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Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom

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ABSTRACT

More than half of patients who recover from COVID-19 experience fatigue. We studied fatigue using neuropsychological and neurophysiological investigations in post-COVID-19 patients and healthy subjects. Neuropsychological assessment included: Fatigue Severity Scale (FSS), Fatigue Rating Scale, Beck Depression Inventory, Apathy Evaluation Scale, cognitive tests, and computerized tasks. Neurophysiological examination was assessed before (PRE) and 2 min after (POST) a 1-min fatiguing isometric pinching task and included: maximum compound muscle action potential (CMAP) amplitude in first dorsal interosseous muscle (FDI) following ulnar nerve stimulation, resting motor threshold, motor evoked potential (MEP) amplitude and silent period (SP) duration in right FDI following transcranial magnetic stimulation of the left motor cortex. Maximum pinch strength was measured. Perceived exertion was assessed with the Borg-Category-Ratio scale.

Patients manifested fatigue, apathy, executive deficits, impaired cognitive control, and reduction in global cognition. Perceived exertion was higher in patients. CMAP and MEP were smaller in patients both PRE and POST. CMAP did not change in either group from PRE to POST, while MEP amplitudes declined in controls POST. SP duration did not differ between groups PRE, increased in controls but decreased in patients POST. Patients’ change of SP duration from PRE to POST was negatively correlated to FSS.

Abnormal SP shortening and lack of MEP depression concur with a reduction in post-exhaustion corticomotor inhibition, suggesting a possible GABAβ-ergic dysfunction. This impairment might be related to the neuropsychological alterations.

COVID-19-associated inflammation might lead to GABAergic impairment, possibly representing the basis of fatigue and explaining apathy and executive deficits.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CNS, Central Nervous System; CMAP, compound muscle action potential; FDI, first dorsal interosseous muscle; RMT, resting motor threshold; MEP, motor evoked potential; SP, silent period; CR100, Borg-C category-Ratio scale; TMS, Transcranial magnetic stimulation; FRS, Fatigue Rating Scale; CRP, C-reactive protein; IL-6, interleukine-6; HC, healthy control; FSS, Fatigue Severity Scale; BDI, Beck Depression Inventory; AES, Apathy Evaluation Scale; MoCA, Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; RT, reaction time; VT, vigilance task; STT, Stroop Interference Task; NV, Navon Task.

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1. Introduction

A large number of patients who recover from the acute phase of coronavirus disease 2019 (COVID-19), caused by the novel “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), manifest a plethora of long-lasting symptoms. Among them, a high proportion of individuals (53.1%) experience fatigue [1]. Fatigue is defined as a debilitating, non-transient feeling of physical and mental tiredness or exhaustion characterized by lack of energy, muscle weakness, slowed reactions, drowsiness, and deficit in concentration [2–4].

Prolonged fatigue after infections could be the consequence of biologic, behavioral, and environmental factors [5]. For decades, clinicians have referred to a controversial disorder historically defined as “post-viral fatigue syndrome” [6]. The main symptoms associated with this condition relate to muscle fatigability, aches, and pain. Nevertheless, the presence of central nervous system (CNS) abnormalities, including sleep disorders, depression, anxiety, and emotional lability, is also frequent [7]. Similar mechanisms can be envisioned for COVID-19, in which neurological, immunological and respiratory dysfunctions may finally cause fatigue [8]. Literature data converge on the assumption that fatigue is a multifaceted phenomenon with contributions of both cognitive and neuromuscular aspects.

Cognitive fatigue is defined as a decline in cognitive functioning, during sustained mental work [9]. The affected cognitive functions, overall named “cognitive control” [10], include vigilance, executive attention, working memory, judgment and long-term memory recall [9]. The feeling that people may experience during or after prolonged periods of cognitive and/or physical activity is called “mental fatigue”. Mental fatigue increases the perception of effort and worsens the performance during subsequent endurance exercise, despite it is not related to the capacity of the CNS to recruit muscles [11]. An imbalance between GABAergic and dopaminergic transmission has been postulated in “fatigue syndromes” [12–14]. Alterations in these neural circuits may partially account for both cognitive and mental fatigue [15].

