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The role of the prefrontal cortex in the development of muscle fatigue in Charcot–Marie–Tooth 1A patients

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Abstract

This study aimed at comparing both peripheral and central mechanisms of muscle fatigue between Charcot–Marie–Tooth 1A patients and healthy individuals during a fatiguing voluntary task by simultaneous electromyographic and electroencephalographic recordings. Six Charcot–Marie–Tooth 1A patients (3 females, 40 ± 11 years) and 6-matched healthy individuals performed four blocks of sub-maximal isometric knee extensions. At the beginning of the session and after each block, electrically-evoked maximal single-twitch, maximal voluntary contraction and surface-electromyography of the vastus lateralis muscle were measured. The movement-related-cortical potentials were averaged in early (block 1–2) and late (block 3–4) stages of fatigue. The effect of fatigue was demonstrated at peripheral level by the decline of maximal voluntary contraction, maximal twitch and surface electromyography amplitude and at central level by the larger amplitude of movement-related-cortical-potentials during late than early stage of fatiguing sub-maximal contractions. Charcot–Marie–Tooth 1A patients showed lower motor cortex activity during motor planning, with earlier onset and larger prefrontal cortex activity during the late stage of the fatiguing task than healthy controls. These data demonstrate the key role of the prefrontal cortex in the development of fatigue in Charcot–Marie–Tooth 1A patients, which may be activated as a compensatory mechanism for the low motor cortex activation, thus reflecting high awareness of movement complexity.

Keywords: Movement related cortical potentials (MRCPs); Electroencephalography (EEG); Surface electromyography (sEMG); Hereditary motor sensory neuropathy (HMSN); Action anticipation

1. Introduction

Charcot–Marie–Tooth (CMT) disease is among the most common hereditary peripheral neuropathies [1]. It affects up to 30 per 100,000 people in the world [2,3]. The most frequent form of CMT is CMT1A, which represents 50% of total cases [4], and is characterised by segmental demyelization, reduction of peripheral nerve conduction velocity and consequent axonal degeneration that impair functions of the distal extremities.

Fatigue is a common symptom in patients with peripheral nerve disorders [5,6] and it appears to be a major determinant of disability and functional impairment in daily life [7,8]. Since fatigue is a complex phenomenon including both psychological and physiological factors, a distinction has been made between 'experienced fatigue', defined as a sense of tiredness, lack of energy and motivation, and 'physiological fatigue', defined as the difficulty in

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initiating or sustaining voluntary activities [9]. Previous studies demonstrated that CMT patients have a significantly higher level of 'experienced fatigue' than healthy controls measured by means of questionnaires [7,8,10,11]. On the other hand, only a few studies examined 'physiological fatigue' using objective measurement techniques [11–13]. These studies showed that CMT patients, as well as healthy individuals, show a decline of force and surface EMG (sEMG) during both sub-maximal and maximal fatiguing contractions and in the 'central activation failure index', measured with percutaneous superimposed electrical stimulation of a contracting muscle. These observations suggest that fatigue in CMT 1A patients could be due to dysfunctions at the central nervous system level as there are no differences at the peripheral level.

One of the most suited techniques to study the brain dynamics associated with human action is the recording of the movement related cortical potential (MRCP), which is a widespread electroencephalographic measure of the brain activities preceding and accompanying voluntary movements. The MRCP has been related not only to physiological factors such as force production [14], but also to psychological factors such as motivation and attention [15]. The MRCP has been investigated in both pathological and healthy volunteers during several tasks [16], including also fatiguing contractions [11,17–20]. During fatiguing contractions, it has been demonstrated that MRCP amplitude in the cortical motor areas increases along with the perception of effort in healthy individuals [21] and to a greater extent in patients with chronic fatigue syndrome [20]. This observation has been recently confirmed and extended by data showing activity in the prefrontal cortex of healthy people experiencing more effort than those reporting less effort during a sub-maximal fatiguing task [22].

Nonetheless, there are no studies in the literature addressing the role of the central motor command in CMT 1A patients during a fatiguing task. Measuring a stronger effect of fatigue on the MRCPs in the prefrontal cortex of CMT 1A patients with respect to controls, with patterns of peripheral fatigue being the same in the two groups, would demonstrate an increase of central voluntary effort, which, in turn, may be one of the mechanisms associated to experienced fatigue in CMT 1A patients. Therefore, the aim of this study was to compare central and peripheral mechanisms of muscle fatigue between CMT 1A patients and healthy individuals during a voluntary sub-maximal fatiguing task. It was hypothesised that during the fatiguing task patients would show a decline in force and sEMG during both voluntary and electrically induced contractions of a similar magnitude with respect to the healthy controls. At central level, it was hypothesised that patients would show higher amplitude than the healthy controls in the MRCP components during the preparation, planning and execution of the isometric contractions in the prefrontal cortex.

2. Methods

2.1. Participants

Six patients with CMT1A (3 women, mean age 39.7 ± 10.8 years, mean body mass 72.5 ± 9.9 kg) and 6 healthy adults (3 women, mean age 38.0 ± 11.1 years, mean body mass 69.5 ± 11.0 kg) participated in this study. Patients' inclusion criteria were: (1) diagnosis of CMT 1A by genetic testing; (2) Barthel index >80 [23]; (3) age between 20 and 50 years; and (4) no clinical signs of cardiac or pulmonary disease. All patients were right-handed, with a mean Barthel index of 96.3 ± 3.8 (mean $\pm$ SD), a CMT neuropathy score [24] of 13.5 ± 3.18 and an MRC score [25] of 4.10 ± 0.88 in the knee extensors. The individuals in the control group were matched to CMT patients for age, gender and body mass. The study was approved by the Ethics Committee of the University of Rome "La Sapienza" and informed consent was obtained from all of the volunteers before beginning the experimental sessions.

