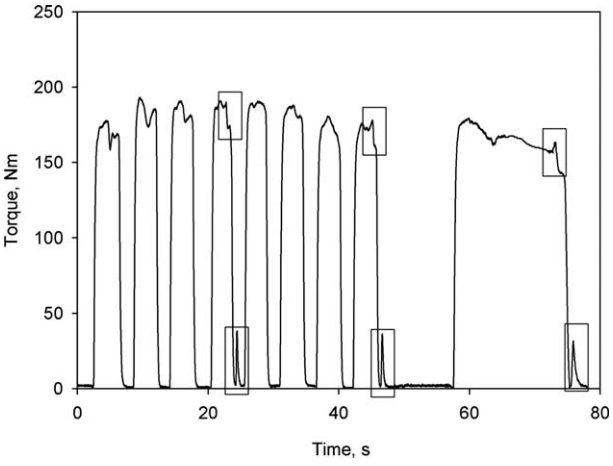

Figure 2 An illustrative example of the exercise test of eight MVC-repetitions followed by a maximal voluntary contraction lasting for 15 s. Time for electrical stimulations are marked with boxes.

8th MVC and the prolonged MVC. This composition was the maximum exercise tolerated by subjects at a pilot setup. To minimize peripheral fatigue (e.g., lactate accumulation), the duration of the prolonged contraction was limited to 15 s.

Statistics

ANOVA was used to compare demographic data, disease duration, time since last attack, and baseline motor values of the three groups. In case of significance, pairwise analyses were conducted (*t*-test). The distributions of voluntary activation of MVCs were constrained to values at or below 100% and data were reported as medians of trials [3]. We found a considerable difference between parametric and nonparametric testing. Consequently, permutation testing was conducted taking the upper limit into account. This led to an even higher significance level than following ANOVA, favoring parametric testing. Repeated-measures ANOVA was used to test isometric data, Kruskal–Wallis test to evaluate differences between EDSS scores and fatigue scale scores, and Spearman's rank correlation to evaluate correlations between baseline motor parameters and fatigue scale scores.

Results

Patient characteristics

Medical records of 906 patients were screened. In all, 195 patients fulfilled the inclusion criteria and were contacted by mail. One hundred sixteen patients responded and subsequently 23 patients were excluded (Figure 3). To ensure a similar number of participants in the three study groups, 33 consecutive responders with secondary fatigue were not included. Sixty patients were investigated, including 19 with primary fatigue, 20 with secondary fatigue, and 21 NF patients. Among patients with secondary fatigue, only four fulfilled three fatigue criteria, one fulfilled two criteria, and 15 fulfilled one criteria. Twelve secondary fatigued patients had poor sleep, six complained of pain, four had poor well-being scores, three had medical-induced fatigue, two had a high depression score, and two had recent urinary tract infection, whereas none had a spasticity score above two. Scores were missing in three patients at the MFI-20 questionnaire, in two at the general fatigue subscale, and in one at the mental fatigue subscale. Primary and secondary fatigued patients scored significantly higher at all the MFI-20 subscales compared with NF patients (Table 1).

Sex, age, height, and weight did not differ between the three groups (Table 2). NF patients had a lower EDSS score than fatigued patients but the EDSS difference corrected for fatigue (Cor. EDSS) was not significant between groups. Furthermore, there was no difference of disease duration between groups, whereas "time since last attack" was longer for NF than for secondary fatigued patients.

Table 1 Fatigue scores in 60 MS patients

	Primary fatigue	Secondary fatigue	Nonfatigue
FSS score	6.3 (5.0–7.0)	6.2 (5.0–7.0)	3.1 (1.0–4.0)*
General fatigue score	14.5 (9.0–20.0)	14.0 (9.0–20.0)	6.5 (4.0–11.0)*
Physical fatigue score	12.0 (8.0–18.0)	13.0 (4.0–18.0)	7 (4.0–13.0)*
Mental fatigue score	11.0 (5.0–19.0)	12.5 (4.0–19.0)	7.0 (4.0–15.0)*
Reduced activity score	8.0 (4.0–18.0)	12.0 (6.0–20.0)	6.0 (4.0–16.0)*
Reduced motivation score	7.0 (4.0–14.0)	8.5 (5.0–17.0)	5.0 (4.0–8.0)*

FSS, fatigue severity scale.
Multidimensional Fatigue Inventory subscale scores for general, physical and mental fatigues, reduced activity and reduced motivation. Data are median (range).
Kruskal–Wallis: *$P < 0.001$.