Neuromuscular fatigue is an exercise-induced reduction in the ability of a muscle to generate force. Within certain limits, it is essential for protecting the body against damage due to excessive exercise. Neuromuscular fatigue is related with peripheral or central causes [16]. “Peripheral fatigue” depends on progressive failure of peripheral nervous system function, i.e., impaired impulse conduction along the nerve or at the neuromuscular junction, deterioration of muscle contractile properties [17,18]. “Central fatigue” is the progressive reduction in the ability of the CNS to maximally activate muscles and depends on spinal and supraspinal mechanisms. Supraspinal fatigue is, at least in part, characterized by reduced output from the motor cortex to the spinal motor neurons [19], which is due to reduced excitability of cortical motor neurons and to activation failure of structures upstream the primary motor cortex, e.g., premotor area and basal ganglia [20,21].

To date, no conclusive studies have characterized the presence of fatigue in patients with SARS-CoV-2-related neurological manifestations, who have recovered from COVID-19. Current literature lacks a neuropsychological characterization of this population and no neurophysiological studies have addressed whether fatigue is of central or peripheral origin. The present study aims to provide a comprehensive clinical, neurophysiological, and neuropsychological profile of fatigued patients suffering from neurological manifestations related to SARS-CoV-2, who recovered from the acute phase of COVID-19.

2. Materials and methods

2.1. Participants

Between April and May 2020, 12 patients (2 females; age 67 ± 9.6 years; 11 right-handers), who had recovered from the acute phase of COVID-19 (post-COVID-19 patients) and who complained of fatigue according to comprehensive medical assessment and anamnestic parameters, were enrolled in the study. Specifically, patients were asked to rate fatigue on a numeric-rating scale (Fatigue Rating Scale, FRS, 0: no fatigue; 10: extreme fatigue) [22].

All patients were hospitalized at the Department of Neurorehabilitation, Hospital of Vipiteno (Vipiteno-Sterzing, BZ, Italy), because of the development of neurological complications following SARS-CoV-2 infection (see Table 1).

All patients admitted to the ward of Neurorehabilitation met the World Health Organization criteria defining the state of recovery from COVID-19. Inclusion criteria were: a) almost total resolution of the neurological symptoms resulting from COVID-19, b) FRS score ≥ 6, arbitrarily, indicating an important level of fatigue c) absence of neurological disorders prior to COVID-19, d) absence of prior or current diagnosis of psychiatric, endocrine, metabolic or cardiopulmonary conditions related to fatigue, e) absence of dyspnoea or other long-lasting sequelae of interstitial COVID-19 pneumonia, f) absence of anaemia, g) no treatment with corticosteroids, antihistaminic, antihypertensive, diuretic, or hypnotic drugs at the time of study.

Table 1

| Patient | Sex | Age [years] | Education [years] | Diagnosis | Clinical features at admission in neurorehabilitation | Time from onset of COVID-19 [weeks] | IL-6 peak level [pg/ml] (<7) | CRP peak level [mg/l] (<0.8) |
|---------|-----|-------------|------------------|-----------|-----------------------------------------------------|-------------------------------------|-------------------------------|-------------------------------|
| 1       | M   | 65          | 8                | CINM      | Flaccid tetraparesis, muscle atrophy, areflexia; deep sensory disturbances in lower limbs | 11                                | 401                           | 18.7                          |
| 2       | M   | 60          | 11               | CINM      | Flaccid tetraparesis, muscle atrophy, areflexia | 10                                | 555                           | 15.9                          |
| 3       | M   | 62          | 17               | GIN       | Predominantly distal tetraparesis, hyporeflexia; anosmia | 11                                | 222                           | 17.1                          |
| 4       | M   | 71          | 8                | Encephalopathy | Severe cognitive impairment; dysphagia; anosmia | 9                                 | 635                           | 25.2                          |
| 5       | M   | 79          | 13               | GBS (AIDP); mild cognitive impairment | Predominantly distal tetraparesis, areflexia; mild superficial and deep sensory disturbances; deficit in attentional processes and impulse control; anosmia | 12                                | 214                           | 39.3                          |
| 6       | F   | 75          | 13               | Stroke (MCA) | Left hemiparesis; left hemisensory loss; left hemispatial neglect | 12                                | N/A                           | 22.4                          |
| 7       | M   | 48          | 8                | Myopathy  | Limb-girdle muscle atrophy and paresis; mild myalgia | 13                                | 6386                          | 20.1                          |
| 8       | M   | 56          | 11               | Myopathy  | Limb-girdle muscle atrophy and paresis; myalgia | 13                                | 2418                          | 32.4                          |
| 9       | M   | 70          | 17               | GBS (AMAN) | Predominantly distal tetraparesis, areflexia | 10                                | 688                           | 18.9                          |
| 10      | F   | 61          | 11               | Encephalopathy | Behavioral changes; primary insomnia, fatigue; anosmia | 12                                | 271                           | 25.7                          |
| 11      | M   | 77          | 8                | Myopathy  | Limb-girdle muscle atrophy and paresis; myalgia | 13                                | 1251                          | 30.4                          |
| 12      | M   | 80          | 17               | Encephalopathy | Severe cognitive impairment; anosmia | 12                                | 129                           | 23.0                          |

