ORIGINAL ARTICLE

UDC: 612.825.1::616.858
DOI: 10.2298/VSP1303298M

Changes in motor cortex excitability associated with muscle fatigue in patients with Parkinson's disease

Promene ekscitabilnosti motorne kore udružene sa zamorom mišića kod obolelih od Parkinsonove bolesti

Sladjan Milanović*, Saša R. Filipović*, Saša Radovanović*, Suzana Blesić*, Nela V. Ilić†, Vladimir S. Kostić‡§, Miloš R. Ljubisavljević*

*** University of Belgrade Institute for Medical Research , Belgrade, Serbia; †Clinic of Rehabilitation Medicine, ‡Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia; §Faculty of Medicine, University of Belgrade, Belgrade, Serbia**

Abstract

Background/Aim. Transcranial magnetic stimulation (TMS) is a standard technique for noninvasive assessment of changes in central nervous system excitability. The aim of this study was to examine changes in responses to TMS in patients suffering from Parkinson's disease (PD) during sustained submaximal isometric voluntary contraction [60% of maximal voluntary contraction (MVC)] of the *adductor pollicis* muscle, as well as during a subsequent recovery period. **Methods.** Cortical excitability was tested by single TMS pulses of twice of the motor threshold intensity applied over the vertex. Testing was carried out during the sustained contraction phase every 10 s before and every 5 s after the endurance point, as well as at rest and during brief 60% MVC contractions before (control), immediately after the sustained contraction, and at 5 min intervals during the recovery period. **Results.** Although the PD patients could sustain the contraction at the required level for as long period of time as the healthy subjects (though contraction level subsided more rapidly after the endurance point), effects of muscle fatigue on the responses to TMS were different. In contrast to the findings observed in the healthy people where motor evoked potentials (MEP) and EMG silent period (SP) in fatigued muscle gradually diminished during contraction up to the endurance point, and increased thereafter, in the majority of patients no changes occurred in MEP size (peak and area) of the *adductor pollicis* muscle, either before or after the endurance point. On the other hand, changes in the SP of this muscle differed among the subjects, showing a gradual increase, a decrease or no changes in duration. The trends of changes in both MEP size and SP duration in the *musculus brachioradialis* varied among the tested PD patients, without any consistent pattern, which was in contrast with the findings in the healthy people where both measures showed a gradual increase from the beginning of the sustained contraction. A complete dissociation between changes in MEP and SP during fatigue was also of note, which differed sharply from the findings in the healthy people in who fatigue induced changes in these measures followed identical patterns. **Conclusion.** These results in the PD patients suggest the presence of impairment and/or compensatory changes in mechanisms responsible for adaptation of voluntary drive as well as for matching between cortical excitation and inhibition which become manifest in demanding motor tasks such as those imposed by muscle fatigue.

Key words:
muscle fatigue; parkinson disease; motor cortex; transcranial magnetic stimulation.

Apstrakt

Uvod/Cilj. Transkranijalna magnetna stimulacija (TMS) je standardna tehnika za neinvazivnu procenu promena ekscitabilnosti centralnog nervnog sistema. Cilj rada je bio da se prikažu promene odgovora na TMS kod obolelih od Parkinsonove bolesti (PB) za vreme trajanja submaksimalne voljne izometrijske kontrakcije [60% maksimalne voljne kontrakcije (MVK)] mišića *adductor pollicis*, kao i tokom perioda oporavka. **Metode.** Kortikalna ekscitabilnost testirana je TMS pulsevima dvostruko većeg intenziteta od motornog praga. Testiranje je vršeno za vreme održavanja kontrakcije na svakih 10 s do tačke izdržljivosti i na svakih 5 s posle toga, a, takođe, u miru kao i za vreme kratkotrajnih 60% MVK u periodu pre (kontrola), neposredno posle održavanja kontrakcije, i u intervalima od pet minuta za vreme perioda oporavka. **Rezultati.** Iako su bolesnici sa PB mogli da održavaju zahtevani nivo kontrakcije jednako dugo kao i zdravi ispitanici (mada je nivo opadao brže nakon tačke izdržljivosti), efekti mišićnog zamora na odgovor izazvan TMS-om

