High-density EEG sleep correlates of cognitive and affective impairment at 12-month follow-up after acute COVID-19: A pilot study

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Highlights

- Sleep spindles may be a biomarker of psycho-affective symptoms in long COVID-19
- A decreased quality of life and post-traumatic stress symptoms are perceived
- Post-traumatic stress symptoms may crucially contribute to cognitive impairment

Abstract

Objective: To disentangle the pathophysiology of cognitive/affective impairment in Coronavirus Disease-2019 (COVID-19), we studied long-term cognitive and affective sequelae and sleep high-density electroencephalography (EEG) at 12-month follow-up in people with a previous hospital admission for acute COVID-19.

Methods: People discharged from an intensive care unit (ICU) and a sub-intensive ward (nonICU) between March and May 2020 were contacted between March and June 2021. Participants underwent cognitive, psychological and sleep assessment. High-density EEG recording was acquired during a nap. Slow and fast spindles density/amplitude/frequency and source reconstruction in brain gray matter were extracted. The relationship between psychological and cognitive findings was explored with Pearson correlation.

Results: We enrolled 33 participants (17 nonICU) and 12 controls. We observed a lower Physical Quality of Life index, higher post-traumatic stress disorder (PTSD) score, and a worse executive function performance in nonICU participants. Higher PTSD and Beck Depression Inventory scores correlated with lower executive performance. The same group showed a reorganization of spindle cortical generators.

Conclusion: Our results show executive and psycho-affective deficits and spindle alterations in COVID-19 survivors – especially in nonICU participants – after 12 months from discharge.

Significance: These findings may be suggestive of a crucial contribution of stress experienced during hospital admission on long-term cognitive functioning.

Keywords: Electroencephalography, nap, neuropsychological assessment, long COVID-19

1. Introduction

Since the beginning of the severe acute respiratory syndrome–related coronavirus-2 (SARS-CoV-2) pandemic, almost 400 million cases of infection have been reported world-wide, with 5.5 million associated deaths (https://covid19.who.int/). Beyond symptoms of the acute disease, which include respiratory tract involvement, gastrointestinal symptoms, anosmia and dysgeusia (Docherty et al, 2020; Petrilli et al, 2020) and neurological signs (Mao et al, 2020; Helms et al, 2020), a still not fully recognized syndrome persisting after 12 weeks from hospital discharge named *long* or *post* Coronavirus disease 2019 (COVID-19) has been described (Shah et al, 2021; Naldabian et al, 2021). Among long COVID-19 symptoms, fatigue, post-exertion malaise, and attention, working memory and executive dysfunctions are most commonly reported (Ziauddeen et al, 2021; Graham et al, 2021; Mao et al, 2020; Helms et al, 2020). COVID-19 follow-up studies have described in up to 40% of COVID-19 survivors concurrent affective disturbances, including depression, post-traumatic stress disorders, anxiety, and non-restorative sleep (Naldabian et al, 2021).

Consensus is still missing on the real clinical entity of long COVID-19. The Post-hospitalisation COVID-19 (PHOSP-COVID) study described 4 symptom clusters, with 3 clusters characterized by mental-health and physical impairments to varying degrees, but few or no cognitive difficulties and a fourth with minimal mental-health and physical impairments, but severe cognitive problems (Evans et al, 2021). Recently, the lack of a clear-cut correlation between cognitive complaints and performance, as well as a relation of cognitive performance with psychological distress, has further questioned the real nature of the reported cognitive component of long COVID-19 (Whiteside et al, 2022).

A biomarker of cognitive dysfunction may help in shedding light on these open issues. Neurophysiology may be a tool in this quest. We know that specific cognitive functions are encoded by neurophysiological signals detected by scalp electroencephalographic (EEG) recordings. Among these neural activities, sleep spindles – i.e., bursts of neural oscillatory activity generated in thalamocortical systems during stage 2 Non-rapid eye movement (NREM) sleep (Steriade, 2005) – are considered the scalp equivalent of hippocampal ripples, which encode memory and are markers of neural plasticity (LaFortune et al, 2014). Sleep spindles consist of