CINM, critical illness neuropathy and myopathy; CIN, critical illness neuropathy; GBS, Guillain-Barré syndrome; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; rMCA, right middle cerebral artery; CRP, C-reactive protein; IL-6, interleukin 6.
A common clinical feature characterizing our post-COVID-19 patients during the acute phase of the infection was the hyperinflammatory state, as demonstrated by both markedly elevated C-reactive protein (CRP) and interleukine-6 (IL-6) serum levels. The study was conducted at the end of the rehabilitation period. Twelve age- and sex-matched healthy subjects served as controls (4 females; age $64.3 \pm 10.5$ years, $p = 0.541$ vs. patients; all right-handers).

2.1.1. Ethic statement
The study was approved by the local Ethics Committee (“Comitato Etico del Comprensorio Sanitario di Bolzano”) (65–2020) and was in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki, 1967). All participants signed an informed written consent form for the use of their clinical data for scientific purposes.

2.2. Neuropsychological assessment

2.2.1. Fatigue assessment
Fatigue was assessed in patients and healthy controls (HC) with FRS (see above) and Fatigue Severity Scale (FSS). The FSS consists of 9 sentences related to the interference of fatigue with certain activities and rates its perceived severity on a 7-point scale ($1 = \text{strongly disagree}'; \ 7 = \text{strongly agree}').

2.2.2. Neuropsychiatric assessment
To assess the participants’ affective condition, we administered the Beck Depression Inventory (BDI) [23] and Apathy Evaluation Scale (AES) [24].

2.2.3. Cognitive assessment
All participants were tested in a laboratory setting, with constant artificial light and without auditory interference. Global cognition and executive functions were evaluated with the Montreal Cognitive Assessment (MoCA) [25,26] and the Frontal Assessment Battery (FAB) [27,28], respectively. For each test, we adjusted the total scores obtained from patients based on normative data validated for the Italian population.

2.2.4. Computerized attentive tasks
We assessed decrements in cognitive function arising during sustained mental work in a controlled laboratory experiment entailing computerized tasks designed for evaluating vigilance and executive attention. Participants underwent three computerized attentive tasks: Vigilance Task (VT), Stroop Interference Task (SIT), Navon Task (NT) [29–34]. For details, see the Fig. 1.

2.3. Neurophysiological evaluation
Neuromuscular fatigue is typically assessed via sustained isometric maximal voluntary contraction [16]. We evaluated various neurophysiological parameters 10 min before (PRE) and 2 min after (POST) a 1-min fatiguing motor task.

2.3.1. Motor task and perceived exertion
We used a pinching task of 1 min duration, in which COVID-19 patients and HC were asked to squeeze a dynamometer (Jamar, Patterson Medical, UK) with their right thumb and index finger as strongly as possible. Participants were verbally encouraged to provide maximum contractions during the whole minute. We a priori decided to evaluate the dominant right hand in all patients, also in the only ambidextrous but predominantly left-handed patient, who however preferred to perform the task with their right hand.