2.2. Instrumentation

The participants were seated on a custom-made chair and stabilised with a waist belt with both hip and knee angles at 90° (Fig. 1A). The isometric torque of knee extensor muscles of the dominant limb was measured using a force transducer (Model 9203; Kistler, Winterthur, Switzerland). The signals from surface electromyography (sEMG) were recorded from the vastus lateralis muscle using adhesive linear arrays of 4 electrodes (LISiN, Torino, Italy) placed halfway between the innervation zone and distal tendon. The force signal was amplified (1000×) and displayed in front of each participant on an oscilloscope (TDS 220; Tectronix, Beaverton, Oregon). The sEMG signal was amplified (×1 K) filtered (band-pass 10–500 Hz) and sampled at 2048 Hz using a multichannel EMG amplifier (EMG USB2, OT Biolelettronica, Turin, Italy). The charge amplifier was connected to both the EMG amplifier and EEG recording systems for signal synchronization.

Electrical simulation was carried out using a high voltage stimulator (Digitimer DS7A/AH, Welwyn Garden City, UK). A cathode electrode (5×10 cm) was placed on the proximal third of the quadriceps femoris muscle and an anode electrode distally on the muscle–tendon junction as previously reported [22].

Continuous EEG was recorded using BrainVision™ system (Brain Products GmbH., Munich, Germany) with 64 active sensors (ActiCap™ Brain Products GmbH., Munich, Germany) mounted according to the 10–10 International system, which was initially referenced to the left mastoid. The EEG was digitised at 250 Hz, amplified (bandpass of 0.01–80 Hz including a 50 Hz notch filter) and stored for off-line averaging. Horizontal eye movements (electrooculogram, EOG) were monitored

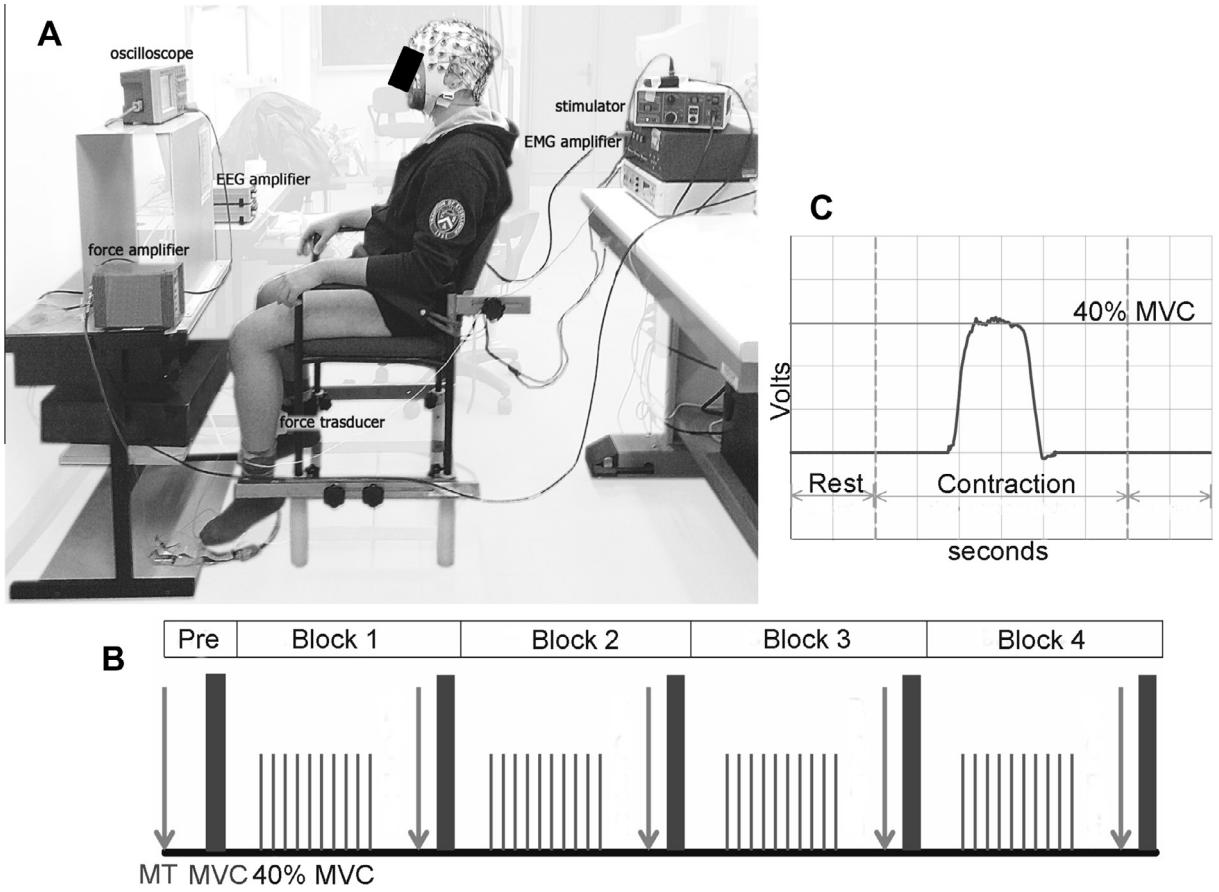

Fig. 1. (A) Experimental setting with the participant positioned during simultaneous EEG, EMG and dynamometric recordings. (B) Schematic representation of the experimental protocol. The "Pre" phase refers to the maximal twitch (MT) and maximal voluntary contraction (MVC) determined before each experimental session. Each block includes 60 self-paced isometric contractions at 40% MVC, followed by maximal twitch and MVC. (C) Real-time visual force feedback regarding the subjects' current force level produced by the leg displayed on the oscilloscope screen.

with bipolar recordings from electrodes at the left and right outer canthi. The blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to site Fp1.

