


Article

Neurocognitive Disorders in Post and Long Covid Patients: Preliminary Data, Gender Differences and New Diabetes Diagnosis

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Abstract: The research is based on a clinical observation of the neurological and neuro-cognitive status of 300 patients, belonging to the Partinico Hospital and the Post-Long Covid clinic, which had contracted the SARS-CoV-2 virus in the period between April 2021 and May 2022. In this paper, we present the analysis of the first 100 patients subjected to a neurocognitive screening protocol. The procedure consists of tests that examine the mechanism of different brain domains to check for the presence of cognitive deficits that arose after the negativization of the viral infection. Through a neurocognitive protocol, the research aims to investigate different brain areas and mental functioning. This allowed us to raise the possibility that the presence of cognitive alterations may be related to the evidence of point-like brain alterations (from the cortex to the trunk) visible through neuroimaging techniques. In the article, we highlight the hypothesis that SARS-covid 2, as stated in recently published studies, can produce an alteration of executive functions such as to configure a real dysexecutive syndrome. This research evaluates the symptomatic gender variability within the sample, the presence of important differences in the affective state, and provides a first observation of the impact of SARS-CoV-2 in diabetic pathology as well.

Keywords: neuroCovid; cognitive disorders; gender; Covid; long covid; diabetes; disexecutive syndrome



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1. Introduction

The SARS-CoV-2 infection has revolutionized scientific paradigms, forcing healthcare professionals to return to the research-intervention model. Gradually, they had to modify their actions and adapt to events, emergencies, and new patient care criteria. The Covid patient is a complex patient with multifactorial and multidimensional symptoms requiring interventions from different branches of specialist medicine [1].

Studies in recent months showed that the psychophysical sequelae of SARS-Cov 2 infection are diversified, and often show symptoms that can be superimposed on different syndromic pictures [2–5]. As observed in recent publications, one of the long-term consequences of Covid is an alteration in cognitive functions, which can lead to multiple disorders such as memory deficits (re-enactment, fixation, and sequencing), attention deficit (immediate and sustained), a deficit in language production and understanding, decoding and execution of programming elements [6–8].

In our view, a careful neurocognitive evaluation allows highlighting the damaged mechanisms and the still-intact processes. The detection of brain regions through neuroimaging techniques (MRI, magnetic resonance imaging), might contribute to determining the relationships between neurocognitive deficits and structural/functional damage [9,10]. Starting from the study published in PLOS ONE, in February 2021 by the IRCCS San

Raffaele Hospital [11], our clinical observation allowed us to observe a further symptom picture characterized by a significant cognitive alteration linked to short and long-term memory, an alteration of attention processes, significantly impaired concentration, planning, abstraction and sensitivity to interference.

Reviewing last year's publications and clinical evidence, the research group of Psychologists and Psychotherapists of Partinico Hospital formulated a neurocognitive protocol that aims to investigate different brain areas and mental functioning.

The aim of the study is to observe three substantial elements:

- The possible presence of encephalic alterations (from the cortex to the brain stem), was verified through neuroimaging techniques, and the possible correlations with neurological alterations and neurocognition were found via the tests.
- The hypothesis is that Covid neuroinflammation, as ascertained by recently published studies, can also produce an alteration of executive functions such as to configure a real dysexecutive syndrome. In this paper, we will focus on this second point.
- Observation in the sample of the presence/absence of diabetic pathology, diabetes with the post-Covid onset, and the correlations between emerging diabetes and mood alterations (depression/anxiety), and executive functions with particular attention to gender differences.

Many studies currently support and confirm the neuro-inflammatory aspect presented by SARS-CoV-2 COVID-19 disease [12–14]. A recent study by Dr. Arianna Di Stadio [15] highlights how the histological, neuroradiological, and clinical aspects of patients affected by the virus “show that, regardless of its origin directly linked to the virus or to the systemic consequences caused by it, patients suffer from brain inflammation”.

Prolonged exposure to infection, or the severity of the syndrome, may produce neurocognitive effects measurable by tests. These will be correlated both with the direct observation of executive functions (with the relative onset of cognitive deficit) and with the neuroinflammation observable through neuroimaging (MRI). Jeffrey S. Fine and his collaborators recently published a very interesting study for cognitive disorders, with a specific focus on the cognitive symptoms of PASC (post-acute sequelae of SARS-CoV-2 infection) that can occur in people diagnosed with an acute COVID19 infection. These patients (hospitalized) experienced mild to severe symptoms.