During the task, participants sat comfortably on a chair with their arms adducted and elbow flexed at 90°. Maximum pinch strength (kg) obtained during 1 min was considered.

At the end of the sustained pinching task, participants were asked to report their level of perceived exertion using the Borg Category Ratio (CR100) scale [35] This scale ranges from 0 to 100 (0 = “nothing at all”; 100 = “extremely strong”). The number 100 implies an extremely strong
perceptual intensity, i.e. the strongest effort and exertion a person has ever experienced.

2.3.2. Peripheral nerve stimulation to assess peripheral motor excitability

Peripheral fatigue can be assessed comparing pre-to-post exercise changes in compound muscle action potentials (CMAP or M-wave) evoked by supramaximal peripheral nerve stimulation in the relaxed muscle [36,37]. The CMAP expresses the neuromuscular propagation of action potentials along the sarcolemma [37,38] and indirectly indexes membrane excitability [39].

Here we stimulated the right ulnar nerve at the wrist using a bar electrode with an interelectrode distance of 3.5 cm. Stimuli of 0.2 ms duration were delivered with a constant current stimulator (Digitimer Ltd., Welwyn Garden City, UK), controlled by Signal 6 software. CMAPs were recorded from relaxed first dorsal interosseous muscle (FDI) on the dominant side with self-adhesive surface electrodes attached in a belly-tendon montage. The site of stimulation that produced the highest observable mechanical twitch and CMAP amplitude was determined. Stimuli were delivered in increments of 5–10 mA until obtaining a maximum response. The stimulation intensity was then increased to 130% to ensure supramaximal stimulation. CMAP baseline-to-peak amplitudes (corresponding to the negative component) were measured.

2.3.3. TMS to assess central motor excitability

Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) allows recording the amplitude of motor evoked potentials (MEP), a measure of cortico-spinal excitability [40]. After a fatigue-isometric exercise, MEPs evoked in the resting target muscle are depressed for about half an hour [41]. In contrast, immediately after the end of exercise, MEPs are, for 1–2 min, larger than before contraction, a phenomenon termed post-contraction facilitation [42]. The cortical silent period (SP), the electromyographic silence following MEPs evoked in the tonically contracted target muscle, is increased after a fatigue-isometric muscle effort likely with the physiological purpose to reduce corticomotor output and prevent excessive peripheral exhaustion [43–47].

Here we recorded MEP from right FDI while participants were at rest, with arms relaxed, elbows flexed at 90 degrees, forearm and supinated hand lying on an armrest. Focal TMS of the hand area of left M1 was performed with a high-power Magstim 200 (Magstim Co., Whitland, UK), which delivers monophasic pulses. We used a 7 cm figure-of-eight coil, held over the optimum scalp position to elicit motor responses in FDI, with the induced current flowing in a posterior-anterior direction [48]. Optimum coil position was defined as the site where TMS consistently resulted in the largest MEP [48]. Intensities were expressed as percentage of maximum stimulator output (% Mso). Surface electromyography signals were band-pass filtered (3–3000 Hz) and amplified with a Digitimer D440–4 amplifier (Digitimer Ltd., Welwyn Garden City, UK). Single sweeps were digitized (sampling rate 10 kHz) and recorded on computer for later analysis using a CED 1401 A/D converter and Signal 6 software (Cambridge Electronic Design, Cambridge, UK).

Resting motor threshold (RMT) was established, defined as the minimum stimulus intensity (in % Mso) that produced a liminal MEP (>50 μV in 5 of 10 trials) at rest [48]. Five MEPs were recorded from relaxed FDI following single TMS pulses (5 s inter-stimulus interval) at 120% RMT intensity. Peak-to-peak amplitude was measured and averaged off-line for each participant.

Some 30 s after evoking MEPs at rest, we investigated SP duration by evoking five MEPs at 140% RMT in right FDI during sustained isometric contraction (thump and index finger extended and pressed against each other) of self-estimated 50% maximum voluntary contraction. SP was defined as the time elapsing from the end of the MEP until the recurrence of voluntary tonic electromyographic activity [48]. In five single sweeps, SP was measured off-line, and the obtained values were averaged for each subject.