2.3. Experimental procedure

At the beginning of the experimental sessions all of the participants were asked to fill in the fatigue severity scale (FSS) [26,27].

The participants carried out the protocol as shown in Fig. 1B. In the period prior to the fatiguing task, referred to as PRE section, maximal twitch and maximal voluntary contraction (MVC) were assessed in all of the participants, as previously reported [28]. Then, participants were asked to perform the fatiguing task, which consisted of 4 blocks of sub-maximal isometric contractions at 40% of PRE MVC. A 10-s window was displayed on the oscilloscope with a horizontal target line set at 40% of the MVC and two vertical cursors set to delimit a central 6-s window, as shown in Fig. 1C. Participants were instructed to voluntary choose, within the 6-s window, the starting time to exert force up to the target line, to maintain it for 2 s and to relax. A series of 60 contractions were performed within each block, with a 2 min interval between blocks. At the end of each block, a single electrical impulse was delivered with a pulse amplitude corresponding to that evoking maximal twitch in the PRE section, which was followed by one attempt of the MVC.

During the experimental sessions, participants were required to concentrate on the task performance and minimise movements and distractions as much as possible. Eye blinks and body adjustments were allowed during the inter-trial periods.

2.4. Data analysis

Mechanical and sEMG data were analysed off-line using OT Biolab software (OT Biolelettronica, Turin, Italy). The MVC torque was chosen as the mean value of a 1-s window around the peak torque and the twitch torque was chosen as the peak torque value. To quantify the EMG amplitude, expressed as the root mean square (RMS), a computer-aided analysis was performed over the 1-s epoch corresponding to the MVC. This procedure has been described in detail elsewhere [29,30].

EEG data were analysed off-line using BrainVision™ Analyzer 2.0.1 software (Brain Products GmbH, Munich,

Germany). Raw EEG data were visually inspected to identify and discard epochs contaminated with artifacts prior to the signal averaging. Trials with artifacts (e.g., blinks or gross movements) were automatically excluded from the averaging, whereas eye movement artifacts were corrected [31]. For each contraction, the onset of contraction was sent to the EEG recording system. The MRCPs were separately segmented and averaged into non-overlapping epochs of 2500 ms, measured 2000 ms before and 500 ms after the onset of contraction. For each data set, the grand average was calculated. The baseline was derived from the mean amplitude over the initial 300 ms of the averaged epochs. To further reduce high-frequency noise, the time group-averaged MRCPs were low-pass filtered at 15 Hz. The MRCP onset latency was calculated as the first deflection larger than twice the absolute value of the baseline mean. The typical negative MRCP components were calculated as follows. The Bereitschaftspotential (BP) was split into two sub-components derived by calculating the mean potential value from 1500 to 1000 ms (early BP) and from 1000 to 500 ms (late BP) before the beginning of the contraction. The negative slope (NS') was calculated as the mean potential value from 500 ms to 250 ms before the onset of the contraction. The motor potential (MP) was calculated as the mean amplitude from 250 ms to the onset of the contraction. On the basis of recent work showing also the presence of a positive activity in the prefrontal cortex (pP) concomitantly to the early BP and the NS' [22,32–34], this activity was measured in a 500 ms time window from 700 to 200 ms before the onset of the contraction. All of these parameters were selected for the statistical analysis because it is known that these reflect the distinct stages of preparation, planning and initiation of the movement [22,35]. The selection of the electrodes for each MRCP component was also based on the scalp topography, which allowed us to identify the electrodes where the signal was maximal.

To visualise the voltage topography of the MRCP components, spline interpolated 3-D maps were constructed using BESA 2000 software (MEGIS Software GmbH, Gräfelfing, Germany).

2.5. Statistics

All of the data were normally distributed in terms of skewness and kurtosis (all of the values <2). Statistical comparison of FSS scores, PRE MVC, PRE maximal twitch and PRE RMS between CMT1A patients and controls was carried out by two tailed Student's *t*-tests. Statistical comparisons of mechanical data (MVC and maximal twitch torques) and sEMG (RMS) between groups (patients and controls) and blocks (block1, block2, block 3 and block 4) were carried out by two-way ANOVA for repeated measure followed by Student's *t*-tests with Bonferroni correction.

For the EEG analysis, the 240 sub-maximal isometric contractions were averaged into 2 main blocks: early stages of fatigue (block 1–2) and late stages of fatigue (block 3–4). The following electrodes were selected for the statistical analysis of the MRCP based on the current literature [22,35]: for the MRCP onset latency Fp2 (which showed the earliest activity among the groups and blocks), for the BP component FC1 (roughly overlaying the contralateral supplementary motor area (SMA)), for the NS' Cz (roughly overlaying premotor areas (PMA)), and for the MP C1 (over the contralateral primary motor cortex (M1)); for the prefrontal positivity (pP) Fp2 over the prefrontal cortex. Statistical comparisons of each components between groups (patients and controls) and blocks (early and late) were carried out by two-way ANOVA for repeated measure, following by Tukey's HSD test.