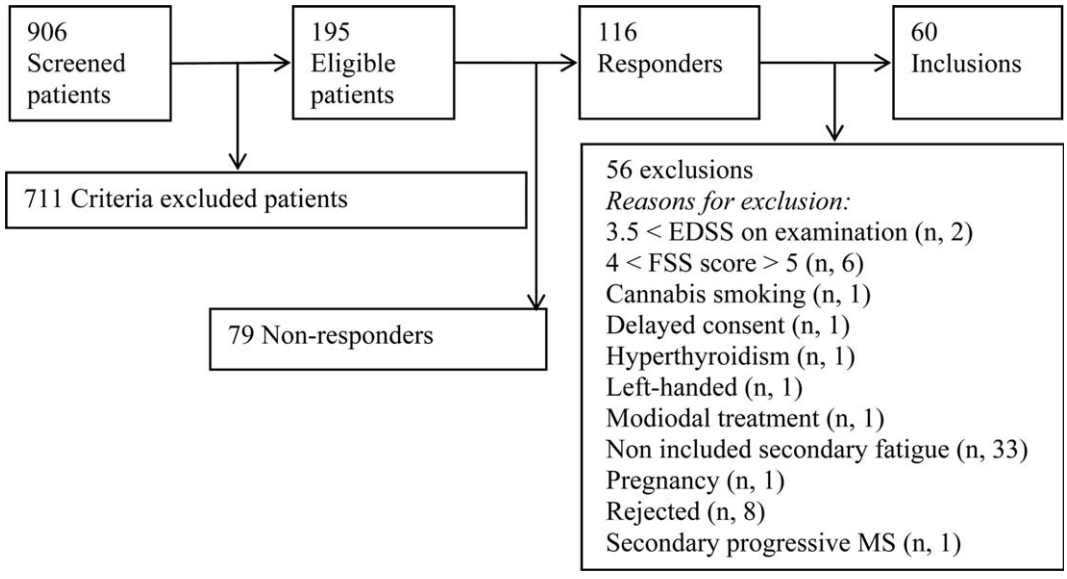

Figure 3 Recruitment of patients.

Walking speed

Primary and secondary fatigued MS patients walked shorter distance during the 6-MWT than NF MS patients ($P < 0.001$). The NF patients walked 623 (74) m, whereas primary fatigued patients walked 525 (85) m and secondary fatigued patients 562 (69) m (the values are reported as mean (SD)). For all patients, the walking distance was related to the FSS score as well as to all the five subscales of MFI-20.

Maximal voluntary contraction

One primary fatigued patient with a runner's knee and one secondary fatigued patient with joint hypermobility were excluded from isometric dynamometry. The MVC was similar between groups with an absolute force of the quadriceps muscle of 148 (32) Nm in PF, 159 (78) Nm in SF, and 173 (49) Nm in NF ($P = 0.39$). In Figure 4A, the relative MVCs are depicted. The ratios support the nonsignificant difference of force between groups 0.74 (0.14) in PF, 0.75 (0.21) in SF, and 0.77 (0.11) in NF ($P = 0.89$). From baseline and throughout the exercise test (Figure 4B), the MVC declined within each group ($P < 0.001$) but to a similar extend between groups ($P = 0.42$) and with respect to time ($P = 0.43$).

Peripheral activation

Three patients could not accept twitch stimulation. PA during MVC of the quadriceps muscle was similar in primary and secondary fatigued MS patients as well as in fatigued versus NF MS patients (Figure 5A). PA was 1.02 (0.08) in PF, 1.04 (0.11) in SF, and 1.05 (0.14) in NF. Throughout the exercise test, PA decreased within each group ($P = 0.001$) (Figure 5B) but to a similar degree with

Table 2 Demographics and disability scores in 60 MS patients

	Primary fatigue ($n = 19$)	Secondary fatigue ($n = 20$)	Nonfatigue ($n = 21$)
Age, years	43 (27–53)	39 (24–52)	39 (23–53)
Height, cm	172 (158–191)	171 (160–187)	174 (160–190)
Weight, kg	68 (46–93)	70 (52–102)	72 (57–97)
Disease duration, years	5.0 (1–14)	3.5 (0–16)	3.0 (0–9)
Time since last attack, years	2 (0–7)	1 (0–6)*	3 (0–10)
EDSS score	3.0 (1.0–3.5)	2.5 (2.0–3.5)	2.0 (1.5–3.5)**
Cor. EDSS score	2.5 (1.0–3.5)	2.0 (1.5–3.5)	2.0 (1.5–3.5)

EDSS, expanded disability status scale; Cor. EDSS, Corrected EDSS.
Data are median (range).
ANOVA: *$P < 0.05$.
Kruskal–Wallis: **$P \leq 0.01$.