The authors of this study propose to observe in patients.

neurological and neuropsychiatric symptoms in individuals with PASC include fatigue, myalgia, headaches, sleep disturbance, anxiety, depression, dizziness, anosmia, dysgeusia, and cognitive symptoms, often called a brain fog. It is important for clinicians to recognize that disease severity may not be a predictor of PASC symptoms as many patients presenting to outpatient COVID recovery centers experienced only mild initial SARS-CoV-2 infection. Primary cognitive symptoms include deficits in reasoning, problem solving, spatial planning, working memory, difficulty with word retrieval, and poor attention. In addition, small studies in patients recovering from COVID-19 who develop postural orthostatic tachycardia syndrome (POTS) have shown worsening executive function and attention in the standing position.13 Assessment and treatment of cognitive symptoms in patients with PASC is the focus of this review.”

In diabetic pathology, new studies show that the COVID-19 virus can attack the pancreas by destroying insulin-producing cells and, in some cases, cause diabetes.

A meta-analysis conducted in 2020 by health researcher Thirunavukkarasu Sathish at McMaster University in Canada [16] found that nearly 15% of patients who contracted a severe form of COVID-19 also developed diabetes. However, he adds, “this number is likely higher among individuals at greater risk, for example, those with prediabetes”.

The research, conducted by endocrinologist Paolo Fiorina at Harvard Medical School, and published in 2021, showed that, in a group of 551 patients hospitalized for COVID-19 in Italy, half of them developed hyperglycemia.

Peter Jackson, a biochemist at Stanford University School of Medicine, estimates that “the percentage of patients with severe COVID-19 who can develop diabetes reaches 30%”.

Chen and Jackson found the connection between COVID-19 and newly onset diabetes. Both have launched independent investigations to find out how SARS-CoV-2 might trigger hyperglycemia. Both groups published their results in the May issue of the scientific journal *Cell Metabolism*.

Chen’s group grew different types of tissue in the lab, to see which ones were vulnerable to the COVID-19 virus; surprisingly they found that the beta cells of the pancreas are very permeable to SARS-CoV-2 infection and produce higher insulin levels by altering sugar metabolism. Their findings offer an essential insight into the basic mechanisms by which COVID-19 can lead to the development of new cases of diabetes in infected patients. The group is currently working on the possibility that the hyperglycemia produced by the covid viral infection might alter the activation of HPA and be responsible for the prolongation of diabetes. If Chen’s hypothesis (on a possible prolongation of diabetes linked to glycemic and HPA alteration in covid patients) were confirmed, researchers will have to evaluate the possibility that there could be a cognitive alteration linked to the hypothalamic-locus coeruleus axis.

Our research has been structured on the bases of clinical observation of the neurological and neuro-cognitive state of the covid patient during the hospitalization period.

Patients experienced brain fog, loss of attention, and both short- and long-term memory problems. In order to better understand this phenomenon, the research team structured a protocol aimed at investigating different brain areas and mental functioning. This allowed us to provide objective evidence and quantify the presence of cognitive alterations. The hypothesis of this research is that the infection of SARS CoV 2 produces alterations to executive functions (point brain alterations from the cerebral cortex to the brain stem, visible through neuroimaging techniques), alterations of the affective state and that these variations can be quantified through the neurocognitive protocol.

At the same time, the research focused on the presence, within the sample, of subjects with diabetes (also new onset diabetes), observing the characteristics of the affective state, the presence/absence of alterations in cognitive functions, and gender variations.

2. Methods

2.1. Patients

The research involves the recruitment of 300 subjects who have contracted from April 2021 to February 2022. After the communication of the research plan to the Ethics Committee of the Policlinico Hospital of Palermo, the neurocognitive protocol was administered to the sample hospitalized at the “Civico” P.O. of Partinico with an average hospital stay of 22 days (20% of them were also hospitalized in Intensive Care with an average hospital stay of 10 days) and reviewed at the Post-Long Covid Clinic in the Day Service. The analysis of the first 100 patients tested is the subject of this paper. The neurocognitive screening protocol consists of tests that examine the mechanism of different brain domains in order to check for the presence of cognitive deficits that arose after the negativization of the viral infection.

The subjects (100 patients, 63 males, and 37 females), admitted to covid hospital from April 2021 to February 2022, with an average age of 60 years, (42% diabetic) underwent psychodiagnostics interviews and were administered tested with neurocognitive tests.