Statistical significance levels were set at $P < 0.05$. Unless otherwise specified, data were presented as mean ± standard error of the mean.

3. Results

3.1. Fatigue severity scale (FSS)

Student's *t*-test showed a significantly higher FSS score in CMT 1A patients (42.67 ± 4.76) than in the control group (24.17 ± 9.33, $P < 0.05$).

3.2. Force and sEMG

ANOVA on torque of the knee extensor muscles in PRE MVC and PRE maximal twitch revealed that CMT 1A patients were weaker than the individuals of the control group (142.17 ± 72.60 vs 238.21 ± 54.53 N m, and 9.34 ± 9.39 vs 30.82 ± 19.57 N m, respectively, $P < 0.05$). Similarly, the ANOVA showed that PRE RMS of the sEMG in the vastus lateralis muscle was significantly lower in CMT1A patients than the individuals of the control group (0.13 ± 0.09 vs 0.35 ± 0.24 mV, respectively; $P < 0.05$).

Fig. 2 shows the maximal twitch, the MVC and the RMS recorded in the PRE section and after block 1, block 2, block 3 and block 4 in both CMT 1A patients and healthy controls. Data are reported as a percentage of the PRE condition. The two-way ANOVA showed no differences between groups ($P > 0.05$), but significant differences between blocks ($P < 0.05$). The post hoc analysis revealed that torque of electrically induced maximal twitch was significantly lower in block 3 ($67.56 \pm 18.96\%$) and block 4 ($71.47 \pm 16.34\%$) when compared to block 1 ($93.66 \pm 11.44\%$, $P < 0.01$) and block 2 ($86.52 \pm 14.08\%$, $P < 0.05$) (Fig. 2A). The MVC torque of the knee extensor muscles (Fig. 2B) and RMS of the vastus lateralis muscle (Fig. 2C) were significantly lower in block 2 ($84.34 \pm 13.83\%$ and $74.66 \pm 15.62\%$) block 3($82.82 \pm 12.10\%$ and $74.94 \pm 13.07\%$) and block 4 ($82.24 \pm 15.02\%$ and $71.53 \pm 11.41\%$) with respect to block 1($89.19 \pm 11.23\%$ and $84.52 \pm 17.78\%$, $P < 0.05$).

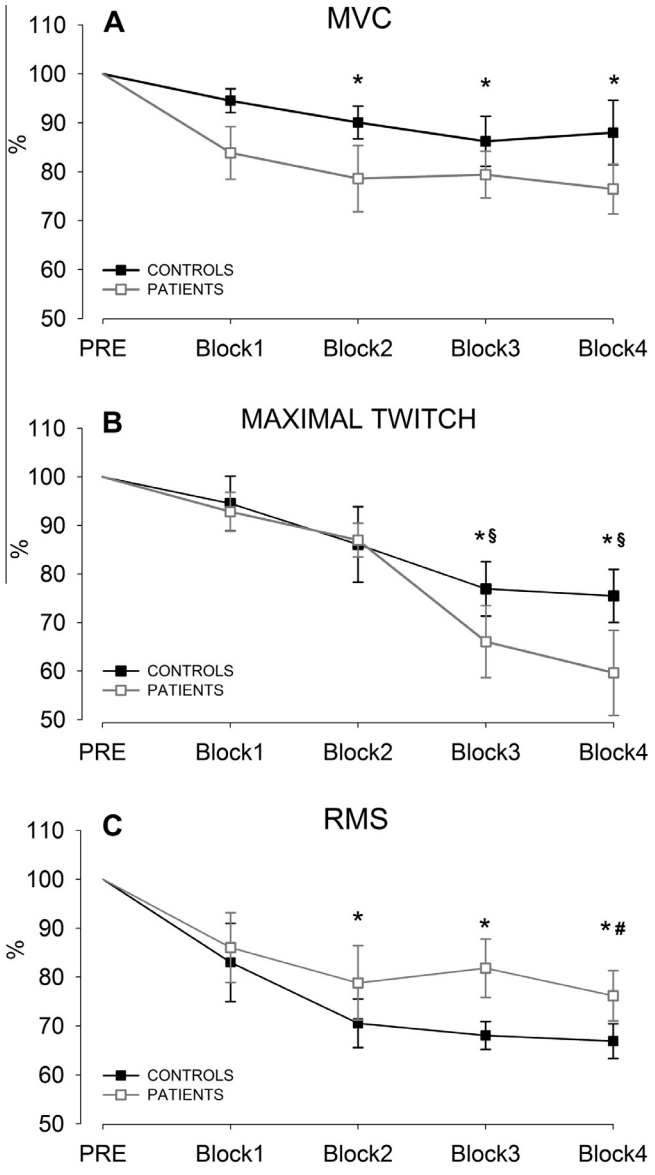

Fig. 2. (A) MVC, (B) maximal twitch and (C) RMS in PRE condition and after block1, block2, block3 and block4. No statistical differences between groups were obtained; *different from block1, § different from block2; # different from block 3 ($P<0.05$).

3.3. MRCP

3.3.1. Waveforms

Fig. 3 shows the grand averaged MRCP waveforms at the representative sites where the mean amplitude was maximal. The waveforms at frontopolar (Fp2), precentral (FC1) and central (Cz) sites for early (on the left panel) and late (on the right panel) stage of fatigue are superimposed in controls (black traces) and patients (red traces).