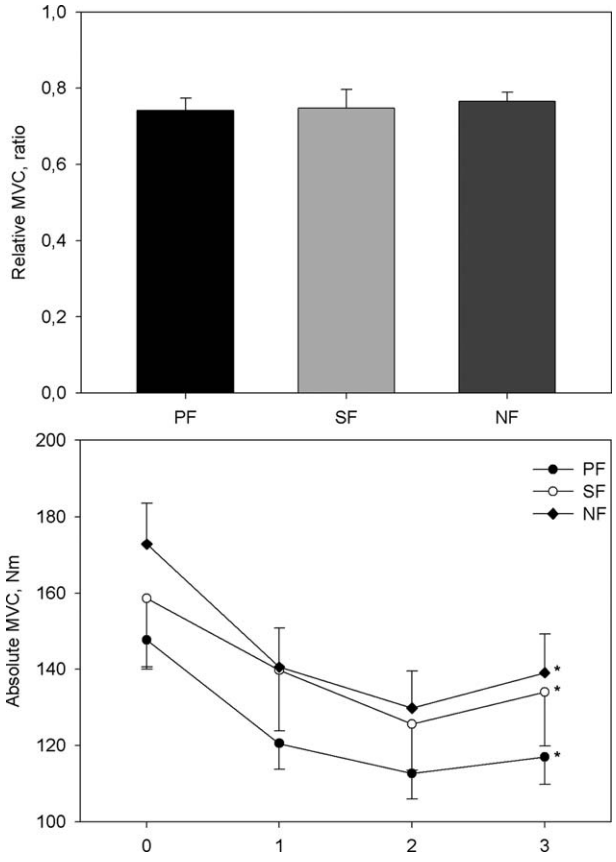

Figure 4 (A) Relative maximal volunary contraction (Relative MVC) (mean(SE)) at baseline in primary fatigued patients (PF), secondary fatigued patients (SF) and non-fatigued patients (NF). (B) Absolute maximal voluntary contraction (Absolute MVC) (mean(SE)) at baseline (0) after 4th MVCrepetition (1), after 8th MVC-repetition (2) and after a prolonged MVC of 15 s (3). *$P < 0.001$ compared to baseline within the same patient group.

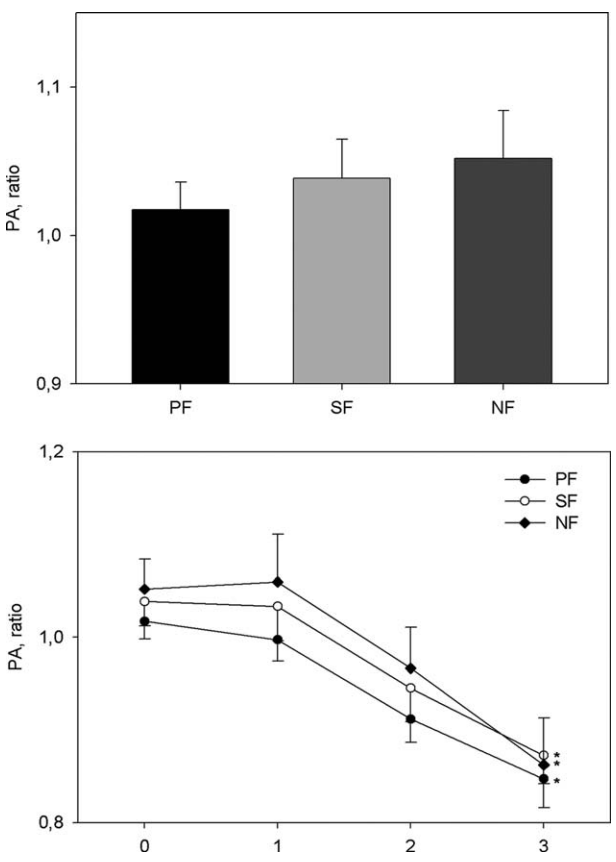

Figure 5 (A) Peripheral activation (PA) (mean(SE)) at baseline in primary fatigued patients (PF), secondary fatigued patients (SF) and non-fatigued patients (NF). (B) Peripheral activation (PA) (mean(SE)) at baseline (0) and after 4th MVC-repetition (1), 8th MVC-repetition (2) and after a prolonged MVC for 15 s (3). *$P < 0.001$ compared to baseline within the same patient group.

respect to time ($P = 0.41$) without any group differences ($P = 0.97$).