2.2. Phases

The research is divided into four phases.

- The first is the administration of the first level protocol [17] with Mini Mental State Examination (MMSE), Immediate and deferred Rey figure, Frontal assessment battery (FAB), Hamilton D, Stay X and Y, Impact of Event Scale–Revised (IES). Each neuropsychological test will be corrected for gender, age, and schooling as required by international guidelines [18].

- Patients found affected by cognitive alterations moved to the second phase of the research with the administration of a second level protocol [17] with the Short Neuropsychological Exam, Davinson Trauma Scale (DTS)-800 (evaluates the 17 symptoms of PTSD) and SF-36 (a questionnaire that aims to quantify health status and measure health-related quality of life).
- The third phase is a correlation study between the test results and the finding of organic alterations in Neuroimaging [19].
- In the fourth phase, the aim is to submit people with a dysexecutive syndrome to a structured cognitive rehabilitation protocol, in association with new embodiment studies for the rehabilitation of executive functions, intervening on the damaged domains.

The expected duration is one year, making retests after 6 and 12 months to evaluate the presence of variations.

2.3. First Level Instruments

The MMSE; consisting of thirty items that are related to seven different cognitive areas: orientation in time, orientation in space, recording of words, attention and calculation, re-enactment, language, and constructional praxis. The total score goes from a minimum of 0 and a maximum of 30 points. Cut off: 25–30 points: normal cognition 21–24 points: mild dementia 10–20 points: moderate dementia 9 points or less: severe dementia.

The Figure of Rey Direct and Deferred evaluates visual spatial function, its perceptual organization and the visual memory of work and re-enactment. Cut off: Copy >28 recall > 6.2.

FAB is a first-level screening battery examining global executive functioning, composed of cognitive and behavioural evidence. It includes the conceptualization of similarities and abstraction, mental flexibility and the use of self-organizational strategies, programming, planning and organization of behaviours, sensitivity to interference, inhibitory control, and ability to manage impulsiveness and environmental autonomy. Cut off >12.

Hamilton D test (depression); it explores and evaluates depressive symptoms regardless of the psychopathological-clinical context in which it is placed. The HAM-D items are graded, some at 3 (0–2) and others at 5 (0–4) levels of severity, and each level is associated with a fairly precise and comprehensive definition. Cut off: <7 normal/absence, 8–17 mild depression, 18–24 moderate depression, <25 severe depression.

STAI: In the X and Y, form it is composed of 40 items, where 20 items measure state anxiety and the others 20 trait anxiety. State anxiety refers to an emotional state at a given time, while trait anxiety refers to a personality trait that characterizes different people. <40 normal/absence, 40–50 mild anxiety, 50–60 moderate anxiety, <60 severe anxiety.

(IES-R); evaluates the presence of post-traumatic disorders. Cut off for Avoidance 0–0.5 normal, 0.5–1.00 mild, 1.01–2.49 moderate, 2.5–4 severe; intrusion 0–0.5 normal, 0.5–1.00 mild, 1.01–2.49 moderate, 2.5–4 severe; Hyperarousal 0–0.5 normal, 0.5–1.00 mild, 1.01–2.49 moderate, 2.5–4 severe.

2.4. Second Level Instruments

ENB-2, a short neuropsychological exam (Mondini, Mapelli, Vestri, Arcara, Bisiacchi, 2011), consisting of the following tests: Digit Span, Trail Making test (TMT version A and version B), Drawing copy, interference memory (10 and 30 s), Abstraction, Token test, Prose memory (immediate and deferred), Tangled figure test, Spontaneous drawing, Phonemic fluency, Cognitive estimations, Praxis tests, Clock test, Corsi's test, Rey's wordlist, Attentional matrices. Davinson Trauma Scale DTS-800 and SF 36.

For the assessment of the presence of diabetes, 100 medical records were examined to verify: the presence/absence of diabetic pathology, the presence/absence of new onset diabetes in post-Covid (parameters: patients that after six months maintain a glycate >of 7 and basal blood glucose of 140), the characteristics of the affective state, the presence of alterations in cognitive functions, the variations between genders.

2.5. Statistical Analysis

The statistical analysis was conducted on the first results of a sample of 100 subjects (the research foresees 300 subjects in all). Descriptive statistics (mean, standard deviation (SD), minimum, median, and maximum) will be used for the continuous/quantitative variables, while frequency tables will be used for the categorical ones.