In both the early and late stages of fatigue, the waveforms show the typical gentle negativity (BP) on medial fronto-central sites (FC1) starting approximately 1500 ms before the movement onset. Afterwards, at around 500 ms the negativity became steeper (NS') and peaked concomitantly to the beginning of the contractions (MP). In addition, a consistent slow rising and early positivity (pP) was also present on the prefrontal scalp especially in patients.

Statistical analysis of the MRCP onset latency showed a significant main effect of group on Fp2 ($P < 0.05$), becoming much earlier in patients (-1645 ± 102 ms) than control (-982 ± 280 ms). The BP amplitude showed a main effect of block ($P < 0.05$) over precentral site (on FC1) with larger negativity at late (-2.60 ± 1 μV) than early (-1.96 ± 0.8 μV) stage of fatigue. The group effect and interaction were not significant. Analysis of the NS' revealed a significant main effect of block ($P < 0.05$) over the vertex (on Cz) with larger negativity at late (-7.29 ± 1.3 μV) than early (-5.02 ± 1 μV) stage. The group effect and the interaction were not significant. Analysis of the MP (on C1) showed a main effect of group ($P < 0.05$), with larger amplitude for control (-12.34 ± 2.2 μV) than patients (-6.11 ± 1.7 μV). No effect of block or any interaction was found. The pP amplitude showed a significant interaction on Fp2 ($P < 0.05$). Post-hoc analysis revealed a significant effect of fatigue in patients ($P < 0.05$) but not in controls. Further, the pP was larger in the patients group than controls in late stage only ($P < 0.05$). No main effect of block or group was found.

3.3.2. Topographical maps

Fig. 4 shows the topographical maps of grand averaged MRCP components for controls and patients during the early (4A) and the late (4B) stages of fatigue. The maps are displayed from left to the right for each MRCP component. It is worth of note that the pP is more pronounced in patients than control; especially in the early stage were control showed minimal pP, contrariwise the negativity over sensorimotor areas is larger in controls than patients. The first maps of Fig. 4A and B display the early BP and the pP, which focuses over prefrontal cortex and is larger in patient than control participants. The late BP distribution is more focused over precentral areas in control participants. The NS' showed a widespread medial distribution over the central areas, and the MP showed a focal positive distribution over the motor cortex slightly contralateral to the leg used for the contractions, which are larger in controls than patients.

4. Discussion

The major finding of the present study was that at central level the CMT 1A patients showed a higher activity in the prefrontal cortex than the healthy controls during the preparation and planning of sustained-isometric fatiguing contractions, together with a lower activity in both the premotor and motor cortex, whilst at peripheral level CMT 1A patients and healthy controls showed a similar decline in force and neural