2.3.4. Sequence of tests

At baseline (PRE), we assessed CMAP amplitude, RMT, resting MEP amplitude, and SP in this order. Following the 1-min maximum pinching task (POST), we inquired Borg CR100 score, and again assessed CMAP amplitude, resting MEP amplitude, and SP in this order. POST/PRE ratios were calculated for CMAP amplitude, resting MEP amplitude, and SP.

2.4. Statistical analysis

Distribution of obtained data was assessed applying Kolmogorov-Smirnov testing. Not all data sets were normally distributed, and some data were ordinal, therefore we applied the more conservative non-parametric testing throughout. Data of patients were compared to those obtained in HC using Mann-Whitney-U tests. CMAP, MEP, and SP data were tested with repeated-measures-ANOVA using between-subjects factor GROUP (patients, controls) and within-subjects factor TIME (PRE, POST). Significant differences were followed up with Mann-Whitney-U test for independent variables (patients-controls), and with Wilcoxon test for paired dependent variables (PRE-/POST-data) within each subject group. Correlation analysis was performed with non-parametric Spearman-rho testing to account for the relatively small number of items. We analysed possible relations among 1) FRS, FSS, AES, BDI, and Borg CR100 score; 2) MoCA, FAB, and computerized tasks; and 3) MoCA and percent change in SP duration (POST/PRE %).

2.4.1. Data availability

The authors confirm that the data supporting the results of this study are saved at the Department of Neurorehabilitation, Hospital of Vipiteno (SABES-ASDAA), Vipiteno-Sterzing, Italy. They are available upon request from the corresponding author.

3. Results

All participants tolerated the procedures well and completed all parts of the study without difficulty. Three patients did not participate in the computerized tasks, FSS, BDI, and AES, because of their severe COVID-19-associated cognitive impairment.

Demographic and clinical data of patients are reported in Table 1. They did not differ significantly from HC in age and education (p > 0.3, each).

3.1. Neuropsychological assessment

3.1.1. Fatigue assessment

Both self-evaluation scales measuring perceived fatigue, FRS and FSS, revealed significantly higher scores in post-COVID-19 patients than in HC (p < 0.001 each).

3.1.2. Neuropsychiatric assessment

With regard to neuropsychiatric symptoms, both AES and BDI showed significantly higher scores in patients than in HC (p < 0.001 each).

3.1.3. Cognitive evaluation

With respect to global cognition, MoCA revealed a significantly poorer performance in patients compared to HC (p < 0.001). The group mean score in post-COVID-19 patients was only little above the cut-off score of 15.5/30 established as normative data in the Italian population [26]. Significantly smaller values in patients compared to HC were also obtained in the FAB (p < 0.001). Here the group mean score in post-COVID-19 patients was smaller than the cut-off score of 13.4/18 indicated in normative data of the Italian population [28].
Table 2
Comparison of COVID-19 patients and healthy controls. Values are group mean (standard deviation in brackets). Significant differences (Mann-Whitney-U tests) are indicated in bold.