3. Results

In agreement with the international scientific data published in the last year, the results show pictures of significant cognitive alterations and different mood alterations (Figure 1).

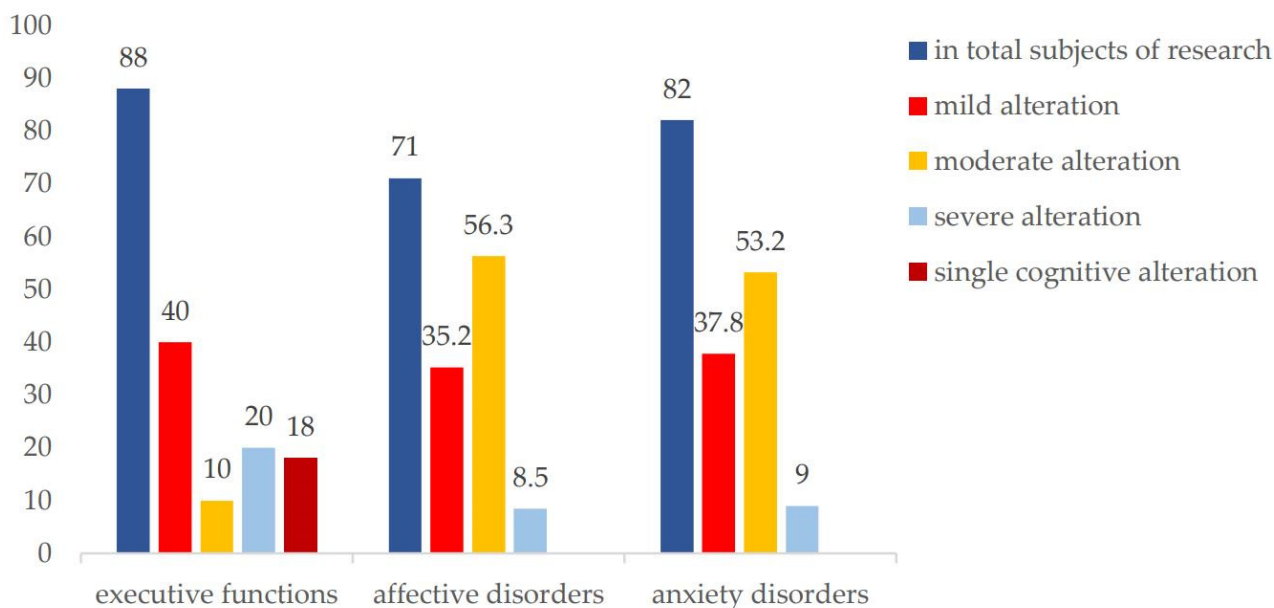


Figure 1. Mild/moderate/severe scores are percentages calculated on the total score of the individual alterations.

3.1. Cognitive Alterations

40% of the sample showed mild alterations in executive functions, with an MMSE >24 to 21 CS (correct score) correct for sex and age-CS (\bar{x} 19.84, DS 1.86) Fab < 12 CS–9 CS. (\bar{x} 10.6 DS 1.11) Rey Complex Figure Copy from 28 to 20 (\bar{x} 23.5 DS 2.80) CS Recall from 6 to 4 CS. (\bar{x} 5.09 DS 0.22).

18% showed a moderate deficit of executive functions with MMSE between 20 CS to 10 (\bar{x} 17.84, DS 1.86) Fab scores between 9 and 6. (\bar{x} 8.6 DS 0.22) Scores to the Figure of Rey copies from 19 to 12 CS (\bar{x} 14.09 DS 1.55). Recall from <4 to 2 CS (\bar{x} 3.09 DS 0.47).

10% showed a severe deficit of executive functions with MMSE between < 9 CS (\bar{x} 8.47, DS 0.26) Fab <6 CS (\bar{x} 5.07 DS 0.31) Rey Complex Figure Copy < 12 (\bar{x} 10.5 DS 1.08) CS Recall < 2. (\bar{x} 1.5 DS 0.32).

20% of the total sample showed an alteration of individual domains (attention 20%, concentration 13%, MBT and MLT 50%, sensitivity to interference 8.9%) without exceeding the cut off of MMSE and FAB, Rey. These isolated elements do not allow to make a diagnosis of dysexecutive functions. However, these clinical elements will have to be taken into account for future observation to verify that isolated alterations remain over time. 88% of the total sample had cognitive alterations.

There are no significant differences in cognitive alterations between men and women ($p > 0.05$).