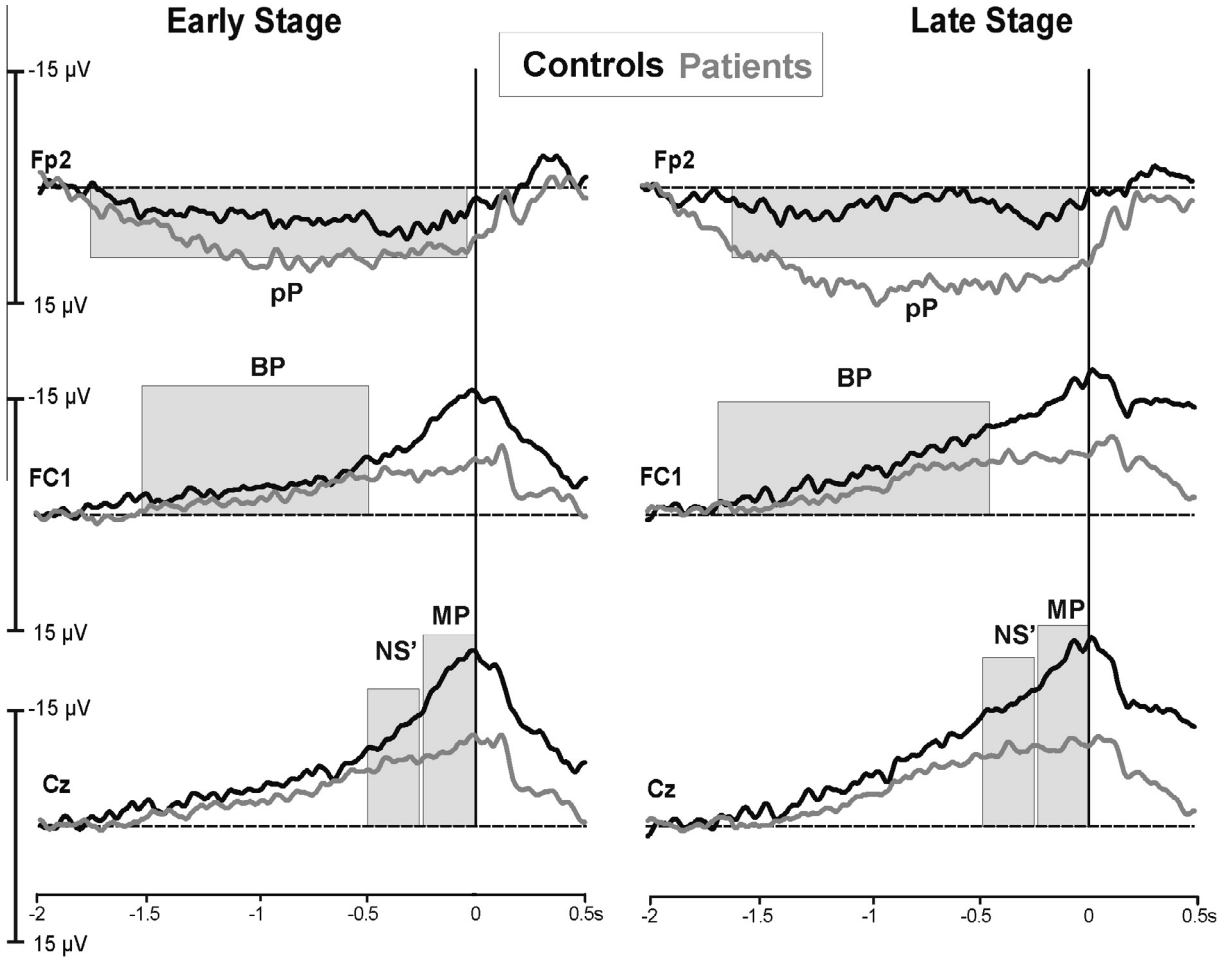

Fig. 3. Grand averaged MRCP waveforms at prontopolar (Fp2), precentral (FC1) and central (Cz) electrodes. Traces for the two groups are superimposed. The early stages of fatigue (block 1-2) are plotted on the left, while the late stages (block 3-4) are plotted on the right.

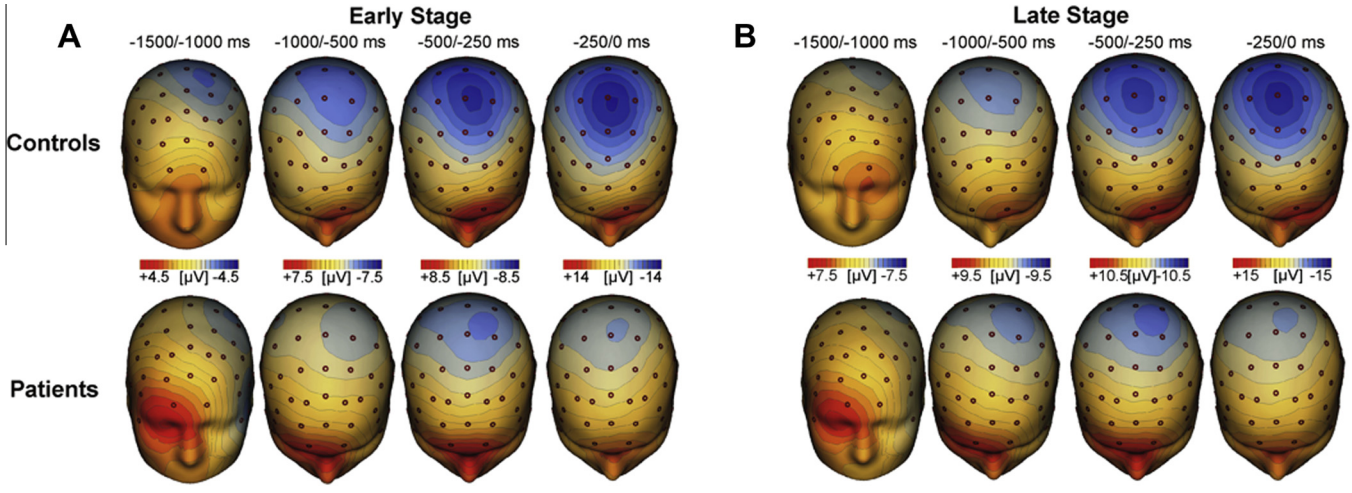

Fig. 4. Topographical scalp potential distribution for the grand average MRCPs across control (top panel) and patient (bottom panel) participants for early (A) and late (B) stages of fatiguing task. The maps are decomposed into four time windows corresponding to each component, aligned from the left to the right. The first maps display the early BP and the pP over PFC; the second maps show the late BP over PFC and precentral areas; the third maps show the NS' over the central areas; the last maps display the MP with a focal negative distribution over sensorimotor regions contralateral to the leg contraction.

activation throughout the fatiguing task. Therefore, since the prefrontal cortex is a cognitive associative area, its enhanced activity may be due to an increased cognitive effort to compensate for the low activity in the premotor and motor cortex, thus reflecting a high awareness of movement complexity and high demand in the cognitive control in relation to preparation and planning of the fatiguing task. Some of the physiological mechanisms underlying fatigue between patients with peripheral neuropathy and healthy individuals have been demonstrated with a novel experimental approach.

The higher score in FSS in patients than healthy controls, which could partially be ascribed to their experienced fatigue, is consistent with the finding of others studying fatigue by means of questionnaires [7,16]. Levels of force in the knee extensor muscles, as show by the PRE MVC and PRE maximal twitch torques, were lower in the CMT1A patients than in the individuals of the control group, which is consistent with previous results either from isometric dynamometry [12,13,36] or manual testing techniques [8]. Neural activation mirrored the trend of torque as RMS was significantly lower in CMT 1A patients than controls in the vastus lateralis muscle. Therefore CMT 1A patients are weaker and with a lower neuromuscular activation than the healthy individuals, which is in line with the physiopathological motor axon degeneration of the CMT disease [37,38].