brief bursts ([0.5, 2] s) of rhythmic activity distinguished in slow spindles ([8, 12] Hz), with a prevalent frontal distribution, and fast spindles ([13, 15] Hz), with a more centro-parietal distribution. Fast and slow frequency types (Cox et al, 2017) display a different coupling to sleep slow oscillations (Mölle et al, 2011; Cox et al, 2014): in the temporal domain, fast spindles are time-locked to the depolarizing up-state of slow oscillations, whereas slow spindles to the up-to-down-state transition of the slow oscillations (Klinzing et al, 2016). These differences in coupling behavior may translate to different functional roles for fast and slow spindle types (Schabus et al, 2006; Cowan et al, 2020; Fernandez et al, 2020), with fast spindles apparently more involved in motor memory encoding (Tamaki et al, 2009) and slow spindles in declarative memory (Lustenberger et al, 2015). In fact, a definite role of these neurophysiological correlates is far from being agreed upon. Other metrics, such as spindle density, relate to verbal learning, visual attention, and verbal fluency performance in healthy middle-age and older individuals (LaFortune et al, 2014). An impairment of spindle density and localization is also reported in psycho-affective disturbances (Shao et al, 2021). In major depression, sleep spindles have an increased density and distribution over frontal and parietal cortices (Plante et al, 2013). In post-traumatic stress disorder (PTSD), fast sleep spindles apparently increase peak frequencies (Denis et al, 2021). The study of cortical generators of neural activity has further extended our knowledge of the neurophysiology of cognition and sleep. Several Magnetoencephalography (MEG) and EEG studies investigated the cortical distribution of spindles, suggesting that two distinct forms of spindles (i.e., slow and fast spindles) propagate to the cortex through different underlying neuronal circuits (Uramaki, 2008; Manshanden et al, 2002; Ishii et al, 2003; Dehghani et al, 2010) with different functional significance (Del Felice et al, 2013; Del Felice et al, 2014). Executive and memory functions, reportedly affected in long COVID-19, are processed in neural networks that encompass the prefrontal cortex, but also engage the parietal cortex (Rabinovi et al, 2015), anatomical areas that are part of the cortico-thalamo-cortical circuit of spindle cortical generators.

Our hypothesis is that features of sleep spindles may provide a biomarker of physiopathology of cognitive/affective symptoms in long COVID-19. The aim of this study is to investigate sleep spindle patterns

and the relation between spindles and cognitive/affective symptoms in people with previous COVID-19 infection at 12-month follow-up after hospital discharge.

2. Methods

2.1 Experimental protocol

People discharged from the Intensive Care Units (ICU) and medical wards (nonICU) of the Teaching Hospital in Padova from March 2020 to May 2020 were contacted by phone between March and June 2021 by a researcher presenting the study. We also enrolled age and sex-matched healthy controls (CTRL). Exclusion criteria were: age < 18 years, previous diagnosis of cognitive impairment, previous diagnosis of neurological disorder, on drugs altering sleep architecture (e.g., benzodiazepines) or with a known diagnosis of Obstructive Sleep Apneas (OSAS).

Participants were asked to wake up at 5 AM and to avoid the intake of stimulant substances (e.g., coffee, coke, tea). The experimental procedure was divided in two stages: 1) the neuropsychological assessment administered by a trained neuropsychologist and 2) the nap EEG recording. Nap sleep recording was performed at about 1.30 PM. The time of sleep was either at least 60 min of sleep or 1h and 30 min of time in bed, whichever came first.

The local Ethics Committee approved the study at Padova (4932/AO/20). It was conducted in compliance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and local regulatory requirements. Informed consent was obtained from all participants.

2.2 Neuropsychological assessment

2.2.1 *Neuropsychological evaluation*

Neuropsychological assessment was performed testing general and specific cognitive domains. Scores were adjusted for age, sex, and education (when applicable). The Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005; Santangelo et al, 2015) was performed as a measure of global cognitive assessment; a score up to 26 indicates poor overall cognitive functioning.

The Frontal Assessment Battery (FAB) (Dubois et al, 2000) and the Stroop task (Caffarra et al, 2002) were used to assess executive functioning. A FAB score up to 13.50 indicates poor executive functioning. For the Stroop task, errors interference (Stroop_e) and time interference (Stroop_i) were considered.