3.2. Mood Disorder: Anxiety e Affective Disorders

In the evaluation of the tests that quantified the mood alterations, we verified that Mood disorders are present in 71% of the total sample; 35.2% of these are characterized by a mild depressive alteration, the remaining 56.3% by moderate depression, and 8.5% by severe depression.

An interesting fact is connected to an affective alteration of an anxious nature with STAI X Y; in fact, 82% of the sample reported clinically significant anxiety symptoms, i.e., scores greater than the cut off of <40. Within the percentage of anxious subjects, 37.8% showed mild anxiety 53.2% showed moderate anxiety, and 9% severe anxiety. Common symptoms include initial and central insomnia, irritability, psychomotor agitation and restlessness, constant state of tension, and getting scared too easily or at inappropriate times.

Gender differences: The level of significance for gender differences is high ($p < 0.01$), with higher levels of anxiety and moderate depression in women than in men; males are found to be in the mild range in both anxiety disorder and depressive disorder. The difference in the range in severe pathology is not statistically significant (Table 1).

Table 1. Gender difference in mood disorders.

	Depression Disorders					
	Mild		Moderate		Severe	
	M	F	M	F	M	F
N 17	20	5	28	25	4	2
	Anxiety Disorder					
	Mild		Moderate		Severe	
	M	F	M	F	M	F
N 82	25	4	20	29	3	1

3.3. Post Traumatic Stress Disorders

The presence of an acute posttraumatic disorder (the diagnosis is made if the symptoms persist for more than a month, and cause a significant amount of stress and difficulty in functioning) was found in 20% of the sample. In this situation of emotional stress, the psychosomatic response was very personal. Many triggers have hyper activated some subjects, activating physiological and behavioural responses when they had to deal with a very stressful context. The data about the area of “avoidance” of the IES-R of situations that reactivate the severe trauma are very high (\bar{x} 3.07 DS 0.47); the area of sensation intrusion shows results high as well (\bar{x} 3.27 DS 0.27); the area of Hyperarousal shows moderate results (\bar{x} 2.01 DS 0.36).

The symptoms were traumatic reactivations of past bereavement, seeing images and having thoughts, nightmares, illusions, or episodes of recurring flashbacks of the traumatic event, feeling as if reliving the traumatic event, and feeling distressed when something brings back memories of the traumatic. Men and women were compared and there were no remarkable differences in the alteration of their traumatic picture.

3.4. Neurocovid and Diabetes

The data of the sample relating to diabetic patients have highlighted the complexity of all the variables investigated.

18% of the sample has a diabetic pathology (DM 1, 2), and 6% of the population has been diagnosed with new-onset diabetes. The data related to anxiety disorder in diabetics are the same as in the general sample. Data on depressive disorder must be differentiated. (Table 2).

Table 2. Mood disorders e executive functions in diabetes and in new onset diabetes.

Diabetes Subjected	Mood Disorders						Executive Functions			
	Mild		Moderate		Sever		Mild		Sever	
	M	F	M	F	M	F	M	F	M	F
Base line 12	11%	11%	22%	11%	11%	0%	11%	18%	29%	31%
New onset diabetes N 6	0%	0%	0.11%	0.06%	0.11%	0.06%	0%	0%	60%	40%

After contracting COVID 19, a higher percentage of patients previously diagnosed with diabetes, especially male patients, are more likely to present moderate depressive symptoms, with a prevalence of the male gender. The feelings predominantly experienced by the male population are connected to a perception of “uselessness” and “brachypsychism”. Women experience more insomnia, “tachypsychism” and sadness. The scientific literature. [20] identifies the presence of a cognitive alteration in 23% of diabetic patients. The results of our sample show the presence of cognitive alterations in 66% (52% moderate and 14% mild alterations) of the cases observed. Even more significant is the correlation between new-onset diabetes and executive functions. Cognitive alterations are severe in 100% of patients.

4. Discussion

Cognitive functions are the set of conscious and unconscious characteristics and processes that allow human beings to identify, process, memorize, recall, use and communicate information in daily life and characterize their quality of life. Executive Functions refer to the cognitive abilities involved in initiating, planning, organizing, and regulating behaviors (Stuss & Benson, 1986). The term indicates a series of cognitive processes that interact with each other to initiate thoughts and organize functional actions to achieve a purpose (Shallice, 1994; Benso, 2010), providing the subject with the skills necessary to manage their behavior. Direct viral, secondary inflammatory, and secondary metabolic pathologies can affect this indispensable psychic functioning, altering the quality of life, and changing the relationships of patients. COVID may cause such changes through all of these three means.