The MRCPs' amplitude in the SMA and PMA (FC1and Cz) was larger in the late than the early stages of fatigue in both CMT 1A patients and healthy individuals, as revealed by the BP and NS' components. This is consistent with previous findings showing an increase in MRCPs along with the development of fatigue in healthy individuals [11,17,19,21,22]. In parallel, at peripheral level, both CMT 1A patients and healthy controls showed a significant reduction of the MVC, maximal twitch and RMS during the late stages of the fatiguing task in comparison to baseline, thus reflecting the effect of fatigue, which is also consistent with previous findings in both healthy and pathological subjects [11–13]. Overall, the present findings confirm that muscle fatigue may modulate the activity in the SMA and PMA [22]. According with Liu et al. [19], neurons located in the supplementary and/or association motor cortices may be activated to inform the output cells in the M1 about the intended motor action and to initiate the motor strategy. Hence, along with the development of muscle fatigue, the SMA may communicate the sensory feedback received from fatigued muscles [19] and/or from the muscle spindle firing [21] to the M1.

The analysis of the activity in M1 (the MP component) of CMT 1A patients was significantly lower than that of healthy individuals in both the early and late stages of fatigue. Previous studies demonstrated that the amplitude of the MRCPs in the motor area is related to the muscle force level and, therefore, to the number of high-threshold motor units [14,39]. In particular, Slobounov et al. [14] demonstrated a larger MP in healthy individuals when performing contractions of the index-finger flexors at 70% of MVC than muscle contractions at 30% of MVC, whereas Fang et al. [39] reported a higher MRCP in eccentric than concentric maximal contractions of the elbow flexor muscles. Consistently, the MVC and the maximal twitch torque of the knee extensor muscles in the PRE session were lower in CMT 1A patients than in individuals of the control group. Therefore, the low levels of both muscle force and MP amplitude in the CMT 1A patients may be the consequence of the reduced number of motor units.

The analysis of the MRCPs on Fp2 demonstrated a larger prefrontal positivity in CMT 1A patients than in the controls during the late stages of fatigue. A recent study [22] showed increasing of the prefrontal cortex activity associated with a high perception of fatigue during fatiguing contraction in healthy individuals. The authors speculated that the development of the sensation of fatigue may have led to a short-term reorganisation within the prefrontal-motor network [40]. Therefore, the positive prefrontal activity observed during the motor preparation phase in the present study could likely be explained by a high cognitive control counteracting the inability to recruit additional motor units to accomplish the task. Indeed, the prefrontal cortex plays a key role in monitoring the motor output, especially when visuo-motor integration and continuous motor adjustment are required, as in the present experimental paradigm. The prefrontal cortex performs executive control on temporal organization of action orchestrating activity in other neural structures. The prefrontal cortex is the highest stage of neural integration in the perception–action cycle which allow us successive interaction with the environment in the goals pursuit [41].

In this study, the selection of a homogeneous sample represents a very good point, but it also brings forth a limitation as far as the generalization of the results. The sample size is small, and therefore this study should be considered as a preliminary investigation. However, although the size of the sample is small, both the hyperactivity of prefrontal cortex and reduced activity in M1 were consistently observed in all of the patients. Further studies are required with a higher sample size, and inclusion of a non-fatigued CMT group. Moreover, this novel experimental approach has the potential to be extended to other groups of neurological patients.

In conclusion, this study demonstrated for the first time the key role of the prefrontal cortex activity in the development of fatigue in CMT 1A patients, which may relate to the awareness of the sensation of fatigue and the perception of effort. In CMT 1A patients there are less motor units available, lower activity in the M1 and sensorial problems than controls; in order to accomplish the task when the muscle fatigue increases, they pre-adapt the executive control for the upcoming action over-recruiting the prefrontal cortex during the preparation of the contraction, which may reflect a high awareness of movement complexity and high demand in the cognitive control. Thus, the peripheral fatigue occurring during this

task is associated with the central fatigue arising from high cognitive processing that is required to correctly perform the task and emotional factors such as levels of motivation and attention.

References

[1] Krajewski KM, Lewis RA, Fuerst DR, et al. Neurological dysfunction and axonal degeneration in Charcot–Marie–tooth disease type 1A. Brain 2000;123(Pt 7):1516–27.

[2] Banchs I, Casasnovas C, Albertì A, et al. Diagnosis of Charcot–Marie-Tooth disease. J Biomed Biotechnol 2009;1:1–10.

[3] Casasnovas C, Cano LM, Albertí A, Céspedes M, Rigo G. Charcot–Marie–Tooth disease. Foot Ankle Spec 2008;1:350–4.

[4] Bird T. Charcot-Marie-Tooth Hereditary Neuropathy Overview. Gene Reviews and Gene Tests: Medical Genetics Information 2010; <http://www.genetests.org>.

[5] Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004;363:978–88.

[6] Feasson L, Camdessanche JP, El Mandhi L, Calmels P, Millet GY. Fatigue and neuromuscular diseases. Ann Readapt Med Phys 2006;49(289–300):375–84.

[7] Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and Hmsn-i. J Neurol Neurosurg Psychiatry 2005;76:1406–9.

[8] Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BG, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. J Psychosom Res 2007;62:571–9.

[9] Zwarts MJ, Bleijenberg G, van Engelen BGM. Clinical neurophysiology of fatigue. Clin Neurophysiol 2008;119:2–10.

[10] Boentert M, Dziewas R, Heidbreder A, et al. Fatigue, reduced sleep quality and restless legs syndrome in Charcot–Marie–Tooth disease: a web-based survey. J Neurol 2010;257:646–52.