| Test                                      | Patients       | Controls      | p-values |
|-------------------------------------------|----------------|---------------|----------|
| Fatigue Rating Scale (FRS)                | 8.1 (1.7)      | 0.7 (0.5)     | < 0.001  |
| Fatigue Severity Scale (FSS)              | 31.6 (10.6)    | 9.5 (0.5)     | < 0.001  |
| Apathy Evaluation Scale (AES)             | 39.3 (13.7)    | 18.9 (1.0)    | < 0.001  |
| Beck Depression Inventory (BDI)           | 3.8 (2.9)      | 0.0 (0.0)     | < 0.001  |
| Montreal Cognitive Assessment (MoCA)      | 17.8 (5.3)     | 26.8 (3.1)    | < 0.001  |
| Frontal Assessment Battery (FAB)          | 12.3 (2.3)     | 16.7 (1.2)    | < 0.001  |
| RT in Vigilance Task (VT)                 | 341.3 (86.3)   | 308.8 (44.2)  | 0.541    |
| Percentage of errors in VT               | 3.2 (1.0)      | 0.9 (0.2)     | < 0.001  |
| RT in Stroop Interference Task (SIT)      | 969.4 (152.1)  | 802.1         | 0.015    |
| Percentage of errors in SIT              | 4.6 (0.8)      | 1.2 (0.3)     | < 0.001  |
| RT in Navon Task (NT)                    | 1327.1         | 850.3         | 0.046    |
| Percentage of errors in NT               | 3.8 (1.2)      | 1.2 (0.3)     | < 0.001  |
| Force in pinch task (kg)                 | 5.6 (1.9)      | 7.3 (2.5)     | 0.101    |
| Exertion (CR100)                         | 75.8 (15.6)    | 54.6 (9.0)    | 0.001    |
| CMAP amplitude PRE (mV)                  | 9.4 (3.8)      | 15.7 (3.6)    | < 0.001  |
| CMAP amplitude POST (mV)                 | 9.2 (3.7)      | 15.4 (3.8)    | 0.092    |
| CMAP amplitude POST/PRE %                | 97.5 (41.1)    | 98.5 (10.5)   | 0.089    |
| RMT (% MSO)                              | 44.6 (5.6)     | 43.1 (4.8)    | 0.713    |
| MEP amplitude PRE (mV)                   | 0.8 (0.5)      | 1.9 (1.1)     | 0.005    |
| MEP amplitude POST (mV)                  | 0.7 (0.3)      | 1.3 (0.8)     | 0.017    |
| MEP amplitude POST/PRE %                 | 90.4 (28.1)    | 72.9 (20.2)   | 0.242    |
| SP duration PRE (ms)                     | 89.7 (32.3)    | 72.4 (25.5)   | 0.242    |
| SP duration POST (ms)                    | 72.0 (33.2)    | 93.5 (21.0)   | 0.052    |
| SP duration POST/PRE %                   | 78.5 (17.0)    | 138.8 (35.8)  | < 0.001  |

Abbreviations: RT, reaction time; CR100, Borg Category Ratio 100 scale; CMAP, compound muscle action potential; RMT, resting motor threshold; MEP, motor evoked potential; SP, silent period.

3.1.4. Computerized tasks
RTs were significantly longer in COVID-19 patients than in HC in both SIT (p < 0.015) and NT (p < 0.046), while in VT the difference did not reach statistical significance (Table 2).

Percentage of errors was significantly larger in patients than HC in all three computerized tasks (all p < 0.001).

Rts of all three computerized tasks correlated negatively to MoCA scores (VT: ρ = −0.710, p = 0.032; SIT: ρ = −0.728, p = 0.026; NT: ρ = −0.862, p = 0.003), while FAB scores correlated indirectly to RTs of the computerized tasks evaluating executive attention (SIT: ρ = −0.750, p = 0.020; NT: ρ = −0.700, p = 0.036).

3.2. Neurophysiological evaluation
3.2.1. Motor task and perceived exertion
Maximum group mean force in the pinching task tended to be higher in HC as compared to post-COVID-19 patients without reaching statistical significance (p = 0.101). The perceived exertion, however, expressed as Borg CR100 score, was significantly higher (range 50–100%, mean value 75.8) in post-COVID-19 patients compared to HC (range 40–70%, mean value 54.6) (p < 0.001).

3.2.2. Peripheral nerve stimulation to assess peripheral motor excitability
Repeated-measures ANOVA revealed a significant main effect on CMAP amplitude of GROUP (F1,22 = 15.776; p = 0.001; ηp2 = 0.418), but no significant effect of TIME (F1,22 = 0.827; p = 0.373; ηp2 = 0.036) nor of the interaction TIME × GROUP (F1,22 = 0.001; p = 0.974; ηp2 = 0.000). CMAP baseline-peak amplitude was significantly smaller in patients compared to HC in both PRE and POST conditions (Table 2), and did not change significantly from PRE to POST conditions in either group, i.e., CMAP was not modified by the fatiguing task (patients: p = 0.099; HC: p = 0.409). Thus, percentage change in CMAP amplitude (POST/PRE %) did not differ significantly between groups (Table 2).