There are thousands of publications about SARS-CoV 2 infection, but we are just starting to study and understand the real impact and the pathology of post and long covid [20].

This is the first study that deals with correlating executive functions (using specific broad-spectrum tests) in post and long covid subjects.

An analysis of the results of the first phase confirms the preliminary hypothesis about the presence of mild and moderate cognitive disorders in 68% of the sample, without gender differences. In post- and long-Covid patients there was a deficit of cognitive flexibility, attention and concentration deficit, working and planning memory deficit and, in some cases, problem solving deficit, deficits in judgment and decision skills, defects in empathy, deficit of interference control with difficulties of abstraction and categorization up to perseveration.

All the skills examined are attributable to the frontal and prefrontal cortex, responsible for executive functions.

The study is currently in progress but the findings in MRI of frontal gliotic foci have already been ascertained.

These first results are partly in line with what emerged from San Raffaele’s research in the 2021 article in which the MRI confirmed the presence of cognitive alteration, depressive, and anxiety disorders in COVID-19 patients.

“This is the first study that correlates functional connectivity, the structure of the white matter, the local volume of the grey matter and affective state. The rise of depressive symptoms in patients who survive the hyper-inflammatory forms of Covid-19 should not

be underestimated. It is a condition whose duration will have to be verified over time, and which could also explain the cognitive problems that usually accompany long-COVID”

As for the alteration of the affective state, the emerging data confirm the condition already expressed in November 2021 in the aforementioned study. However, the quantification emerging from our research shows a clear picture of the presence of post-Covid alterations in both the depressive type (higher percentage in women), and the anxious type (higher percentage in women). The observational study has an element of weakness: the gender variable cannot be measured. The presence of interactions was exposed in percentages.

The data referable to the presence of a high index of post-traumatic stress disorder (20% of the sample) in hospitalized tested patients, in the post and long Covid in an outpatient setting, were quite predictable.

Even if no significant differences were observed between males and females, clinicians developed a hypothesis, a result of the observation of patients over time, stating that different affective states (see results) can induce the traumatic picture to evolve in a different way. The environmental and relational variables that will intervene over time (resumption of one's own pace of work, resilience, and family environment) will be decisive for the prolongation of the post-traumatic disorder.

Two observations about data on diabetes. The first concerns the presence of a new post-Covid diabetic pathology as an element that provides for further research and in-depth analysis [18,21–31]. The second observation is related to the comorbidity of depression and cognitive functions. Right now, the long-term effects of covid are the real clinical challenge of the coming years. First observation: Data that emerged shows that patients with new onset diabetes are complex patients also from a neurocovid point of view (Table 2).

The data show, in fact, that all the samples diagnosed with newly onset diabetes has a severe or moderate alteration of the mood (Tables 1 and 2), and all the newly diagnosed manifest an alteration of the executive functions (moderate and severe degree). One of the strengths of the observational study was the chance to follow patients from the moment of admission to the outpatient setting, verifying the progressive loss of some cognitive skills, then confirmed by the testological evaluation.

A further strength of our study and its continuation is the compilation of variables on cognitive function, mood disorders, and diabetes that have been investigated too little in COVID patients. The weaknesses are related to the inability to standardize the sample (and guarantee the same percentage of males' and females' samples) and the smallness of the preliminary sample.

5. Conclusions

The results of our research are comparable to the earlier data in the literature. The results of neuropsychological tests represent an evolution, a chance to quantify the cognitive states observed in clinical practice, and the neuropathological states currently studied. All the data currently collected converge towards confirmation of the hypothesis formulated by the research group regarding the presence of a post-Covid dysexecutive syndrome. This neuropsychological protocol, in association with clinical scales, represents a first evaluation that provides objective evidence and quantifies the data collected during the observation of post and long Covid patients. However, our study shows that much of the pathophysiology relating to the prolongation of covid pathology may relate not just to autoimmunity and pulmonary phenomena (as stated in recent international literature), but also to significant metabolic and neuropsychopathological alterations.