Digit Span forward (DigitFW) and backward (DigitBW) (Monaco et al, 2013) and Rey Auditory Verbal Learning test (Carlesimo et al, 1995; Caltagirone et al, 1995) (immediate memory – Rey_i ; delayed recall – Rey_d) were performed to assess short-term memory, working memory, and long-term memory. The Trail Making Test (version A – TMT-A – and B – TMT-B) (Giovagnoli et al, 1996) and Digit Symbol Modalities Test (Symbol) (Nocentini et al, 2006) assessed focused selective and divided attention.

2.2.2 *Psychological evaluation*

The Beck Depression Inventory (BDI) (Beck et al, 1996) was administered to assess depressive symptoms; the COVID-19 post-traumatic stress disorder (PTSD) scale to assess PTSD symptoms related to COVID-19 (Forte et al, 2020); a 12-item short-form health survey to assess the quality of life – i.e., physical and mental component summary scores, PCS-12 and MCS-12 (Pezzilli et al, 2006).

2.2.3 *Subjective sleep assessment*

The Epworth Sleepiness Scale (Vignatelli et al, 2003) was performed to test subjective sleepiness; Pittsburgh Sleep Quality Index (PSQI) (Curcio et al, 2013) was used to measure the major components of subjective sleep – i.e., quality, latency, duration, efficiency, disturbance, medication, daytime dysfunction.

Eventually, participants' handedness dominance in everyday activities was defined through Edinburgh Handedness Inventory (EHI) – i.e., a 10-item self-response inventory.

2.3 Nap EEG assessment

2.3.1. EEG recording

High-density EEG recordings were acquired at the Padova Neuroscience Center inside a dimly lit sound-attenuated and electrically shielded room using the Geodesic Sensor Net system with 256 electrodes (Electrical Geodesic, Inc, Eugene, OR). Electrode-skin impedances were maintained < 50kΩ. The recordings were sampled at 250 Hz, referenced to Cz. As a measure of electrooculogram activity, electrodes on the left and right eye canthus were considered (electrodes 10 and 248 referring to Sensor layout for 256-channel Hydrocel Geodesic Sensor Net). As a measure of muscular activity, electrodes in the area of the masseter were selected (electrodes 231, 249).

2.3.2. EEG pre-processing

EEG data were zero-phase-high-pass-filtered above 1 Hz through a 4th order Butterworth filter and then zero-phase-low-pass-filtered below 40 Hz through a 4th order Butterworth filter avoiding phase distortion. Channels in the cheeks and in the neck were discarded (204 channels left). Noisy channels were identified by visual inspection and interpolated using the nearest-neighbor spline method (average percentage of channels interpolated: 2%). Individual epochs containing non-stereotyped artifacts, eye movements were also identified by visual inspection and removed from further analysis (average percentage of epochs removed: 1%).

2.3.3. Sleep scoring and spindles detection

Sleep scoring (Wake; Non-Rapid-Eye-Movement - NREM Sleep, Stage 1 – N1; NREM Sleep, Stage 2 – N2; Slow-Wave Sleep – SWS; and Rapid-Eye-Movement – REM) was visually performed on 30-s EEG epochs from C3 in line with American Academy of Sleep Medicine (AASM) guidelines (Berry et al, 2012).

During NREM sleep, sleep spindles were automatically scored according to AASM guidelines on monopolar montage, considering frontal, central, and occipital leads (F3, C3, O1, F4, C4, O2), referenced to contralateral mastoids (93 as A1, 201 as A2). Then, frontal (F3 and F4) and central (C3 and C4) sleep spindles were automatically detected using an algorithm implemented by Wonambi 6.12 (https://wonambi-python.github.io/) (Lacourse et al, 2019) – Fig. 1a. This method detects spindles using a combination of 4 parameters related to sigma power (we refer the reader to (Lacourse et al, 2019) for more details). Based on the peak frequency, we divided sleep spindles into slow ([9–12] Hz) and fast spindles (]12–16] Hz) – Fig. 1b. We computed the density (i.e., number of spindles per 60-s epoch), duration (s), peak frequency (Hz), amplitude/topography (mV) of the spindles.

