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# Impaired sleep-associated modulation of post-exercise corticomotor depression in multiple sclerosis

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ABSTRACT

*Objective:* To compare the beneficial effect of nap versus rest on the recovery of motor evoked potentials (MEPs) after a fatiguing exercise performed in patients with multiple sclerosis (MS) and healthy controls.
*Methods:* In 12 MS patients and 12 healthy controls, MEPs were recorded from the adductor pollicis muscle before, 10 and 60 min (T0, T10, and T60) after an effort of thumb adduction at 25% of maximal voluntary contraction force for 24 min. After the effort, the subject was maintained at rest or invited to have a nap while monitored with polysomnography. The two sessions (nap and rest) were randomly performed in each subject during the same day. The impact of nap and rest on post-exercise changes in MEP amplitude were studied in each group (patients and controls) and then compared between the two groups.
*Results:* Although MEP amplitude at baseline was lower in MS patients than in controls, post-exercise corticomotor depression (PECD), expressed as T10/T0 MEP amplitude ratio, was similar in both groups. Regarding MEP amplitude recovery at T60, nap was significantly more beneficial than rest in healthy subjects, but not in MS patients.
*Conclusion:* Motor recovery from PECD following a fatiguing exercise can be enhanced by sleep (at least a short nap) in healthy subjects. In MS patients, sleep restorative effect is reduced or lost, maybe contributing to the excessive fatigue or fatigability characterized in these patients.



## 1. Introduction

A severe fatigue syndrome affects the quality of life of 53 to 92% of patients with multiple sclerosis (MS) [1]. The pathophysiology of fatigue in MS is multidimensional and not well understood. Among other factors, physical fatigue could be a major component of fatigue in MS [2]. Physical fatigue is the feeling that the effort required to accomplish a task is disproportionally high [3]. It appears as a reduction in the ability to exert muscle force, regardless of whether or not the task can be really sustained [4]. Although post-exercise fatigue has peripheral neuromuscular origins [5], there is increasing evidence that a central component is involved in MS patients [6]. Central fatigue represents the failure of the nervous system to drive the muscle to its maximal exertion [7]. Positron emission tomography studies demonstrated the existence of metabolic disorders involving the white matter and different structures in MS patients with fatigue compared to those in MS patients without fatigue [8,9].

Most studies on fatigue in MS used subjective self-report questionnaires [2,10]. However, it is possible to objectively appraise post-exercise fatigue associated with changes in motor cortex excitability, by recording the motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). In healthy subjects, several studies showed a major reduction of MEP amplitude for a period of several minutes following an exercise [11–14]. This post-exercise corticomotor depression (PECD) and the following recovery period have been assessed in several studies performed in MS patients [4,14,15]. Patients with MS showed a reduction of voluntary contraction strength and central activation drive during exercise, together with a more marked PECD [4,16].

Patients with MS are also known to have poor sleep quality and various sleep disturbances, such as insomnia, excessive daytime sleepiness, periodic leg movements, restless legs syndrome, abnormal sleep–wake regulation, sleep disordered breathing, narcolepsy and rapid eye movement sleep behavioral disorder [17]. Sleep disorders may likely contribute to the fatigue presented by these patients [18,19]. In this study, we examined whether an alteration of the restorative function of sleep

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could be involved in the particularly marked post-exercise fatigability characterizing these patients.

## 2. Methods

### 2.1. Patients and controls

From January 2012 to June 2013, we consecutively enrolled 30 patients who complained of fatigue from the cohort of MS patients followed in the Department of Neurology of Henri Mondor Hospital (Créteil, France). Inclusion criteria were: (i) definite diagnosis of MS according to the 2010 revised Mc Donald criteria [20]; (ii) age between 18 and 70 years; (iii) Expanded Disability Status Scale (EDSS) [21] score between 0 and 6; (iv) Fatigue Severity Scale (FSS) [22] score superior to 1; (v) absence of relapses for the last three months; and (vi) no therapeutic change during the last month. Exclusion criteria were: (i) EDSS higher than 6; (ii) clinical sleep apnea syndrome (apnea–hypopnea index (AHI) [23] ≥ 10/h of sleep); (iii) severe restless legs syndrome (International Restless Legs Syndrome Rating Scale (IRLS-RS) [24] score > 20); and (iv) benzodiazepine or antidepressant drug intake, including selective serotonin reuptake inhibitors. A polysomnography (PSG) was performed in all patients to identify sleep disorders.

Fifteen volunteers were recruited as healthy controls. Inclusion criteria were: (i) age between 18 and 70 years and (ii) absence of sleep complaint. Exclusion criteria were: (i) travel over more than four lag time 3 months before the procedure; (ii) night shift work; (iii) suspected sleep apnea syndrome; and (iv) benzodiazepine or antidepressant drug intake. The study received local IRB approval and all subjects gave written and informed consent.