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References

1. The Lancet Neurology. The neurological impact of COVID-19. *Lancet Neurol.* **2020**, *19*, 471. [[CrossRef](#)]
2. Herman, C.; Mayer, K.; Sarwal, A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology* **2020**, *95*, 77–84. [[CrossRef](#)] [[PubMed](#)]
3. Mao, L.; Jin, H.; Wang, M.; Hu, Y.; Chen, S.; He, Q.; Chang, J.; Hong, C.; Zhou, Y.; Wang, D.; et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* **2020**, *77*, 683–690. [[CrossRef](#)]
4. Pleasure, S.J.; Green, A.J.; Josephson, S.A. The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: Neurologists move to the frontlines. *JAMA Neurol.* **2020**, *77*, 679–680. [[CrossRef](#)]
5. Beyrouti, R.; Adams, M.E.; Benjamin, L.; Cohen, H.; Farmer, S.F.; Goh, Y.Y.; Humphries, F.; Jäger, H.R.; Losseff, N.A.; Perry, R.J.; et al. Characteristics of ischaemic stroke associated with COVID-19. *J. Neurol. Neurosurg. Psychiatry* **2020**, *91*, 889–891. [[CrossRef](#)] [[PubMed](#)]
6. Xiong, W.; Mu, J.; Guo, J.; Lu, L.; Liu, D.; Luo, J.; Li, N.; Liu, J.; Yang, D.; Gao, H.; et al. New onset neurologic events in people with COVID-19 in 3 regions in China. *Neurology* **2020**, *95*, e1479–e1487. [[CrossRef](#)]
7. Zanin, L.; Saraceno, G.; Panciani, P.P.; Renisi, G.; Signorini, L.; Migliorati, K.; Fontanella, M.M. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir.* **2020**, *162*, 1491–1494. [[CrossRef](#)]
8. Zubair, A.S.; McAlpine, L.S.; Gardin, T.; Farhadian, S.; Kuruvilla, D.E.; Spudich, S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. *JAMA Neurol.* **2020**, *77*, 1018–1027. [[CrossRef](#)]
9. Varatharaj, A.; Thomas, N.; Ellul, M.A.; Davies, N.W.S.; Pollak, T.A.; Tenorio, E.L.; Michael, B.D. CoroNerve Study Group. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *Lancet Psychiatry* **2020**, *7*, 875–882. [[CrossRef](#)]
10. Benussi, A.; Pilotto, A.; Premi, E.; Libri, I.; Giunta, M.; Agosti, C.; Alberici, A.; Baldelli, E.; Benini, M.; Bonacina, S.; et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology* **2020**, *95*, e910–e920. [[CrossRef](#)] [[PubMed](#)]
11. Alemanno, F.; Houdayer, E.; Parma, A.; Spina, A.; Del Forno, A.; Scatolini, A.; Angelone, S.; Brugliera, L.; Tettamanti, A.; Beretta, L.; et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. *PLoS ONE* **2021**, *16*, e0246590. [[CrossRef](#)]
12. Beghi, E.; Helbok, R.; Crean, M.; Chou, S.H.; McNett, M.; Moro, E.; Bassetti, C.; Jenkins, T.; Oertzen, T.; Bodini, B.; et al. EAN Neuro-COVID Task Force. The European Academy of Neurology COVID-19 registry (ENERGY): An international instrument for surveillance of neurological complications in patients with COVID-19. *Eur. J. Neurol.* **2020**, *28*, 3303–3323. [[CrossRef](#)]
13. Helms, J.; Kremer, S.; Merdji, H.; Schenck, M.; Severac, F.; Clere-Jehl, R.; Meziani, F. Delirium and encephalopathy in severe COVID-19: A cohort analysis of ICU patients. *Crit. Care* **2020**, *24*, 491. [[CrossRef](#)] [[PubMed](#)]
14. Zádori, N.; Vánca, S.; Farkas, N.; Hegyi, P.; Erőss, B.; KETLAK Study Group. The negative impact of comorbidities on the disease course of COVID-19. *Intensive Care Med.* **2020**, *46*, 1784–1786. [[CrossRef](#)]
15. Di Stadio, A.; Brenner, M.J.; De Luca, P.; Albanese, M.; D’Ascanio, L.; Ralli, M.; Roccamatì, D.; Cingolani, C.; Vitelli, F.; Camaioni, A.; et al. Olfactory Dysfunction, Headache, and Mental Clouding in Adults with Long-COVID-19: What Is the Link between Cognition and Olfaction? A Cross-Sectional Study. *Brain Sci.* **2022**, *12*, 154. [[CrossRef](#)]
16. Sathish, T.; Kapoor, N.; Cao, Y.; Tapp, R.J.; Zimmet, P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes Obes. Metab.* **2021**, *23*, 870–874. [[CrossRef](#)]
17. Kandel, E.R.; Schwartz, J.H.; Jessell, T.M.; Siegelbaum, S.A.; Hudspeth, A.J.; Perri, V.; Spidalieri, G. *Principi di Neuroscienze*; Casa Editrice Ambrosiana: Milano, Italy, 2014.
18. Song, I.U.; Choi, E.K.; Oh, J.K.; Chung, Y.A.; Chung, S.W. Alteration patterns of brain glucose metabolism: Comparisons of healthy controls, subjective memory impairment and mild cognitive impairment. *Acta Radiol.* **2016**, *57*, 90–97. [[CrossRef](#)] [[PubMed](#)]
19. Joseph, S. Psychometric Evaluation of Horowitz’s Impact of Event Scale: A Review. *J. Trauma Stress* **2000**, *13*, 101–113. [[CrossRef](#)]
20. Yong, S.J. Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. *Infect. Dis.* **2021**, *53*, 737–754. [[CrossRef](#)]
21. Burgmer, M.; Rehbein, M.A.; Wrenger, M.; Kandil, J.; Heuft, G.; Steinberg, C.; Junghöfer, M. Early Affective Processing in Patients with Acute Posttraumatic Stress Disorder: Magnetoencephalographic Correlates. *PLoS ONE* **2013**, *8*, e71289. [[CrossRef](#)] [[PubMed](#)]
22. Fine, J.S.; Ambrose, A.F.; Didehbani, N.; Fleming, T.K.; Glashan, L.; Longo, M.; Merlino, A.; Ng, R.; Nora, G.J.; Rolin, S.; et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). *PM&R* **2022**, *14*, 96–111. [[CrossRef](#)]