2.3.4. Spindles localization

Slow and fast spindles containing non-stereotyped artifacts or muscle activity were detected and excluded from the following analysis – Fig.1c-d. The remaining slow and fast spindles were averaged to obtain the two inputs for the source reconstruction – i.e., one time-series representing the averaging of slow spindles and one time-series representing the averaging of fast spindles for each participant – Fig. 1c. We applied the LORETA algorithm implemented in Cartool [cartoolcommunity.unige.ch] to compute the source reconstruction of the averaged spindles (Del Felice et al, 2014) taking into account the participant's age to calibrate the skull conductivity (Michel et al, 2019) – Fig. 1d. The method restricts the solution space to the gray matter of the brain. The gray matter was then parcellated using the 83 cortical regions of the Desikan–Killiany (DK) atlas (Desikan et al, 2006). The dipoles in each region-of-interest (ROI) were represented with one unique time-series by applying a singular-value decomposition (Rubega et al, 2018; Glomb et al, 2020a, 2020b; Pascucci et al, 2020). The amplitude at the onset of the source-waveforms representing the sleep spindles were extracted and compared between the three groups (i.e., CTRL, nonICU participants and ICU participants).

2.4. Statistical analyses

After testing data distribution with a Shapiro-Wilks normality test, either Kruskal-Wallis test or ANOVA were performed among the three groups (CTRL, ICU, nonICU). Subsequently, based on the test results, either a two-sided Wilcoxon rank sum test or a two-sample t-test was performed on: 1) cognitive and psychological tests scores; 2) slow and fast spindle density/frequency/amplitude; 3) spindle onset amplitude values for each ROI; comparing CTRL vs ICU, CTRL vs nonICU, and ICU vs nonICU to test for significant differences. Considering the sample size and the exploratory nature of the study, no corrections for multiple comparisons were performed in hypothesis testing. We assessed the relationship between psychological and cognitive results through Pearson correlation coefficient (r). r measured the linear correlation between each combination of neuropsychological tests scores ($r \in [-1, 1]$). Then, multiple linear regression modeled the linear relationship between the explanatory variables and response variables. We used as explanatory variables the psychological scores and as response variables the cognitive ones and vice versa.

3. Results

Ninety-one COVID-19 survivors were contacted. Twelve were unreachable, 17 could not participate because of severe disabling long COVID-19 physical symptoms (mainly shortness of breath, myalgia and fatigue), 17 refused to participate because of fear of contagion and safety concerns, 3 could not be recruited for sleep disorder comorbidities (i.e., insomnia, obstructive sleep apnoea syndrome) or for taking medications that alter sleep architecture (e.g., benzodiazepines, antidepressants), and 9 dropped out. Eventually, 33 COVID-19 participants (27% female (F), F age interval: [50, 69] y, male (M) age interval: [49, 80] y) and 12 age and sex-matched control participants (33% F, F: [50, 63] y, M: [49, 76] y) were enrolled. The COVID-19 cohort consisted of Intensive Care Unit (ICU) discharged participants (N=16, 25% F, F: [64, 69] y, M: [55, 80] y) and participants (nonICU) admitted to a sub intensive medical ward (N=17, 29% F, F: [53, 62] y, M: [50, 78] y). Among these participants, 7 reported persistence fatigue (4 nonICU).

All participants admitted to ICU suffered from Acute Respiratory Distress Syndrome (ARDS), requiring invasive ventilation and in most cases also sedation and curarization. This was never the case in the medical ward (i.e., nonICU participants).

3.1. Neuropsychological assessment

COVID-19 survivors reported worse Physical Quality of Life compared to controls (CTRL) ($median_{CTRL}$ = 53.07 vs $median_{ICU}$ = 46.19 and $median_{nonICU}$ = 43.33, $p_{value} < 0.04$) – Fig. 2a. Post-Traumatic Stress Disorder – Fig. 2b (CTRL vs nonICU: $p_{value} = 0.06$) – and Beck Depression Inventory – Fig. 2c – scores showed a decreasing trend from the nonICU group, ICU group and CTRL. The cognitive assessment revealed a trend towards worse performance in executive functions in COVID-19 survivors, in particular in nonICU in the Trail Making Test (TMT-B, CTRL vs nonICU: $p_{value} = 0.04$ – Fig. 2d; TMT-B-A, CTRL vs nonICU: $p_{value} = 0.08$ – Fig. 2e).