Correspondence to: Sladjan Milanović, University of Belgrade Institute for Medical Research, Dr Subotica 4, PO BOX 102, 11 129 Belgrade, Serbia. Phone: +381 11 2684 484. E-mail: sladjan.milanovic@imi.bg.ac.rs

bili su različiti. Za razliku od zdravih ispitanika kod kojih se motorni evocirani potencijali (MEP) i trajanje perioda EMG tišine (PT) u zamaranom mišiću postepeno smanjuju tokom kontrakcije do tačke izdržljivosti, a zatim rastu, kod većine bolesnika nije došlo do promena veličine (maksimalna amplituda i površina) MEP mišića *adductor pollicis*, bilo pre ili posle tačke izdržljivosti. S druge strane, promene PT ovog mišića su se razlikovale među ispitanicima, pokazujući bilo postepeno povećanje, smanjenje ili odsustvo promena. Promene kako amplitude MEP tako i trajanje PT u EMG mišića brahioradialisa varirale su među bolesnicima sa PB, bez nekog dominantnog obrasca, po čemu su se, takođe, razlikovale od promena nađenih kod zdravih ispitanika, kod kojih su se oba parametra postepeno povećavala od početka održavanja tonične kontrakcije. Upadljiva je, takođe, i potpuna disocijacija između promena MEP i PT tokom zamora, što je u oštroj suprotnosti sa nalazom kod zdravih ispitanika gde su promene ovih parametara pratile identičan obrazac. **Zaključak.** Rezultati kod bolesnika sa PB ukazuju na postojanje oštećenja i/ili kompenzatornih promena mehanizmima odgovornih za adaptaciju voljne pobude i usklađivanja kortikalne eksitacije i inhibicije, koji se manifestuju tokom mišićnog zamora i u drugim zahtevnim motornim zadacima.

Ključne reči:
mišići, zamor; parkinsonova bolest; motorna kora; stimulacija, magnetna, transkranijalna.

Introduction

A possibility that the central motor drive might also be affected in fatigue has received the least experimental attention as a possible factor in the development of muscular fatigue. In fact even though few would argue that the changes in voluntary effort to adequately maintain desired contraction level, is the most likely explanation of fatigue in the majority of normal activities, it was only until recently that this phenomenon was examined in a more direct way. Using transcranial magnetic stimulation (TMS), standard technique for noninvasive assessment of changes in central nervous system excitability [1], several studies have reported on changes in central motoneurone drive during muscle fatigue [2–5]. In our previous study [6], it was shown in healthy subjects that both the motor evoked potential (MEP) magnitude (peak and area) and duration of the silent period (SP) in electromyoneurography (EMG) of the *adductor pollicis* muscle change in parallel during a sustained 60% maximal voluntary contraction (MVC): they gradually decrease up to the endurance point and increase thereafter. MEPs elicited at rest immediately after the fatiguing contraction were larger while those elicited later on during the recovery period did not differ significantly from the controls. MEPs and SPs of the *musculus brachioradialis*, which was not activated voluntarily, increased gradually throughout the sustained 60% MVC of the *adductor pollicis* muscle, while those during the recovery period did not differ from the controls. The changes in both MEP magnitude and SP duration have been supposed to be due mainly to changes in central excitatory and inhibitory processes, foregoing to motor cortex output neurons, in an attempt to sustain muscle activity in spite of its fatigue.

Cerebral motor cortex areas receive most of the basal ganglia output, therefore deficits in movement control that occur in basal ganglia diseases should inevitably be reflected on the activity of cortical cells. In monkeys, it was shown that lesion of the substantia nigra can produce substantial changes in the activity of neurons in the motor areas of the cortex [7]. Also, involvement of basal ganglia in the regulation of motor activity in healthy humans was presented in the study by Dettmers et al. [8], by showing that basal ganglia take part in sustaining submaximal isometric contraction. On the other hand, fatigue has long been recognized as a common and frequently disabling symptom in Parkinson's (PD) disease [9–11]. Patients with PD report that fatigue prevents sustained physical activity [11]. A pathophysiological correlate of fatigue associated with PD is unknown, with the emphasize on the mental aspects [12]. However, impaired adaptation of cortical motor activity to muscle fatigue in PD disease could also be expected.