23. Solerte, S.B.; D'Addio, F.; Trevisan, R.; Lovati, E.; Rossi, A.; Pastore, I.; Dell'Acqua, M.; Ippolito, E.; Scaranna, C.; Bellante, R.; et al. Sitagliptin Treatment at the Time of Hospitalization Was Associated With Reduced Mortality in Patients with Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. *Diabetes Care* **2020**, *43*, 2999–3006. [[CrossRef](#)] [[PubMed](#)]
24. Wu, C.-T.; Lidsky, P.V.; Xiao, Y.; Lee, I.T.; Cheng, R.; Nakayama, T.; Jiang, S.; Demeter, J.; Bevacqua, R.J.; Chang, C.A.; et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab.* **2021**, *33*, 1565–1576.e5. [[CrossRef](#)] [[PubMed](#)]
25. Denes, G. *Manuale di Neuropsicologia. Normalità e Patologia dei Processi Cognitivi*; Zanichelli: Bologna, Italy, 2019.
26. Ceriello, A. Hyperglycemia and COVID-19: What was known and what is really new? *Diabetes Res. Clin. Pract.* **2020**, *167*, 108383. [[CrossRef](#)]
27. Nassar, M.; Nso, N.; Gonzalez, C.; Lakhdar, S.; Alshamam, M.; Elshafey, M.; Rizzo, V. COVID-19 vaccine-induced myocarditis case report with literature review. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 102205. [[CrossRef](#)]
28. Steenblock, C.; Schwarz, P.E.H.; Perakakis, N.; Brajshori, N.; Beqiri, P.; Bornstein, S.R. The interface of COVID-19, diabetes, and depression. *Discov. Ment. Health* **2022**, *2*, 5. [[CrossRef](#)]
29. Chen, J.; Wu, C.; Wang, X.; Yu, J.; Sun, Z. The impact of COVID-19 on blood glucose: A systematic review and meta-analysis. *Front. Endocrinol.* **2020**, *11*, 574541. [[CrossRef](#)]
30. Zhu, L.; She, Z.-G.; Cheng, X.; Qin, J.-J.; Zhang, X.-J.; Cai, J.; Lei, F.; Wang, H.; Xie, J.; Wang, W.; et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.* **2020**, *31*, 1068–1077.e3. [[CrossRef](#)]
31. Kochhann, R.; Varela, J.S.; Lisboa, C.S.M.; Chaves, M.L.F. The Mini Mental State Examination: Review of cutoff points adjusted for schooling in a large Southern Brazilian sample. *Dement. Neuropsychol.* **2010**, *4*, 35–41. [[CrossRef](#)]