Pearson correlation coefficient (r) reports a statistically significant linear correlation in the nonICU participants between:

- PTSD and Digit BW ($r = -0.6$, $p_{value} = 0.0033$), TMT-B ($r = 0.59$, $p_{value} = 0.01185$), TMT B-A ($r = 0.56$, $p_{value} = 0.01185$) – i.e., a higher likelihood of PTSD is correlated to a worse performance in Digit BW (i.e., lower number of digits that the subject repeated correctly) and TMT-B (i.e., more time needed to complete the task and higher number of errors),
- BDI and MoCA ($r = -0.55$, $p_{value} = 0.02$) – i.e., a higher score in BDI (i.e., higher risk of depression) is correlated to a lower score in MoCA (i.e., higher risk of cognitive impairment), Fig. 2f

In ICU participants, a negative linear correlation emerged between PTSD and PCS-12 ($r = -0.53$, $p_{value} = 0.03467$) – i.e., higher likelihood of PTSD is correlated to a worse perception of physical health, Fig. 2g.

Multiple linear regression analyses highlighted that nonICU lower scores in cognitive tasks evaluating executive function and working memory can be predicted by psychological scores (i.e., PTSD and BDI) – Tab. 1.

See Supplementary Material (*Supplementary_material_neuropsy.pdf*) for all the neuropsychological test scores.

3.2. Nap EEG assessment

Two ICU and seven nonICU participants did not fall asleep during the recording. Results report EEG data from 14/16 (88%) ICU, 10/17 (59%) nonICU and 12/12 (100%) CTRL.

Slow and fast spindle density did not differ among the three groups. Slow spindles frequency was decreased in ICU participants compared to controls ($p_{value} = 0.0477$) – Fig. 3i. Descriptively, in CTRL, slow and fast spindles showed different EEG topographical distributions – Fig. 3 – with slow spindles more frontal and fast spindles more centro-parietal. In COVID-19 survivors the physiological sleep spindles distribution is not clear-cut. Slow spindles shift to more posterior regions (central in nonICU – Fig. 3b – and temporal in ICU participants – Fig. 3c); fast spindles tend to become more anterior in ICU participants – Fig. 3f. In CTRL, slow spindle onsets were generated in the frontal cortices – Fig. 4a – and fast spindle onsets in the central brain regions – Fig. 4d. In COVID-19 survivors, slow spindle onsets shifted to central-temporal regions in nonICU – Fig. 4b – and ICU participants – Fig. 4c –, whereas fast spindle onset shifted to tempo-parietal brain regions in nonICU – Fig. 4e – and to frontal brain regions in ICU – Fig. 4f. Indeed, we observed statistically significant differences in slow and fast EEG source-waveforms spindle amplitude onset among the three groups. All statistically significant amplitude differences are reported in Fig. 4g, h, i, l, m, n. The differences in fast spindle sources between CTRL and nonICU is worthy of note – Fig. 4m. Frontal and tempo-parietal brain regions have higher amplitude in nonICU than in CTRL at fast spindle onset.

See Supplementary Material (*Supplementary_material_EEGspindles.pdf*) for the EEG results not discussed in the manuscript because of the lack of statistically significant differences among groups.

4. Discussion

We report the presence of executive performance impairments, reduced physical quality of life and symptoms of PTSD at 12 months after discharge in people previously admitted to hospital for COVID-19 infection. The neurophysiological correlate of these findings – for the first time, investigated through high-density EEG – is a modification of cortical generators of sleep spindles, with generators of slow spindles shifting towards more posterior cortical regions and fast spindle generators shifting anteriorly in COVID-19 participants compared to CTRL. These phenomena are more evident in people discharged from medical wards than to ICUs. The identification of neurophysiological abnormalities – i.e., sleep spindles cortical generators – may provide additional information on the still non fully elucidated clinical picture of long COVID-19.

Reports on effects on cognition after COVID-19 infection emerged in the early days of the pandemic, although a clear-cut definition of these symptoms has not yet been defined, with the umbrella definition of *brain fog*. In fact, the PHOSP-COVID study identified only a fraction of long COVID-19 survivors with clinically relevant cognitive problems (Evans et al, 2021). The systematic inclusion of neurophysiological biomarkers in our dataset aimed at providing quantifiable data to support this research. The combination of comprehensive neuropsychological and psycho-affective testing and advanced EEG analysis aims at disentangling the physiopathology of cognitive impairment in long COVID-19.