Central activation

Figure 6A shows that CA during MVC of the quadriceps muscle was significantly impaired in primary fatigued MS patients ($P = 0.009$) and in secondary fatigued MS patients ($P = 0.002$) compared to NF MS patients. CA was 95.9 (5.1) in PF, 95.8 (4.4) in SF, and 99.2 (0.99) in NF ($P = 0.01$). CA was similar in the two fatigued groups ($P = 0.93$). In Figure 7, the distributions of CA are presented for each patient in the three groups. It appears that the distribution of CA is skewed to the left towards lower values in primary and in secondary fatigued patients. During the fatiguing exercise test, CA fell to a similar extend ($P = 0.45$) without any difference between groups ($P = 0.10$). Within each group, there was a significant reduction of CA from baseline to the end of exercise ($P = 0.001$) (Figure 6B).

Relationships between fatigue and baseline motor performances

For all patients, FSS scores of fatigue were related to CA without any relationship to neither PA nor relative MVC (Table 3). For the MFI-20 subscales, the physical fatigue scores related to CA and to relative MVC but not to PA (Table 3). Also, the general fatigue subscale of MFI-20 related to CA (r = –0.37; $P = 0.01$).

Discussion

Our main finding is that subjectively fatigued MS patients have impaired central muscle activation compared to NF patients. The reduced CA is found

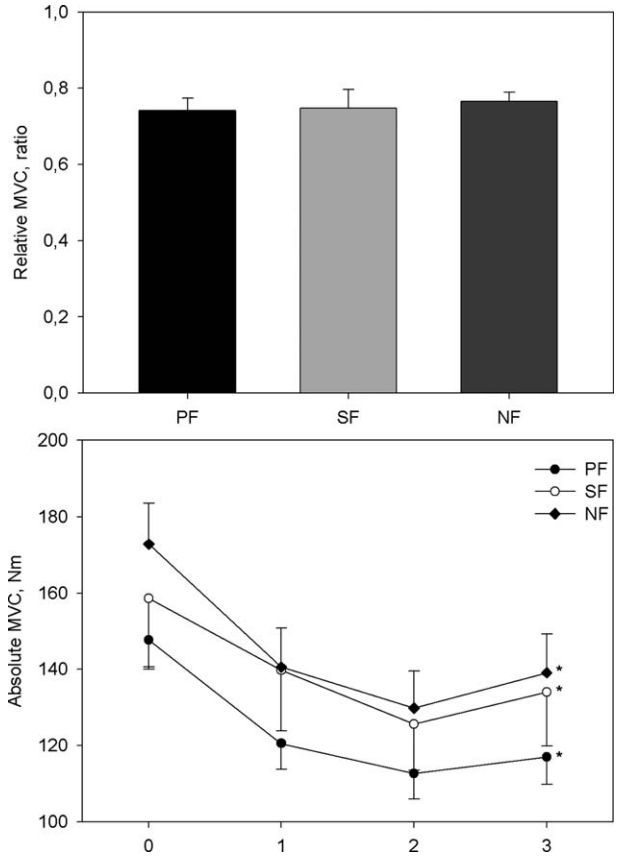

Figure 6 (A) Central activation (CA) (mean(SE)) at baseline in primary fatigued patients (PF), secondary fatigued patients (SF) and non-fatigued patients (NF). § $P < 0.01$. (B) Central activation (CA) (mean(SE)) at baseline (0) after 4th MVC-repetition (1), 8th MVC-repetition (2) and after a prolonged MVC for 15 s (3). * $P < 0.001$ compared to baseline within the same patient group.

in primary- and secondary fatigued patients and occurs a few seconds after onset of MVC.

Isometric strength of the quadriceps muscle was similar in primary fatigued, in secondary fatigued, and in NF patients. However, in the total group of all fatigued and NF patients, the degree of fatigue was related to isometric strength (Table 3). Furthermore, the walking distance during a 6-min performance was shorter in primary and in secondary fatigued patients than in NF patients. The 6-MWT is a complex measure closely reflecting activities of daily living but did relate to the FSS and all the MFI-20 subscores.

