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# Tremor in multiple sclerosis: The intriguing role of the cerebellum

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ABSTRACT

Tremor is frequently encountered in multiple sclerosis (MS) patients. However, its underlying pathophysiological mechanisms remain poorly understood. Our aim was to assess the potential role of the cerebellum and brainstem structures in the generation of MS tremor. We performed accelerometric (ACC) and electromyographic (EMG) assessment of tremor in 32 MS patients with manual clumsiness. In addition to clinical examination, patients underwent a neurophysiological exploration of the brainstem and cerebellar functions, which consisted of blink and masseter inhibitory reflexes, cerebello-thalamo-cortical inhibition (CTCi), and somatosensory evoked potentials. Tremor was clinically visible in 18 patients and absent in 14. Patients with visible tremor had more severe score of ataxia and clinical signs of cerebellar dysfunction, as well as a more reduced CTCi on neurophysiological investigation. However, ACC and EMG recordings confirmed the presence of a real rhythmic activity in only one patient. In most MS patients, the clinically visible tremor corresponded to a pseudorhythmic activity without coupling between ACC and EMG recordings. Cerebellar dysfunction may contribute to the occurrence of this pseudorhythmic activity mimicking tremor during posture and movement execution.



## 1. Introduction

Tremor is thought to occur in up to 75% of patients with multiple sclerosis (MS), including various subtypes of postural, kinetic, proximal, or distal tremor [1,2]. However, its exact prevalence remains unknown, since the functional scales used to assess MS patients do not evaluate tremor [1]. In the past fifteen years, only two studies have addressed this issue: tremor was found to occur in 25% and 58% of MS patients in an American and English cohorts, respectively [3,4].

The pathophysiology of MS tremor is difficult to appraise due to the multiplicity of central nervous system lesions encountered in MS. However, various experimental studies and clinical observations have highlighted the potential role of the cerebellum in the production of MS tremor. In this perspective, lesions affecting the inhibitory cerebellar projections to thalamo-cortical connections appear to have an important impact [1]. Lesions within the brainstem, notably those affecting the pons, could also be involved [5].

In the present study, we aimed to further characterize tremor in MS patients by means of neurophysiological assessment and to investigate the potential relationship between cerebellar or pontine dysfunction and tremor generation in this context.

## 2. Materials and methods

### 2.1. Patients

Among the different subtypes of upper limb MS tremor described by Alusi et al. [3], one subtype consisted of a fine, distal, postural tremor without kinetic component, barely clinically visible, and almost unnoticed by the majority of patients. This type of hand tremor, although subtle, could result in clumsiness, a common symptom in MS patients. Therefore, in order to include any MS patient who may have tremor, we screened over a three-month period all MS patients who presented with clumsiness in the Neurology Department of Henri Mondor hospital. Clumsiness was defined as the presence of functional difficulty to perform at least one of the daily life tasks listed in the Chedoke Arm and Hand Activity Inventory (CAHAI) [6]. Thirty-two consecutive MS patients were enrolled according to the following criteria: (i) the presence of clumsiness in one or both upper extremities according to CAHAI screening; (ii) a definite MS diagnosis as per the 2010 McDonald criteria [7]; (iii) age between 18 and 70 years; (iv) the absence of other neurological or psychiatric diseases; and (v) no contra-indication for transcranial magnetic stimulation, namely with no history of epilepsy

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or intracranial ferromagnetic implant [8]. The study was approved by the local Institution Review Board and all patients voluntarily gave their written informed consent prior to the study.

### 2.2. Clinical examination

The patients were interviewed and a standard neurological examination was carried out. The presence or absence of cerebellar signs was determined. The scores of the Extended Disability Status Scale (EDSS) [9] and Ataxia Clinical Scale (ACS) [3] were calculated. Patients with severe dysmetria or dysdiadochokinesia (ACS score > 2 for each item) were excluded from the study. Upper limb tremor was assessed on visual inspection at rest, posture and movement, according to a previously described procedure [3] and the classification of the Consensus Statement of the Movement Disorder Society [10]. Postural tremor was assessed by asking the patients to keep their forearms and arms outstretched forward ("oath position") or flexed with facing index fingers ("swordsman position"). Kinetic tremor was assessed during the finger-nose-finger test. The examiner (SSA) was trained to pay attention to the rhythmicity of the displayed movement. Tremor was classified as proximal, distal or both.

### 2.3. Neurophysiological examination

#### 2.3.1. Accelerometric and electromyographic (EMG) tremor recording

Two piezoresistive single-plane accelerometers (TREM0000, Neuroservices, Evry-Lisses, France) were attached, one to the dorsal aspect of the distal phalanx of the index finger, the other one to the anterior face of the shoulder. Surface EMG recordings were obtained from the first dorsal interosseous muscle (FDI) of the hand, flexor and extensor carpi radialis muscles of the forearm, and deltoid muscle of the shoulder, using pre-gelled disposable electrodes (Ref 9013S0242, Natus-Dantec, Skovlunde, Danemark) placed 2 cm apart over the muscle belly. Recordings were performed with a Keypoint EMG machine (Natus-Dantec), the signals were filtered (bandpass: 0.5–50 Hz for accelerometric recordings and 20 Hz–5 kHz for EMG recordings), amplified, and stored on a laboratory computer. An off-line Fast Fourier Transformation (FFT) analysis was performed on 10-second recordings using short sliding windows with the MATLAB software (MathWorks, Natick, MA, USA). The dominant peak of frequency was determined in the power spectrum for each recording and the coherence was studied between accelerometric recordings at the index finger and shoulder, and EMG recordings of the FDI and deltoid muscles. The presence of coherence was defined as at least two contiguous bins of 0.1 Hz on the coherence plot that rose above the 99% confidence limit for random coherence, at a frequency where there were corresponding peaks in the power spectra of accelerometric and EMG recordings [11]. The threshold value for significant tremor-related coherence was calculated as 0.5, as previously reported in other studies [12,13].