Sleep spindles are a robust biomarker of cognition. They have widely been studied as the scalp biomarkers of hippocampal ripples encoding memory (Cairney et al, 2018), with a hierarchical frequency nestling paced by the de- and hyper-polarizing slow oscillations (Staresina et al, 2015). Slow oscillation dynamics and sleep spindle density, topography and distribution of cortical generators have largely been related to visuo-motor (mainly fast spindles) and verbal (mainly slow spindles) memory formation (Debarnot et al, 2011). In mild cognitive impairment, sleep spindles are decreased (D'Atri et al, 2021; D'Rozario et al, 2020) or shorter (Lam et al, 2021); in memory impairment in temporal epilepsies, cortical source generators of sleep spindles shift their physiological location (Del Felice et al, 2013). Our focus on these biomarkers is based on specific changes

described also in depression and PTSD. In major depression, sleep spindles increase density and shift toward frontal and parietal cortices (Plante et al, 2013; Ferrarelli et al, 2019). In PTSD, fast sleep spindles increase peak frequencies (Denis et al, 2021). Indeed, we observed a shift of fast spindles toward parietal regions in people discharged from non-ICU and towards anterior areas in people discharged from ICU. The shift of generators has already been described in association with affective, i.e., major depression, PTSD, schizophrenia among others (Wang et al, 2020; Ferrarelli et al, 2019; Plante et al, 2013, De Maertelaer et al, 1987), and neuropsychological abnormalities, i.e., memory (Del Felice et al., 2013-2015).

We observed a lower physical quality of life in COVID-19 survivors, suggesting the perception of physical symptoms persistence (Alkodaymi et al, 2022) even after 12 months from acute infection resolution. Indeed, long COVID-19 is defined as the persistence of at least a symptom for more than 12 weeks from acute infection, but long-term follow-up data are just starting to be reported, suggesting a multifaceted and more prolonged picture. PTSD scores were significantly higher in nonICU admitted participants. This finding is more striking considering the growing wealth of evidence of long-term harmful effects after ICU discharge, termed post-intensive care syndrome (PICS). PICS encompasses multi-domain dysfunctions ranging from reduced physical performance, cognitive impairments, and failed social construction (Needham et al, 2012; Hanifa et al, 2018; Torres et al, 2017). These symptoms persist for at least three months (Hanifa et al, 2018) and up to 5 years (Torres et al, 2017) from discharge. In fact, clinical practice suggests that this counterintuitive finding may be based on the higher levels of anxiety and stress experienced by conscious patients, especially during non-invasive high flow ventilation. Emerging data demonstrated that up to 30% of COVID-19 survivors experience PTSD (Greene et al, 2022): the later the diagnosis and appropriate care is put in place, the worse the outcome and prognosis. Lastly, we observed higher depression scores in our nonICU participants, although this finding remains only a non-significant trend: this subclinical symptom may well be considered a reactive phenomenon.

We clinically ruled out the presence of hypoxic encephalopathy among our participants: all of them had a negative neurological examination and were fully independent. In fact, hypoxic encephalopathy may have

only occurred in severe ARDS not adequately supported in ICU, with catastrophic neurological sequelae. In fact, the role of microvascular bleedings and endothelial dysfunction has been widely reported in COVID-19 infections and is at the moment of this writing considered the leading cause of cerebral involvement. Whereas cases of hypoxic encephalopathy have been described, these are extremely rare and possibly related to a therapeutic failure (Popescu C, 2021).

Our data report an involvement of executive functions more evident in nonICU participants than ICU. On the one hand, memory impairment – a predominant symptom in the so-called brain fog clinical picture – appears at a subclinical level in our cohort. A possible explanation may be the high prevalence of PTSD: PTSD is characterized, among other symptoms, by poor cognitive flexibility, processing speed, controlled and sustained attention, higher response inhibition, and recall memory (Schultebraucks et al, 2022), all traits observed in our cohort. On the other hand, processing speed and executive/working memory are the most commonly impaired domains in depression (Varghese et al, 2022).