During the exercise tests, there was a significant within-group reduction of MVC, PA, and CA, without any differences between groups. The repetitive contractions during the exercise test challenged the participants. They performed work with high intensity, but at the same time, the test required a great effort with respect to coordination between rest and contraction periods. The variation of MVC, PA, and CA during repetitive contractions was considerable and standard deviations were overlapping. During exercise, the central muscle activation decreased especially in fatigued patients (Figure 6B), and this difference between fatigued and NF patients might well increase further if a longer exercise period had been applied. It is possible that a larger study group and a prolongation of the exercise test would have augmented the differences between groups. However, we chose the present regimen for the purpose of allowing blood to perfuse into the relaxed muscle during short periods of rest and, thereby, minimize the production of anaerobic metabolic products. Findings from this study suggest that an end point defined by a relative reduction in baseline MVC force could be an alternative. Furthermore, a setup without intermediate electrical stimulations might well have been appropriate. Due to the large difference of performance during the 6-MWT between fatigued and NF patients, it would be interesting to quantify CA after a fatiguing regimen of 6 min similar to the 6-MWT. The biological meaning of a mild reduction in baseline CA is uncertain. The exercise test could not produce a significant difference between fatigued and NF subjects, whereas the 6-min walking test separated the two groups. It is possible, therefore, that the baseline reduction in CA is associated with muscle fatigue.

Due to the small experimental differences in the degree of knee flexion between the healthy subjects composing our normal material and the MS patients (70 and 90 degrees, respectively), the relative strength in MS might be slightly underestimated. To reduce discomfort, we decided to stimu-

Table 3 Relationship between fatigue scores and baseline motor parameters in 58 MS patients

	MVC ($n = 58$)	PA ($n = 55$)	CA ($n = 55$)	6-MWT ($n = 60$)
FSS	–0.28*	0.04	–0.26*	–0.42**
Physical fatigue (MFI-20)	–0.35***	–0.02	–0.37***	–0.27*

MVC, maximal voluntary contraction; PA, peripheral activation; CA, central activation; 6-MWT, six-minute walk test; FSS, fatigue severity scale; MFI-20, multidimensional fatigue inventory.
Data are correlation coefficients.
Spearman's rank correlation: *$P < 0.05$.
Spearman's rank correlation: **$P < 0.001$.
Spearman's rank correlation: ***$P \leq 0.01$.

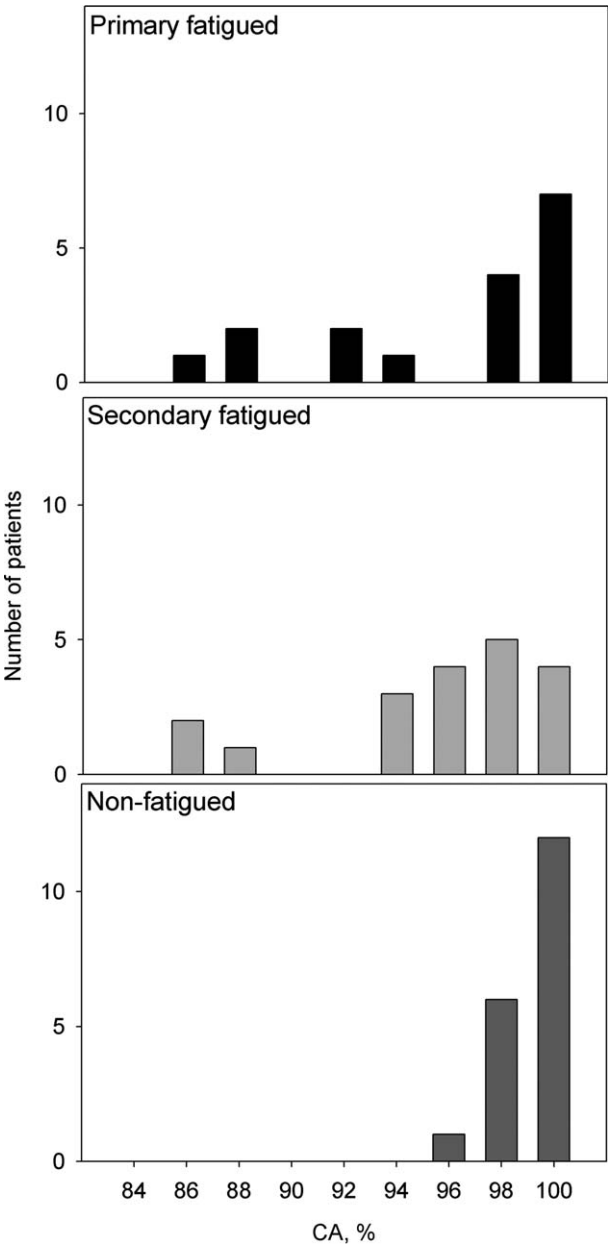

Figure 7 Distribution of individual values of central activation (CA, %) of primary (*n*, 17), secondary (*n*, 19) and non fatigued (*n*, 19) patients with multiple sclerosis.