Therefore, the aim of this study was to examine changes in the excitatory and inhibitory motor processes in PD patients, during fatiguing submaximal (60% MVC) voluntary contraction of the *adductor pollicis* muscle using TMS. Responses of a remote muscle (*brachioradialis*), not voluntarily activated, were also recorded.

Methods

The study involved 11 right-handed PD patients (4 women), aged 39–67 years (mean 56.2 ± 9.7 years). All the patients were on optimal dopaminomimetic therapy for at least three months, had no medication related complications and/or side effects, and showed neither marked motor deficits nor signs of dementia (in all the patients the Mini Mental State Examination score was above 24; 8 patients were in stages I or II according to Hoehn and Yahr, and 3 patients in stage III). The patients with marked tremor were excluded from the study. The procedures were approved by the local Ethics committee and all the subjects gave their informed consent.

For comparison, we used data from our previous study obtained in a group of healthy people using the same experimental design [6]. The group consisted of 13 right-handed people (5 women) aged 25–45 years. This historical control group was younger than the group of PD patients in this study. However, in view of a recent report of lack of aging effect on the MEP/SP ratio in healthy people by Oliviero et al. [13], and given that the study was designed to study the pattern of changes in MEP and SP during development of fatigue, rather than their absolute values, and that one of the main findings of our previous study was the same pattern of changes of MEP and SP, this control group might be considered as good enough for the purpose of the study.

Muscle contraction and EMG recording

Experiments were performed on the *adductor pollicis* muscle as described previously for healthy subjects [6]. The forearm and fingers were firmly fixed and held in pronated position. The thumb was attached to the force transducer (Grass FT-10). Its output was fed to the computer (see later) and displayed on the oscilloscope screen to provide a visual feedback signal for the sustained muscle tension. Surface EMG was recorded from the *adductor pollicis* muscle as well as *musculus brachioradialis* (in 10 PD patients) by Arbo silver/silver chloride electrodes positioned, for the thenar, as described by Bigland-Ritchie et al. [14]. EMG signals were amplified (2.000x) using QT-5B Leaf Electronics amplifiers and filtered (1 Hz–3 kHz). Both the force and EMG (actual and full wave rectified) signals were digitized (sampling rate 3,000 Hz) by CED 1401 plus. SIGAVG computer program was used for further analysis. MEP latency, amplitude (base to peak in the rectified signal), area and duration were measured. To minimize the errors that might be induced due to basic EMG and/or mechanical artifacts MEP start and end were estimated by observing both unrectified and rectified records. Also, some records were analyzed independently by two experimenters. In the activated muscls, duration of the SP, from the end of MEP to the reappearance of EMG, was also measured.

Transcranial magnetic stimulation

Motor cortex was stimulated by a Magstim 200 stimulator with 90 mm diameter round coil. The coil was centered at the vertex and held tangentially with respect to the skull. Threshold at rest was estimated by applying magnetic pulses of increasing strength until MEPs ≥ 100 μV occurred in 6/10 trials [15]. To elicit MEPs during the experiment, TMS of twice of the threshold strength was applied. Particular care was taken to preserve the initial position of the coil throughout the experiment.

Electrical nerve stimulation

Electrical nerve stimulation of the ulnar nerve was applied to the wrist to obtain maximal M waves in order to check the appearance of peripheral muscle fatigue. In total 6 single 500 μs stimuli were delivered at 5 s intervals, before and immediately after fatiguing contraction was performed. When changes in H-reflex were observed (see later) the same stimuli were applied of the strength eliciting 50% of the maximal H-reflex amplitude.

The experimental protocol

The experimental protocol was as described before [6]. Briefly, first the MEP threshold and 60% MVC had been determined. Given that the patients with PD have bradykinesia, MVC was measured during the 3 consecutive attempts at 1 min intervals, each time allowing sufficient time to the patients to reach maximum force. It should also be noted that there were no significant differences in the absolute level of the exerted forces between the PD patients and normal subjects [6]. After MVC had been determined 20 min rest was allowed to the muscle. Thereafter 6–10 TMSs of twice as the threshold intensity were applied at rest and during 6–10 short-lasting (3–4 s) 60% MVC contractions at 10 s intervals. Electrical ulnar nerve stimulation was then applied. After 10 min rest sustained 60% MVC contraction was performed. It was maintained up to the endurance point (60–140 s in 8 subjects and around 3 min in the remaining 3) and as long as possible thereafter (up to 30 s in 6 subjects, 50 s in the additional 4 and 160 s in 1 subject). Since this period was rather short, in the most of the subjects, TMS was carried out at 10 s intervals up to the endurance point but at 5 sec thereafter. Electrical nerve stimulation was then applied to check for the peripheral fatigue. Immediately after that, 6–10 TMSs at 10 s intervals were applied at rest. During the period of recovery, 5 and 10 min after the end of the fatiguing contraction, 6–10 TMSs both at rest and during short-lasting (2 s) contractions of 60% MVC intensity were applied.