3.2.3. TMS to assess central motor excitability
RMT did not differ significantly between COVID-19 patients and HC. Repeated-measures ANOVA revealed a significant main effect on MEP amplitude of GROUP (F1,22 = 8.722; p = 0.007; ηp2 = 0.284) and of TIME (F1,22 = 9.910; p = 0.005; ηp2 = 0.311), but no interaction TIME × GROUP (F1,22 = 2.827; p = 0.107; ηp2 = 0.114). Peak-to-peak amplitudes of resting MEP were significantly smaller in patients compared to HC in both PRE and POST conditions (Table 2). After the fatiguing exercise, the decline in MEP amplitude did not reach statistical significance in COVID-19 patients (p = 0.108) but was significant in HC (p = 0.003). Percentage change in MEP amplitude (POST/PRE %) did not differ significantly between groups (Table 2), likely because of the large variance of independent variables in either group.

Repeated-measures ANOVA revealed no significant main effect on SP duration of GROUP (F1,22 = 0.032; p = 0.860; ηp2 = 0.001) nor of TIME (F1,22 = 0.523; p = 0.477; ηp2 = 0.023), but revealed a notable significant interaction TIME × GROUP (F1,22 = 66.812; p = 0.000; ηp2 = 0.752). At baseline, SP duration did not differ significantly between COVID-19 patients and HC (Table 2). The fatiguing pinching task caused the expected significant SP shortening in HC (p = 0.002), while it led to significant shortening of the SP in COVID-19 patients (p = 0.004). Thus, percent change in SP duration (POST/PRE %) differed significantly between post-COVID-19 patients and HC (Table 2). SP POST/PRE % correlated negatively to FSS (p = −0.711, p = 0.032).

For comprehensive neurophysiological results overview see supplementary Table 1.

4. Discussion
The present study presents evidence for abnormal neuromuscular fatigue, cognitive fatigue, apathy, and executive dysfunction in a sample of post-COVID-19 patients.

Our data demonstrate a significant impact of SARS-CoV-2 infection on both feeling of fatigue and exhaustion. We administered the multidimensional FSS for a gross, non-specific evaluation of the feeling of fatigue in daily life, while the CR100 was adopted for evaluating the perceived effort immediately following a physical engagement. Finally, the FRS allowed us to obtain a quantification of the patients’ perceived fatigue at the moment of the clinical assessment. As a common denominator, the scores provided by these instruments express how people, subjectively, feel and perceive fatigue. In line with previous evidence [1,49], the results from these scales show that post-COVID-19 patients perceive physical exhaustion, and experience sense of tiredness and lack of energy affecting their daily living.

Among the twelve reported patients, eight presented the clinical sequela of acute neuromuscular affections (e.g., critical illness neuropathy and myopathy, Guillain-Barre syndrome, see Table 1) and therefore, they were prone to abnormal fatigability linked, at least in part, to the peripheral neuromuscular dysfunction [50]. However, they shared, with other patients, clear aspects of cognitive and motivational dysregulation.

COVID-19 impacts negatively on motivational aspects. AES scores were found to be higher in patients compared to HC. Apathy is a disorder associated with the disruption of the frontal-subcortical circuit involved in the generation of motivation [51].

BDI scores were significantly higher in post-COVID-19 patients than in HC. However, no patient had evidence of major depression, and only five reported BDI scores compatible with minor depression. Fatigue and apathy have been closely related to affective disorders, including mood disturbances [52,53]. Our data showed no correlations of fatigue to depressive symptoms, nor to apathy. In contrast, a direct correlation was found between apathy and depressive symptoms. All these symptoms could be observed in neurological disorders of different aetiologies, including neurodegenerative and inflammatory conditions [54–57]. It is...
also noteworthy that a significant proportion of patients suffering from psychiatric and neurological disorders exhibit a chronic, low-grade inflammation [58–61].

Our post-COVID-19 patients manifested a hyper-inflammatory state during the acute phase of COVID-19, as demonstrated by the marked elevation of their serum IL-6 levels. IL-6 relate hyper-inflammation is considered playing a role in COVID-19 pathogenesis [62] and has been associated with central and peripheral nervous system complications: altered mental status, psychosis, affective disorders, neurocognitive disorders (dementia-like), headache, encephalitis, myelitis, stroke, myopathy and/or myositis, Guillain-Barré like syndrome (and its variants) and mono- or multineuritis) [63–66].