[11] Schillings ML, Kalkman JS, van der Werf SP, Bleijenberg G, van Engelen BG, Zwarts MJ. Central adaptations during repetitive contractions assessed by the readiness potential. Eur J Appl Physiol 2006;97:521–6.

[12] Lindeman E, Spaans F, Reulen JPH, Leffers P, Drukker J. Surface emg of proximal leg muscles in neuromuscular patients and in healthy controls. Relations to force and fatigue. J Electromyogr Kinesiol 1999;9:299–307.

[13] Menotti F, Bazzucchi I, Felici F, Damiani A, Gori MC, Macaluso A. Neuromuscular function after muscle fatigue in Charcot–Marie–Tooth type 1A patients. Muscle Nerve 2012;46:434–9.

[14] Slobounov S, Hallett M, Newell KM. Perceived effort in force production as reflected in motor-related cortical potentials. Clin Neurophysiol 2004;115:2391–402.

[15] Kristeva R. Study of the motor potential during voluntary recurrent movement. Electroencephalogr Clin Neurophysiol 1977;42:588.

[16] Schillings ML, Kalkman JS, Janssen HM, van Engelen BGM, Bleijenberg G, Zwarts MJ. Experienced and physiological fatigue in neuromuscular disorders. Clin Neurophysiol 2007;118:292–300.

[17] Dirnberger G, Duregger C, Trettler E, Lindinger G, Lang W. Fatigue in a simple repetitive motor task: a combined electrophysiological and neuropsychological study. Brain Res 2004;1028:26–30.

[18] Johnston J, Rearick M, Slobounov S. Movement-related cortical potentials associated with progressive muscle fatigue in a grasping task. Clin Neurophysiol 2001;112:68–77.

[19] Liu JZ, Zhang L, Yao B, Sahgal V, Yue GH. Fatigue induced by intermittent maximal voluntary contractions is associated with significant losses in muscle output but limited reductions in functional Mri-measured brain activation level. Brain Res 2005;1040:44–54.

[20] Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. Clin Neurophysiol 2004;115:2372–81.

[21] de Morree HM, Klein C, Marcora SM. Perception of effort reflects central motor command during movement execution. Psychophysiol 2012;49:1242–53.

[22] Berchicci M, Menotti F, Macaluso A, Di Russo F. The neurophysiology of central and peripheral fatigue during sub-maximal lower limb isometric contractions. Front Hum Neurosci 2013;7:135.

[23] Jacelon CS. The Barthel index and other indices of functional ability. Rehabil Nurs 1986;11:9–11.

[24] Shy ME, Blake J, Krajewski K, et al. Reliability and validity of the cmt neuropathy score as a measure of disability. Neurology 2005;64:1209–14.

[25] Medical-Research-Council. Aids to the Investigation of Peripheral Nerve Injuries. London: Her Majesty's Stationery Office 1976.

[26] Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res 2004;56:157–70.

[27] 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;46:1121–3.

[28] Macaluso A, De Vito G. Comparison between young and older women in explosive power output and its determinants during a single leg-press action after optimisation of load. Eur J Appl Physiol 2003;90:458–63.

[29] Macaluso A, Young A, Gibb KS, Rowe DA, De Vito G. Cycling as a novel approach to resistance training increases muscle strength, power, and selected functional abilities in healthy older women. J Appl Physiol 1985;2003(95):2544–53.

[30] Laudani L, Vannozzi G, Sawacha Z, della Croce U, Cereatti A, Macaluso A. Association between physical activity levels and physiological factors underlying mobility in young, middle-aged and older individuals living in a city district. PLoS One 2013;8:e74227.

[31] Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. Electroencephalogr Clin Neurophysiol 1983;55:468–84.

[32] Berchicci M, Lucci G, Pesce C, Spinelli D, Di Russo F. Prefrontal hyperactivity in older people during motor planning. Neuroimage 2012;62:1750–60.

[33] Bozzacchi C, Giusti MA, Pitzalis S, Spinelli D, Di Russo F. Awareness affects motor planning for goal-oriented actions. Biol Psychol 2012;89:503–14.

[34] Lucci G, Berchicci M, Spinelli D, Taddei F, Di Russo F. The effects of aging on conflict detection. PLoS One 2013;8:e56566.

[35] Shibasaki H, Hallett M. What is the bereitschaftspotential? Clin Neurophysiol 2006;117:2341–56.

[36] Lindeman E, Leffers P, Reulen J, Spaans F, Drukker J. Quadriceps strength and timed motor performances in myotonic dystrophy, Charcot–Marie-Tooth disease, and healthy subjects. Clin Rehabil 1998;12:127–35.

[37] del Porto LA, Nicholson GA, Ketheswaren P. Correlation between muscle atrophy on Mri and manual strength testing in hereditary neuropathies. J Clin Neurosci 2010;17:874–8.

[38] Lewis RA, Li J, Fuerst DR, Shy ME, Krajewski K. Motor unit number estimate of distal and proximal muscles in Charcot–Marie–Tooth disease. Muscle Nerve 2003;28:161–7.

[39] Fang Y, Siemionow V, Sahgal V, Xiong F, Yue GH. Distinct brain activation patterns for human maximal voluntary eccentric and concentric muscle actions. Brain Res 2004;1023:200–12.

[40] Desmurget M, Sirigu A. A parietal-premotor network for movement intention and motor awareness. Trends Cogn Sci 2009;13:411–9.

[41] Fuster MJ. Cognitive functions of the prefrontal cortex. In: Stuss DT, Knight RT, editors. Principles of Frontal Function. New York: Oxford University Press; 2013. p. 11–22.