H-reflex was tested, on separate days, in 6 subjects. It was obtained in 4 of them and its changes were observed following the same protocol.

Data analysis

Statistical significance of the differences between the measured characteristics of MEPs (latency, peak, area) and SPs (duration) elicited after the sustained 60% MVC contraction and those elicited before (control) was estimated using the Student's *t*-test. Changes in M-wave and H-reflex amplitude were estimated in the same way. A significance of trends of changes in MEP magnitude (peak and area), SP duration and H-reflex amplitude during the sustained contraction was estimated by linear regression analysis.

Results

Both MEPs and SPs of normal characteristics occurred in EMG records of both *adductor pollicis* and *brachioradialis* muscle in response to TMS.

Fatigue-associated changes in TMS cortical excitability in the adductor pollicis muscle

In contrast to the responses we had previously described in healthy subjects MEP magnitude (both peak and area) showed no consistent changes, either before or after the endurance point, in all but one of the PD patients examined, in which it gradually decreased from the start up to the end of the sustained 60% MVC contraction. A significant gradual decrease in the peak but not in the area was found in an additional subject. Actual EMG records of one subject and the mean MEP areas for the group, normalized for every subject with respect to the mean of control MEPs elicited during the short-lasting contractions before the fatiguing one, and centered at the endurance point are presented in Figures 1A and B, respectively. The trend of changes in the MEP area for the group was not significant either up to the endurance point ($p = 0.747$) nor thereafter ($p = 0.683$), as well as for the whole period ($p = 0.573$). No significant differences were found in the areas and/or peaks of MEPs neither at rest nor during the short-lasting contractions, during the recovery period in

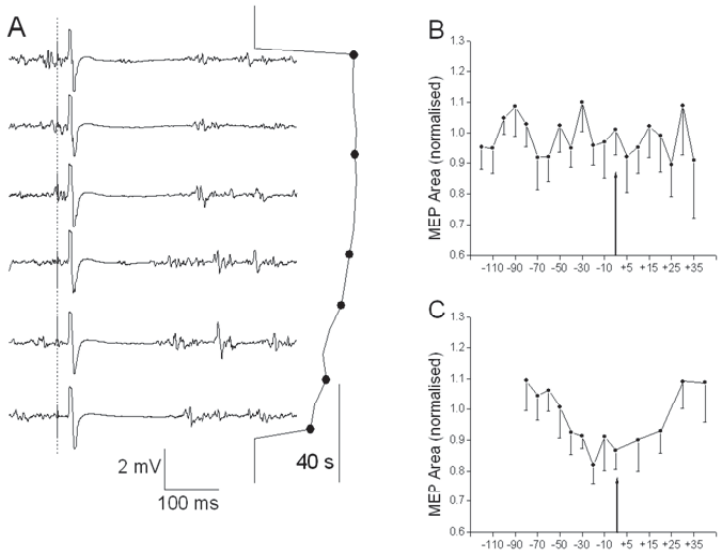

Fig. 1 – Changes in the *adductor pollicis* motor evoked potential (MEP) magnitude and cortical silent period during and after sustained 60% maximal voluntary contraction (MVC)

A – electromyoneurographic records (left) taken at the moments indicated on the 60% MVC force trace (right). Vertical broken line in MEP records indicates transcranial magnetic stsimulation (TMS) pulse. B – Parkinson diseases (PD) patients; MEP area, mean and standard deviation (SD) for 11 subjects, normalized for each subject with respect to the control MEP during short-lasting 60% MVC contractions before the sustained contraction, and centered at the endurance point (arrow). Abscissa – time of TMS, starting from the endurance point (0). C – healthy subjects (data taken from [6])

comparison to those obtained before the sustained contraction (control). Neither MEP latency nor duration showed consistent changes either before or after the endurance point during the sustained 60% MVC contraction or during the recovery thereafter.