### 2.2. Study design

Three sessions of MEP recordings before and after exercise were performed during the same day. The first session started at 9 am by measuring resting motor threshold (RMT) and MEP amplitude on the non-dominant hand (see below) at baseline (T0). Then, maximal voluntary contraction force (MVC) of thumb adduction was measured with a dynamometer, while the hand was maintained flat on a horizontal plane. The average MVC value was calculated from three trials. Then, exercise was performed by maintaining thumb adduction constant for 6 min at 25% of MVC against the dynamometer, under visual feedback and encouragement by the examiner. Four 6-min efforts were realized, separated by 1 min of rest between each. In preliminary experiments performed on healthy volunteers, this set of 4 efforts was able to produce PECD as revealed by MEP size reduction, which was maximal at 10 min after the exercise and lasted for more than 1 h. Therefore, MEP recordings were performed 10 and 60 min after exercise (T10, T60).

One objective of the study was to determine the respective influence of nap and rest on the recovery from PECD. To this end, we performed a second session of MEP recordings before and after exercise in the afternoon, at 2 pm, and we managed a 50-min period of nap or rest between T10 and T60 in each condition. To avoid bias due to daytime, the order of nap and rest was randomized between the morning and afternoon sessions in the series of patients and controls.

### 2.3. MEP recording

MEPs were recorded on the adductor pollicis (AP) muscle of the non-dominant hand, with one self-adhesive surface electrode placed at the internal palmar aspect of the thenar compartment and the reference at the proximal phalanx of the thumb. Single-pulse TMS was performed using a C-100 circular coil connected to a MagPro R30 magnetic stimulator (MagVenture, Farum, Denmark; distr. Mag2Health, France). The coil was placed at the vertex, tangentially to the skull, with the A/B face chosen for preferentially stimulating the motor cortex contralateral to MEP recordings. A special attention was paid to keep the placement of the coil during and between each session constant, benefiting from the hole in the center of the coil to place it always at the same place, indicated by a mark on a cap covering subject's head. MEPs were recorded using a Dantec Keypoint electromyogram (EMG) machine (Natus France, Paris, France) with a bandpass filter of 10–2,000 Hz. For all recordings, patients and subjects were seated comfortably in an armchair with auditory feedback of EMG activity to ensure good muscle relaxation.

First, the RMT was determined, as the minimum stimulation intensity required for obtaining a response of at least 50 μV half the time [25]. Then, all experiments were performed at an intensity of 120% of RMT with the AP muscle fully relaxed. At each time point (T0, T10, and T60) in each condition (nap and rest), the average MEP amplitude was calculated from a series of 8 trials of cortical stimulation (Fig. 1). The investigator who measured MEPs was blinded for the nap/rest condition (single-blind cross-over study). Finally, at T0 and T60, we recorded the maximal amplitude (Mmax) of the compound muscle action potential (CMAP) of the AP muscle to mixed median + ulnar nerve stimulation at the wrist (to take into account dual innervation of this thenar region by both the median and ulnar nerves).

### 2.4. Rest and nap

The 50-min period of nap or rest was performed under PSG recordings. In the rest condition, the subjects were allowed to sit and read or relax, but not to fall asleep. If any feature of sleepiness or micro-sleep was found in PSG, i.e. at least one epoch of stage 1 sleep, the session was excluded from the analysis. In the nap condition, the subjects were asked to fall asleep within 20 min, to obtain total sleep duration of at least 30 min. If the subject was not able to fall asleep within 20 min, the experiment was interrupted and the session was excluded from the analysis. In all cases, the rest or nap period was stopped after 50 min, possibly waking up the sleeping subjects.

PSG recordings included eight-channel electroencephalographic (EEG) montage, electro-oculogram (EOG), electrocardiogram (ECG), and submental and tibial EMGs, using surface electrodes and standard techniques. The sleep patterns were analyzed according to Rechstschaffen and Kales criteria revised by the American Academy of Sleep Medicine (AASM) [26]. Sleep stages and latencies were visually scored by a trained investigator.

Finally, all participants were asked to fill out the Epworth Sleepiness Scale (ESS) [27] to identify excessive diurnal sleepiness in eight situations. Quality of sleep was evaluated by administering the Pittsburgh Sleep Quality Index (PSQI) [28]. Fatigue was evaluated by the FSS [29]. Perceived exhaustion after exercise was evaluated by the Perceived Exhaustion Scale (PES) (Borg's scale) [30].

### 2.5. Statistical analyses

Since not all data passed the normality test, as assessed by the Kolmogorov–Smirnov test, nonparametric tests were used. First, baseline demographic data between MS patients and controls were compared using the Mann–Whitney test for quantitative variables (age, force, ESS, FSS, PSQI, and PES scores) and the Fisher test for qualitative variable (gender). Second, regarding the nap, sleep latency and duration were compared between MS patients and controls, also using the Mann–Whitney test.

Regarding MEP recordings, post-exercise MEP amplitudes at T10 and T60 were normalized to baseline MEP values (T0) to provide a T10/T0 MEP amplitude ratio to appraise the effect of exercise and a T60/T0 ratio to appraise the influence of nap or rest. For the MEP variables, (T0, T10/T0, and T60/T0), all comparisons between patients and controls were performed using the Mann–Whitney test, as well as for the T60/T0 CMAP amplitude ratio. In each group (patients or controls), the comparisons between two time points (T0 versus T10 or T60) or regarding MEP variables (T0, T10, T60, T10/T0, and T60/T0) between