Based on neuropsychological data, post-COVID-19 patients presented with cognitive deficits, particularly in the executive domain, in comparison with HC. MoCA scores were on average borderline compared to the Italian normative data cut-off [26], but they were lower than in the control group, concurring with a reduction in global cognition following COVID-19 with respect to HC. Moreover, three post-COVID-19 patients developed such a severe cognitive impairment that they were unable to participate in the computerized tests. In line with previous data [67], the abnormally low FAB scores we found in more than half of our post-COVID-19 patients clearly demonstrate evidence of a dysexecutive syndrome. The neuropsychological pattern we found, which is characterized by both dysexecutive syndrome and dysregulation of certain emotional-motivational aspects, often anticipates the development of dementia in patients suffering from neuroinflammatory and neurodegenerative diseases [68,69].

The coexistence of executive impairments and abnormal fatigue in post-COVID-19 patients is further supported by the performance in computerized tasks, which were implemented to evaluate the executive components of attention and the impact of fatigue on cognitive control [10]. The inferior performance in these tasks suggests diminished executive attention and cognitive control in post-COVID-19 patients compared to HC. Certainly, while a reduced executive attention could be the expression of the dysexecutive syndrome, the deficits in cognitive control relate to cognitive fatigue. Indeed, cognitive control tends to decrease when a subject undergoes a cognitively demanding task for a long time: this condition leads to increased distractibility, reducing the subject’s capabilities to monitor the performance [70–72]. The impairment in executive attention emerges from RTs in both SIT and NT, which were significantly longer in post COVID-19 patients than in HC. NT and SIT evaluate the ability to inhibit inappropriate or irrelevant responses, to monitor conflicts, and to evaluate stimuli or resource allocation [73]. RTs in VT did not differ significantly between patients and HC. However, a low accuracy of performance, i.e. the percentage of errors, in all computerized tasks, leads to conclude for a decrease of cognitive control, which probably does not only depend on the dysexecutive syndrome, but is also related to fatigue.

We explored neurophysiological correlates of physical fatigue by studying the effects of a fatiguing isometric maximal muscle contraction on excitability measures of peripheral nerve and motor cortex [16]. During a fatiguing task, the CNS processes the level of perceived exertion computerized tasks, which were implemented to evaluate the executive post-COVID-19 patients is further supported by the performance in and neurodegenerative diseases [68,69].

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Previous studies from animal models suggest that IL-6 hyper-inflammatory-induced state may decrease the density of functional GABAergic receptors and shifts the balance between synaptic inhibition and excitation [84]. This imbalance could be responsible for alterations of neurophysiological responses [85] and for the misprocessing of information that largely regulate emotionally salient information and cognitive functions [86,87]. Neuroinflammation may induce central GABAergic impairment, representing a common denominator for neuromotor impairments and fatigue, executive deficits, and apathy in post-COVID-19 patients (see Fig. 2).

It is conceivable that fatigue and stress-related exhaustion may be of major importance for the reduced cognitive performance in these patients [88].

This study has some limitations that need to be acknowledged. First, we did not follow-up our patients during a prolonged period and are unable to predict, whether or not the described disturbances tend to disappear over time or to become chronic. Further, we did not explore
Fatigue either in a sample of post COVID-19 patients who did not sustain neurological (especially neuromuscular) complications or in a control group of patients with similar neurological affections unrelated to COVID-19. This would have made our findings on fatigue and cognitive dysfunction related directly to COVID-19 after-effects. Further studies will broaden the initial knowledge resulting from the present study.

5. Conclusions

This is the first study linking neuropsychological with neurophysiological data in a sample of post-COVID-19 patients with neurological complication. We demonstrated the presence of central neuromotor and cognitive fatigue, apathy, and executive dysfunction. A cortical impairment of GABAergic neurotransmission could underlie these findings. It needs to be investigated whether such a mechanism may also be present in other post-viral chronic fatigue syndromes.

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Declaration of Competing Interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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