late the muscle percutaneously instead of via the femoral nerve [9], possibly leading to slight overestimation of true voluntary activation [19].

We found that PA during muscle contractions was similar in primary and secondary fatigued patients and similar to the activation level in NF patients. To determine PA, we applied electrical stimulation during rest before and just after MVC. The mean PA in all groups was higher than one, reflecting that the contraction has intramuscular potentiating effects.

Causality models encompassing both physiological and cognitive factors [2,22,43] supported the argument for the distinction between primary and secondary fatigued groups. Consequently, a battery to distinguish between primary and secondary fatigue was constructed, which of course cannot identify primary fatigue in secondary fatigued patients. Rating depressive symptoms and poor well-being a cutoff corresponding to moderate depression was used. No patients fulfilled the core symptoms for depression and, consequently, no diagnosis of depression could be established. We considered signs of depression and poor sleep as risk factors for lack of motivation during isometric testing. It was assumed that distinction between patients with primary and secondary fatigue would lead to a cohort of patients with pure physical fatigue without lack of motivation. It is our experience though that patients were highly motivated during test performances in all groups, an observation supported by the finding of similar MVCs in the two groups of fatigued patients.

Secondary fatigue was categorized as signs of poor sleep, poor well-being, depression, pain, infection, spasticity, or tiredness related to pharmaceutical side effect in MS patients with a FSS score ≥ 5. As subjects with short disease duration and low degree of disability were included secondary fatigue was expected to be predominant in some patients. In this cross-sectional study, it was not possible to include reliable longitudinal data on the relationship between the secondary factors and the report of fatigue. However, FSS data indicate that fatigue levels were quite similar in primary and secondary fatigued patients and that the effect of secondary factors did not lead to a significant increase of fatigue.

The FSS fatigue score was used to define patients as fatigued and NF. The fatigue characterization was further expanded using the MFI-20 fatigue scores. In the group of all patients, CA correlated with the FSS and with general fatigue and physical fatigue of the MFI-20. Ng, *et al*. have studied the functional relationships of central and peripheral muscle alterations in patients with MS applying a twitch interpolation technique [19]. They found that weakness and walking impairment, but not fatigue, were related to impaired central muscle activation in MS. The lack of an association between fatigue and central muscle activation may be explained only by the wider range of disability (EDSS scores: 1.5–6) applied in their study of 16 patients.

Evaluation of physiological factors contributing to motor fatigue at the spinal level shows that motor unit discharge usually declines too rapidly to maintain a maximal evocable force. Accompanying this decline are changes of the properties of most classes of muscle receptors and of the reflexes

that they influence. It is likely that there is a net reduction in spinal reflex facilitation and an increase of inhibition during isometric MVC, leading to a condition at which motorneurons are harder to drive maximally by volition. Given that transcranial stimulation of the motor cortex can add progressively more force to the voluntary performance, and physiological central fatigue during isometric MVCs also contains a supraspinal component. This component can be differentiated from changes occurring locally at the level of the motor cortex during and after fatiguing voluntary contractions [3].

Demyelination associated with MS causes slowing of nerve conduction and conduction block, and demyelinated central nervous system axons might well be unable to transmit trains of high-frequency electrical impulses [44]. Conduction block and slowing of conduction of the primary central motor pathways have been carefully investigated but seems unable to explain increased central fatigue in MS. In the peripheral nervous system, neuromuscular transmission has been found to be normal in MS [8,20,45].

A physiological association between peripheral muscle fatigue and supraspinal fatigue has been established. If muscle tissue at the end of a fatiguing contraction is prevented from recovery by ischemia, the restoration of the supraspinal component of fatigue will not take place [46,47]. One possible explanation for this phenomenon is that firing from fatigue sensitive muscle afferents acts upstream to the motor cortex and, thereby, impair the voluntary descending drive, leading to avoidance of high-frequency fatigue and preservation of maximal strength [48]. As suggested by Sheean, *et al*. [20], this may play a role in MS-related central motor fatigue.