In contrast to previous findings, we did not observe a relation between disease severity and worse cognitive performance (Cristillo et al, 2022). Although our definition of disease severity was based on the admission ward (ICU vs medical wards) and we did not factor in inflammatory markers or other biochemical indexes, we observed higher depression and PTSD scores in people discharged from medical wards. We would have expected a combined effect of ICU admission and long COVID-19 symptoms. Indeed, in our cohort the worst cognitive and psycho-affective performance has been observed in nonICU admitted participants, suggesting a long-term persistence of non-physical symptoms. Our finding has inconsistently been replicated in previous studies on neuropsychological and neurological sequelae in long COVID-19 (Premraj et al, 2022), with a reportedly higher association of fatigue, anxiety, depression in ICU admitted persons than non-ICU participants. These data rarely refer to follow-ups longer than 6 months, with sporadic correlation of psycho-affective symptoms with cognitive impairment. Our findings suggest a strong effect of stress experienced during admission, a well-known determinant of worse cognitive performance.

We may speculate on a correlation among psycho-affective and neuropsychological impairments and sleep spindle generators by inferring from correlation between these deficits. We observed lower memory and executive function performance in subjects with higher PTSD scores; spindle generators shift may signal impaired neural circuitries regulating these functions. While we have no clear hypothesis on the direction of the shift, we observed that fast spindles, contributing to memory consolidation, may have an altered function when appearing in areas remote from physiologically occurring ones. In addition, a competitive phenomenon may take place, in which either fast or slow spindles may be generated in a given cortical region. In the specific case, anterior fast spindles are not effective as they should be and at the same time prevent memory consolidation by naturally occurring slow spindles.

To sum up, we could observe a distribution of spindles generators more in line with depressive and PTSD symptoms. A reflection of these altered distributions is an impairment of the physiological function of sleep spindles, mainly memory consolidation and for slow spindles embedded in slow waves also a decrease of executive functions. We did not observe a clear reduction of spindle density as described in cognitive impairment, suggesting a functional nature of the observed neuropsychological symptoms.

A major limitation of our study is the lack of inclusion of people with likely more severe symptoms, who refused to reach the laboratory for assessment. This inclusion bias may probably have contributed to our finding of mostly subclinical impairments, likely related to PTSD and depression. The lack of inclusion of a high number of people for fear of contagion may indirectly reflect high levels of anxiety possibly related to long COVID-19. Since recruitment and recordings were performed during the second lock-down in Italy (i.e., Veneto region shut schools and barred residents from leaving their homes except for work, health or basic needs, and among commercial activities, only supermarkets and pharmacies stayed open), this might explain the high refusal rate. Type I errors are conceptual and it is not possible to ascertain if they have occurred after statistical testing and we could not prevent type I errors from occurring by increasing the sample size. Another limitation of statistical analysis is the lack of correction for multiple comparisons. Eventually, the missing information about the socioeconomic status of included participants may have affected symptoms

severity. The information of state and trait anxiety status would also have supported a more comprehensive evaluation, which is strongly suggested by the observation of a lower percentage of nonICU falling asleep despite deprivation.

4.1. Conclusion

To sum up, based on clinical neuropsychological and neurophysiological features in a cohort of long COVID-19 participants, we observed a persistence of PTSD symptoms and reduced physical performance, which are likely to impact on cognitive performance. The neurophysiological sleep signatures suggest a more likely psycho-affective nature of the subtle impairment in cognition. The finding that participants admitted to medical wards experience worse stress and long-term psycho-affective symptoms is of note for the development of clinical pathways that incorporate care of these issues.

Supplementary material. *Supplementary_material_neuropsy.pdf* and *Supplementary_material_EEGspindles.pdf*

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Consent to participate and publication. Informed consent was obtained from all participants.

Availability of data, materials and code. Anonymous Data and Code will be made available upon reasonable request to the Corresponding Author. None of the experiments was preregistered.

Authors' contribution. ADF, MR and EF designed the project. ADF granted financial support; ADF, MR, MB and EF conceived the experiment; AV, ADF, LC and MR recruited the participants; LC, MR, EF, MB recorded the data; LC ran neuropsychological assessments and scoring and scored sleep; MR analyzed EEG data; EF and GS supervised data analysis; MR, MP, LC and MB run the statistics; MR drafted the manuscript; ADF and EF contributed to manuscript editing; SM, AV, and GS reviewed the manuscript. All authors critically discussed the results.