#### 2.3.2. Blink reflex (BR) recording and prepulse inhibition (PPI) measurement

Surface EMG was recorded at the orbicularis oculi muscle using pre-gelled disposable electrodes and a Phasis II machine (EsaOte, Florence, Italy). Electric stimulations were delivered to the supraorbital nerve at the supraorbital notch using a bipolar electrode (stimulation intensity: 25 mA, pulse duration: 0.2 ms). The filtered EMG signals (bandpass 20 Hz-5 kHz) were rectified online. Four trials were averaged. We only analyzed the latency of the ipsilateral R2 response, which reflects the activation of the bulbo-pontine trigeminal pathways. Results were compared to the normative data of our laboratory (upper limit of normal: 42 ms).

By using a paired pulse paradigm, we investigated the PPI of the BR following acoustic and somatosensory conditioning stimuli. The acoustic stimulus was a sound generated by discharging the circular coil of a magnetic stimulator (Magstim 200, Carmentshire, Wales, UK), hanging freely in the air at a one-meter distance from the patient's head [14]. The somatosensory stimulus was an electric shock, set at an intensity of 1.5 times the individual perception threshold, and delivered through a pair of ring electrodes placed at the index finger. The interstimuli interval (ISI) between the conditioning stimulus (acoustic or somatosensory) and the test stimulus was set at 100 ms. To calculate the percentage of inhibition (PPI), the area of the ipsilateral rectified R2 obtained in response to the paired stimulation was measured and compared to that obtained in response to test stimulation alone. Then, the calculated percentage of inhibition was compared to the normative data of our laboratory (lower limit of normal: 40%).

This test explores the control exerted by cholinergic neurons of the pedunculopontine nucleus on reticular structures, in response to the activation of medial or lateral lemniscal pathways [15–17].

#### 2.3.3. Masseter inhibitory reflex (MIR) recording

This test was performed as previously described [18]. Surface EMG was recorded at the masseter muscle using pre-gelled disposable electrodes and a Phasis II machine. The patient was instructed to clench the teeth in order to produce the maximum EMG activity in the masseter muscles and maintain it for several seconds with the aid of an auditory feedback. Then, electric stimuli were delivered to the mental nerve using a bipolar electrode (stimulation intensity: 25 mA, pulse duration: 0.2 ms). The area under the curve of SP2, which explores trigeminal afferents entering the pons and projecting to bulbar reticular formation [19], was measured and compared to pre-stimulus raw EMG activity of the same duration; hence we calculated the percentage of inhibition. Results were compared to the normative data of our laboratory (lower limit of normal: 40%).

#### 2.3.4. Cerebello-thalamo-cortical inhibition (CTCi) measurement

By means of a paired pulse paradigm of transcranial magnetic stimulation using a Bistim module (Magstim), we investigated the inhibition produced by a conditioning cerebellar stimulation on the motor evoked potentials (MEPs) obtained in response to the stimulation of the primary motor cortex, as previously described [20]. The MEPs were obtained (bandpass 20 Hz-5 kHz) from the FDI muscle at rest using pre-gelled disposable electrodes and a Phasis II machine. The test stimulation was performed using a figure-of-eight coil connected to a Magstim 200 magnetic stimulator. The handle of the coil was oriented 45° away from the interhemispheric fissure, perpendicular to the central sulcus to optimally deliver the current postero-anteriorly in the primary motor cortex contralaterally to the MEP recording side. Stimulus intensity was set at the stimulator output required to elicit MEPs of around 1 mV peak-to-peak amplitude. The conditioning cerebellar stimulation was performed ipsilaterally to the MEP recording side using a double-cone coil connected to a MagProX100 magnetic stimulator (MagVenture [Mag2Health], Farum, Denmark). The coil was placed over the cerebellar hemisphere, centered on the midpoint of the line joining the inion and the mastoid process [20]. Stimulus intensity was set at 80% of the maximal stimulator output. The ISI between the conditioning stimulus and the test stimulus was successively set at 5, 6, 7, and 8 ms. Four trials were averaged for each condition (test stimulation alone and paired stimulation at each ISI). The percentage of inhibition was calculated as the reduction in MEP size between the responses obtained to the conditioned stimulation to that obtained with the test stimulation alone. This inhibition reflects the activation of inhibitory efferent projections from the cerebellum to thalamo-cortical motor pathways. The maximal and mean percentage of inhibition was calculated, from all the recordings performed at the four different ISIs. Results were compared to the normative data of our laboratory (lower limit of normal: 50% for maximal inhibition and 30% for mean inhibition).

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