In the healthy subjects SP duration in EMG activity changed in parallel with the MEP magnitude during sustained 60% MVC contraction. In 6 PD patients SP duration behaved in the same way as MEP magnitude, showing no changes during the sustained contraction. In the remaining subjects it showed changes that differed in trend both from changes in MEP magnitude and among the subjects (Figure 2A). SP duration in response to TMS during the recovery period did not differ significantly from the responses recorded before the sustained 60% MVC.

Fatigue-associated changes in TMS cortical excitability in the brachioradialis muscle during sustained contraction of the adductor pollicis muscle

As we previously showed in the healthy subjects both MEP magnitude and SP duration of the *brachioradialis* muscle increased gradually throughout sustained 60% MVC of the *adductor pollicis* muscle. In contrast, in the PD patients their changes showed different trends both within and between the subjects (Figure 2B). The magnitudes of the MEPs and duration of SPs in response to TMS, applied both at rest

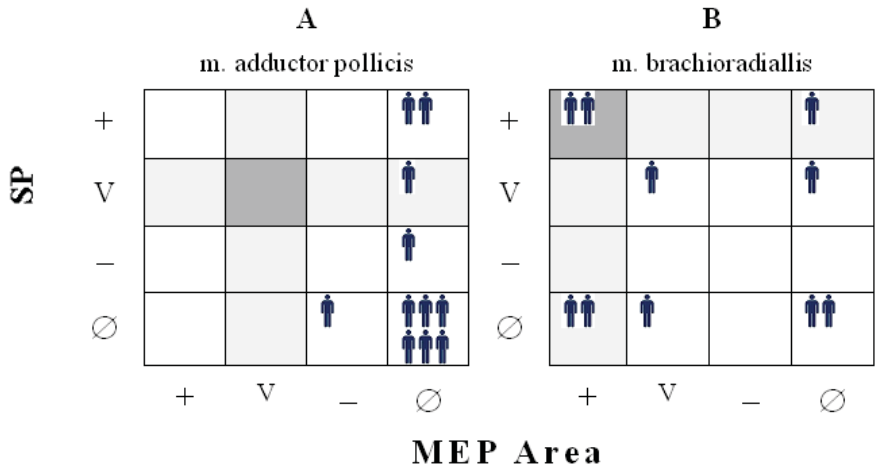

Fig. 2 – Distribution of patterns of changes in motor evoked potential (MEP) magnitude and silent period (SP) duration in electromyography (EMG) of the *adductor pollicis* muscle (A) and *musculus brachioradialis* (B) during sustained 60% maximal voluntary contraction (MVC) of the *adductor pollicis* muscle

+ indicates increase, - decrease, 0 no changes, "V" profile – decrease up to endurance point and increase thereafter. Shaded areas indicate patterns found in the healthy subjects [6]

and during short-lasting *adductor pollicis* contractions during the recovery period did not differ significantly from those elicited before the sustained contraction. Neither MEP latency nor duration showed consistent changes either before or after the endurance point in the sustained contraction or in the recovery thereafter.

H-reflex and M-wave amplitude

The amplitude of the M-wave in the *adductor pollicis* muscle, elicited by ulnar nerve electrical stimulation after the sustained, fatiguing 60% MVC contraction, in 6 of the subjects did not differ significantly from the responses to the same stimulation applied before this contraction, while in the other 5 it showed a decrease with simultaneous increase in duration.

H-reflex was tested in 6 subjects and it was possible to obtain it in 4 of them. In 3 subjects its amplitude showed no changes during the sustained fatiguing 60% MVC contraction, while in the remaining one it was decreased after the endurance point. In this subject it was smaller also at rest immediately after this contraction, while later on during the recovery its amplitude did not differ from the control.