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Tables

Table 1: Multiple linear regression in nonICU participants' scores

Predictor	Predicted variable	*Pr*(> t)*	Adjusted r^2**	F-statistics
PTSD	Digit BW	0.02998	0.3363	3.703 (p_{value} = 0.03998)
PTSD	TMT-B	0.02	0.2536	2.812 (p_{value} = 0.08088)
BDI	MoCa	0.0304	0.2248	2.546 (p_{value} = 0.1012)

* *Pr*(> t) stands for the probability of the value of the t-distribution; ***r is the* Pearson correlation coefficient

Figure titles and captions

Fig. 1: Overview of the analysis pipeline. (a) Electroencephalography (EEG) was recorded during a nap in COVID-19 survivors and age-sex matched controls. (b) Slow (i.e., [9-12] Hz) and fast (i.e.,]12-16] Hz) spindles were identified and (c) averaged obtaining one time-series (for each electrode) representing the slow spindles and one representing the fast spindles for each participant. (d) The cortical grey matter (e.g., considering age, sex, cortical thickness) was reconstructed and the brain parcelled from cortical regions-of-interest (ROI) of Desikan–Killiany atlas. For each participant, sleep grapho-elements cortical generators were computed with Electrical Source Imaging (ESI).

Fig. 2: Psychological & Cognitive assessment. Boxplots display the scores in (a) Physical Quality of life, (b) COVID-19 Post-Traumatic Stress Disorder, (c) Beck Depression Inventory; (d) Trail Making Test-B and (e) the difference between Trail Making Test-B and A performance. Blue circles stand for controls (CTRL) scores, orange ones for intensive care unit (ICU) participants and yellow ones for participants admitted to sub-intensive ward (nonICU). Physical quality of Life resulted significantly lower in nonICU vs CTRL (p_{value} = 0.0149), in nonICU vs ICU (p_{value} = 0.0377) and in ICU vs CTRL (p_{value} = 0.0377). Non ICU participants scored significantly lower than CTRL (p_{value} = 0.0429) in TMT-B. Panels (f) and (g) display Pearson Correlation Coefficient between psychological score (i.e., *Beck Depression Inventory: BDI; Post-traumatic stress disorder scale: PTSD; Physical and mental component summary scores: PCS-12 and MCS-12*); cognitive performance (i.e., *Montreal Cognitive Assessment: MoCA; Frontal Assessment Battery: FAB; Stroop task: Stroop_t; Stroop_e; Digit Span forward and backward: DigitFW, DigitBW; Rey Auditory Verbal Learning test: Rey_i, Rey_d; Trail Making Task: TMT A; TMT B, TMT B-A; Digit Symbol Modalities Test: Symbol*) and participants' handedness dominance (*Edinburgh Handedness Inventory: EHI*). Circle dimension and color identify the value of the Pearson correlation coefficient, i.e., largest dark red circle indicates maximum positive correlation (1) and largest dark blue circle represents maximum negative correlation (-1) between variables in the two axes.

Fig. 3: Scalp spindles. Panels (a), (b) and (c) report the average amplitude (mV) values for slow spindle onset in controls (CTRL), participants admitted to sub-intensive ward (nonICU) and intensive care unit (ICU),

respectively, visualized as a topography. Panels (d), (e) and (f) report the average values for fast spindle onset in CTRL, nonICU and ICU, respectively, visualized as a topography. Boxplots display (g) slow spindle density (h) fast spindle density and (i) slow spindle peak frequency.

Fig. 4: Amplitude of the source-waveform onset of slow and fast spindles. Panels (a), (b) and (c) report the average values ($\mu A/mm^3$) for slow spindles in controls (CTRL), participants admitted to sub-intensive ward (nonICU) and intensive care unit (ICU). Panels (d), (e) and (f) report the average values for fast spindles in CTRL, nonICU and ICU participants. Panels (g), (h) and (i) report amplitude differences of the source-waveform onset of slow spindles and panels (l), (m) and (n) of fast spindles between (g-l) nonICU and ICU; (h-m) CTRL and ICU; (i-n) CTRL and nonICU: Only regions-of-interest (ROIs) in which the differences between the two groups were statistically significant ($p_{value} < 0.05$) are reported. Node dimension and color (centered in each ROI) identify the value of the spindle onset amplitude ($\mu A/mm^3$) of the reconstructed source-waveforms. The brain networks were visualized with the BrainNet Viewer (Xia et al, 2013).