Leocani, *et al*. recorded EEG during a simple motor task, and Liepert, *et al*. applied TMS in mildly disabled fatigued and NF MS patients. Both studies conclude that fatigued MS patients show signs of intracortical hyperactivity and of impaired cortical inhibitory circuits [15,49]. Studies using MR spectroscopy, fMRI, and PET have found a relationship between fatigue and diffuse axonal dysfunction or dysfunction of cortical and subcortical circuits [16,17,50].

In previous studies [7,9,12], the metabolic properties of muscles of moderately to highly disabled MS patients showed signs of deconditioning. If the altered metabolic muscle properties are related to supraspinal fatigue, training should be further investigated as a treatment strategy. However, we found a direct relationship between decreased central motor activation and fatigue in patients without a sedentary lifestyle due to loss of walking performance. Since fatigue is related to altered cortical activity and diffuse axonal dysfunction, it is likely that there is a direct connection between fatigue and neuronal dysfunction. If so, treatment strategy should be directed toward the development of disease-modifying therapies.

Our observation of an impaired CA in fatigued patients with MS suggests that impaired cortical motor activation is a neurobiological substrate underlying fatigue in MS, independent on whether patients can be categorized as primary or secondary fatigued.

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References

1. Lerdal, A, Celius, EG, Krupp, L, Dahl, AA. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol* 2007; **14**: 1338–1343.
2. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Washington (DC): Paralyzed Veterans of America; 1998. http://pva.convio.net/site/News2?page=NewsArticle&id=8101.
3. Gandevia, SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001; **81**: 1725–1789.
4. Iriarte, J, de Castro, P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. *Eur J Neurol* 1998; **5**: 579–585.
5. Lambert, CP, Archer, RL, Evans, WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. *Med Sci Sports Exerc* 2001; **33**: 1613–1619.
6. Surakka, J, Romberg, A, Ruutiainen, J, Virtanen, A, Aunola, S, Maentaka, K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clin Rehabil* 2004; **18**: 652–659.
7. Kent-Braun, JA, Ng, AV, Castro, M, *et al*. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *J Appl Physiol* 1997; **83**: 1998–2004.
8. Kent-Braun, JA, Sharma, KR, Miller, RG, Weiner, MW. Postexercise phosphocreatine resynthesis is slowed in multiple sclerosis. *Muscle Nerve* 1994; **17**: 835–841.
9. Sharma, KR, Kent-Braun, J, Mynhier, MA, Weiner, MW, Miller, RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. *Muscle Nerve* 1995; **18**: 1403–1411.
10. Kent-Braun, JA, Sharma, KR, Weiner, MW, Miller, RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* 1994; **17**: 1162–1169.