Discussion

Transcranial magnetic stimulation (TMS) has been shown to activate motor cortical output neurons both directly and transsynaptically [1]. Therefore, changes in the responses to TMS, both in MEPs as well as in the SP should reflect changes in excitability of corticospinal neurons and/or their inputs, of both cortical and subcortical origin. While SP duration depends primarily on central nervous activity [16, 17] indicating the level of inhibition in the cortex at the time of the stimulus [18, 19], MEP magnitude might be influenced by changes in spinal cord neurons and muscle excitability. Contribution of changes at the levels below the motor cortex should therefore also be taken into account. Changes in the M-wave amplitude and duration in the 5 examined subjects indicate that peripheral fatigue [20, 21] might contribute to the decrease in MEP magnitude. At the spinal level, however, fatigue-induced changes in either skeletomotor neuron activity or reflex mechanisms have, to our knowledge, not been investigated in PD patients. It could be expected that in PD patients, as in normal subjects, the firing rate of skeletomotor neurons would tend to decline during the prolonged contraction due to their intrinsic properties [22, 23] as well as due to the development of inhibitory reflexes [24] with muscle fatigue. These effects, however, might be less expressed in PD patients in which skeletomotor neurons are under different central drive causing difficulties not only in their activation, but also in their deactivation [25, 26]. However, the absence of any consistent changes in H-wave amplitude related to fatiguing contraction, found in three subjects, would not be in accordance with the presence of changes in excitability at spinal level. It seems, therefore, that the observed changes in both MEP amplitude and SP duration mainly reflect changes in the cortical activity.

In this study we were able to record MEPs and SPs in EMG records of both *adductor pollicis* and *brachioradialis* muscle in response to TMS. The MEP sizes and SP durations were comparable in magnitude to those recorded in healthy people in our previous experiments performed under simular conditions [6]. This was in accordance to the existing data [18, 27–32].

The main finding of this study was that the effects of submaximal voluntary fatiguing contraction on TMS responses in PD patients differed markedly from those in normal subjects. In a few patients only, the pattern of either MEP or SP changes was similar to those found in normal subjects, i.e. in the *adductor pollicis* a decrease in their magnitude up to the endurance point an increase thereafter, and, in *brachioradialis* an increase either from the start or soon after the start of the sustained contraction. On the contrary, in the majority of the patients examined MEP magnitude, not only in the voluntarily activated *adductor pollicis*, but also in the remote *brachioradialis* muscle, remained at the control level both up to the endurance point and beyond. This could be interpreted as if the central excitatory drive, both in terms of the magnitude of input to motor cortex output cells, as well as to its spreading, did not change in muscle fatigue. On the other hand, changes in SP duration would indicate that the inhibitory input to both the agonist *adductor pollicis* and *brachioradialis* muscle is modified differently in different patients. It is of particular note that responses to TMS in the PD patients differed sharply from those in the healthy subjects in almost complete dissociation of patterns of changes in MEP magnitude and SP duration during sustained 60% MVC contraction in both observed muscles, *adductor pollicis* and *brachioradialis*. This would suggest differential effect of the disease process on inhibitory and facilitatory cortical motor systems during development of motor fatigue in PD.

The PD patients studied were on therapy and their parkinsonian symptoms were mild to moderate. Also, their responses to TMS at rest and during short lasting 60% MVC contractions were not different from those found in healthy subjects [6]. Therefore, the differences in pattern of responses to TMS during sustained 60% MVC contraction could indicate that in PD patients the central mechanisms responsible for adaptation of motor drive to prolonged contraction failed under more demanding conditions of fatigue. On the other hand, the patients could sustain the required 60% MVC level for at least as long period of time as healthy subjects [6]. Thus, it could also be supposed that they used mechanisms of central motor control in sustaining muscle contraction that differed from those acting in healthy subjects. Dissociation of patterns of MEP and SP changes in PD patients, in contrast to matching patterns found in healthy subjects [6], further supports the proposal that the differences are due to central changes at a level preceding the cortical motor output cells, the input to cortex from subcortical nuclei included, rather than to changes in excitability of these cells. Nevertheless, the rapid fall in tension after the endurance point could also speak for the failure of compensation in central motor drive.

Conclusion

These results in the PD patients suggest the presence of impairment and/or compensatory changes in mechanisms responsible for adaptation of voluntary drive as well as for matching between cortical excitation and inhibition which become manifested in demanding motor tasks such as those imposed by muscle fatigue.

Acknowledgments

This work was supported by the Ministry of Education Science and Technological, Development of the Republic of Serbia, project No. 175012.

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Received on September 22, 2011.
Revised on December 7, 2011.
Accepted on December 8, 2011.