11. Thickbroom, GW, Sacco, P, Kermode, AG, *et al*. Central motor drive and perception of effort during fatigue in multiple sclerosis. *J Neurol* 2006; **253**: 1048–1053.
12. de Haan, A, de Ruiter, CJ, van Der Woude, LH, Jongen, PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. *Muscle Nerve* 2000; **23**: 1534–1541.
13. Latash, M, Kalugina, E, Nicholas, J, Orpett, C, Stefoski, D, Davis, F. Myogenic and central neurogenic factors in fatigue in multiple sclerosis. *Mult Scler* 1996; **1**: 236–241.
14. Rice, CL, Vollmer, TL, Bigland-Ritchie, B. Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* 1992; **15**: 1123–1132.
15. Liepert, J, Mingers, D, Heesen, C, Baumer, T, Weiller, C. Motor cortex excitability and fatigue in multiple sclerosis: a transcranial magnetic stimulation study. *Mult Scler* 2005; **11**: 316–321.
16. Roelcke, U, Kappos, L, Lechner-Scott, J, *et al*. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study. *Neurology* 1997; **48**: 1566–1571.
17. Filippi, M, Rocca, MA, Colombo, B, *et al*. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* 2002; **15**: 559–567.
18. Mainero, C, Inghilleri, M, Pantano, P, *et al*. Enhanced brain motor activity in patients with MS after a single dose of 3,4-diaminopyridine. *Neurology* 2004; **62**: 2044–2050.
19. Ng, AV, Miller, RG, Gelinas, D, Kent-Braun, JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. *Muscle Nerve* 2004; **29**: 843–852.
20. Sheean, GL, Murray, NM, Rothwell, JC, Miller, DH, Thompson, AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. *Brain* 1997; **120**(Pt 2): 299–315.
21. Schwid, SR, Covington, M, Segal, BM, Goodman, AD. Fatigue in multiple sclerosis: current understanding and future directions. *J Rehabil Res Dev* 2002; **39**: 211–224.
22. van Kessel, K, Moss-Morris, R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* 2006; **61**: 583–585.
23. Krupp, LB, LaRocca, NG, Muir-Nash, J, Steinberg, AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; **46**: 1121–1123.
24. Lloyd, AR, Gandevia, SC, Hales, JP. Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. *Brain* 1991; **114**(Pt 1A): 85–98.
25. Merton, PA. Voluntary strength and fatigue. *J Physiol* 1954; **123**: 553–564.
26. Poser, CM, Paty, DW, Scheinberg, L, *et al*. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227–231.
27. Polman, CH, Reingold, SC, Edan, G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; **58**: 840–846.
28. Kurtzke, JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33**: 1444–1452.
29. Janardhan, V, Bakshi, R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* 2002; **205**: 51–58.
30. Bakshi, R, Shaikh, ZA, Miletich, RS, *et al*. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler* 2000; **6**: 181–185.
31. Tellez, N, Rio, J, Tintore, M, Nos, C, Galan, I, Montalban, X. Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Mult Scler* 2005; **11**: 198–202.
32. Buysse, DJ, Reynolds III, CF, Monk, TH, Berman, SR, Kupfer, DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193–213.
33. Bech, P, Olsen, LR, Kjoller, M, Rasmussen, NK. Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. *Int J Methods Psychiatr Res* 2003; **12**: 85–91.
34. Bonsignore, M, Barkow, K, Jessen, F, Heun, R. Validity of the five-item WHO Well-Being Index (WHO-5) in an elderly population. *Eur Arch Psychiatry Clin Neurosci* 2001; **251**(Suppl. 2): II27–II31.
35. Bech, P, Rasmussen, NA, Olsen, LR, Noerholm, V, Abildgaard, W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord* 2001; **66**: 159–164.
36. Marrie, RA, Cutter, G, Tyry, T, Hadjimichael, O, Vollmer, T. Validation of the NARCOMS Registry: pain assessment. *Mult Scler* 2005; **11**: 338–342.
37. Bohannon, RW, Smith, MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987; **67**: 206–207.
38. Smets, EM, Garssen, B, Bonke, B, De Haes, JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**: 315–325.
39. Watt, T, Groenvold, M, Bjorner, JB, Noerholm, V, Rasmussen, NA, Bech, P. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. *J Epidemiol Community Health* 2000; **54**: 827–833.
40. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111–117.
41. Shield, A, Zhou, S. Assessing voluntary muscle activation with the twitch interpolation technique. *Sports Med* 2004; **34**: 253–267.
42. Morton, JP, Atkinson, G, MacLaren, DP, *et al*. Reliability of maximal muscle force and voluntary activation as markers of exercise-induced muscle damage. *Eur J Appl Physiol* 2005; **94**: 541–548.
43. Crayton, HJ, Rossman, HS. Managing the symptoms of multiple sclerosis: a multimodal approach. *Clin Ther* 2006; **28**: 445–460.
44. McDonald, WI, Sears, TA. The effects of experimental demyelination on conduction in the central nervous system. *Brain* 1970; **93**: 583–598.
45. Sandroni, P, Walker, C, Starr, A. 'Fatigue' in patients with multiple sclerosis. Motor pathway conduction and event-related potentials. *Arch Neurol* 1992; **49**: 517–524.
46. Gandevia, SC, Allen, GM, Butler, JE, Taylor, JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. *J Physiol* 1996; **490**(Pt 2): 529–536.
47. Woods, JJ, Furbush, F, Bigland-Ritchie, B. Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates. *J Neurophysiol* 1987; **58**: 125–137.
48. Bigland-Ritchie, B, Woods, JJ. Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle Nerve* 1984; **7**: 691–699.
49. Leocani, L, Colombo, B, Magnani, G, *et al*. Fatigue in multiple sclerosis is associated with abnormal cortical activation to voluntary movement–EEG evidence. *Neuroimage* 2001; **13**: 1186–1192.
50. Tartaglia, MC, Narayanan, S, Francis, SJ, *et al*. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Arch Neurol* 2004; **61**: 201–207.