Egyptian Journal of Medical Research

Print ISSN: 2682-4396 / Online ISSN: 2682-440X

Assessment Of the Cognitive Function In Patients Recovered From COVID-19 Infection Using P300.

Mona Ali Ashmawy Soliman [a], Hanan Hosny Abdel Alim [a], Mona Hussein Tawfik [b], Manal Mohamed Gaber[a].

[a] *Clinical Neurophysiology department, Faculty of Medicine, Beni-Suef University.*

[b] *Neurology department, Faculty of Medicine, Beni-Suef University.*

Article Info

Article history:

Received 25 September 2023

Accepted 29 October 2023

Corresponding Author:

Mona Ali

alimona451@gmail.com

Keywords

Cognitive Function, COVID-19, Event Related Potentials (ERPs), P300.

Abstract:

The aim of our work was to assess the cognitive function in patients recovered from COVID-19 infection using P300 analysis. **Methods** 50 subjects recovered from COVID-19 infection (at least 8 weeks following recovery). The patients were recruited in the period between April 2022 and December 2022.The cases were recruited from the Chest hospital, Beni-Suef governorate and from chest department, Beni-Suef University hospital. **Results** Our results revealed significantly impaired cognitive function, delayed P300 latency and small P300 amplitude among severe cases. Also, there was a significantly delayed P300 latency and small amplitude in hypoxic critically severe patients. In addition, our results revealed a significant positive correlation between cognitive function, P300 latency, and the duration of hospital stay. Also, our study detects the value of vaccination we revealed that patients who received vaccination before COVID-19 infection had less delay in P300 latency in comparison to those who did not receive vaccination before infection **Conclusion** COVID-19 can affect cognitive function demonstrated by increased P300 latency and small p300 amplitude.

1. Introduction

There is a wide range of neurological symptoms associated with COVID-19 in up to 25% of those who survived the disease, one of the most often reported is the so-called brain fog, Brain fog appears two to three months after the infection and can last up to six months or sometimes longer [1].

Event Related Potentials (ERPs) also have many practical advantages as measures of brain activity: They are relatively cheap and fast to collect; data collection itself is portable, can be administered in a variety of settings, and does not require particularly extensive training; file size makes storage non prohibitive; data can be analyzed relatively quickly; ERPs can be measured across a wide-range of ages (e.g., very young to very old) and have relatively few contraindications. Also, ERPs can be used to differentiate clinical groups and predict the onset of psychiatric disorders [2].

The P300 is one of the most important ERP components that is used to evaluate cognitive function, such as attention, working memory, and concentration [3]. The P300 component has been considered a potential marker of cognitive dysfunction, with an average latency 300 ms after an infrequent stimulus. The waveform of the P300 component is described by its amplitude and latency.

And since P300 event-related brain potential (ERP) is thought to reflect neuroelectric activity related to cognitive dysfunction [4], so it can be used as an accurate tool to detect early cognitive dysfunction.

It is observed that after the infection brain P300 computer interface performance is slightly lower than that of the before COVID-19 infection performance [5].

Recent studies have confirmed the utility of ERPs as prognostic indicators in patients with severe brain injuries of different etiologies and consciousness levels.

Fischer et al., 2006 found that MMN can be used in this capacity.[6]

P300 may also serve as a mediating response, allowing brain control of prosthetic devices [7]. So, the aim of our work was to assess the cognitive function in patients recovered from COVID-19 infection using P300.

2. Patients and Methods

2.1. Patients

This was a cross-sectional study that was carried out on 50 subjects recovered from COVID-19 (at least 8 weeks following recovery). The subjects were recruited in the period between April 2022 and December 2022. The cases were recruited from the Chest hospital, Beni-Suef governorate and from chest department, Beni-Suef University hospital.

2.2. Ethics

All the individuals included in the study were informed about the procedures of the study, and all agreed to participate. The participants were informed of their rights to refuse participation or withdraw from the study without giving reasons. All information was treated with confidentiality. Prior starting of the research study, an approval was obtained from the ethical approval of the faculty of medicine, Beni-Suef University research ethical committee (REC). The ethical approval number is FMBSUREC/08052022/Soliman.

2.3. Eligibility criteria

The diagnosis of COVID-19 in the included subjects was based on a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction on a nasopharyngeal sample and/or typical pulmonary involvement on computed tomography. The criteria of recovery were based on World Health Organization (WHO) (for symptomatic patients; 10 days after symptom onset, plus at least three additional days without symptoms, and for asymptomatic cases; 10 days after a positive test for SARS-CoV-2 without requiring retesting) [8].

According to the WHO, the definition of post-COVID-19 symptoms was applied if symptoms persisted for at least two months in people with a history of SARS-CoV-2 infection and three months from the onset of COVID-19 symptoms, provided no better explanation [8].

Severity of infection was defined according to WHO classification. COVID-19 infection was categorized into a mild, moderate, or severe infection. The mild state was defined by typical symptoms without evidence of viral pneumonia or hypoxia, while moderate or severe cases were identified if there was any clinical and radiological evidence of pneumonia. In moderate infection, patients had to have SpO2 ≥ 90% on room air while one of the following was required to define the severe cases: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air [9].

The following patients were excluded from the study: patients with major language disturbance, severe physical, auditory or visual impairment affecting their ability to complete cognitive testing, patients with a history of drug intake known to affect cognition e.g. anti-epileptic, anti-psychotic or anti-cholinergic, patients with neurodegenerative diseases, patients with brain imaging showing structural brain lesion, patients with medical or metabolic illness known to affect cognition, and patients with a history of alcohol or any substance abuse.

2.4. Event-related potentials (ERPs) were studied using Galileo NT PMS device.

Oddball paradigm was used in P300 recordings. This paradigm is based on distinguishing a target stimulus repeated randomly and less frequently from the non-target stimuli of frequent repetition, and the subject is asked to count the stimuli or to press a button when he/she encounters the stimuli. Binaural auditory stimuli were presented by headphones. Twenty percent of stimuli were rare (target) tones of 1000 Hz (95dB) whereas the remainder was frequent (non-target) tones of 8000 Hz (95dB). The stimulus sequence was random. The recordings were made by the same electrodes used in EEG. By using the 10—20 system the reference electrodes were placed over the mastoid regions and the active electrodes over Fz, Cz and Pz. All the electrodes had a resistance of 5 kV or less and the frequency limits were set at 0.1—50 Hz. twenty responses recorded by the target stimuli were averaged. The latency and the amplitude of the P300 wave recorded from Pz were taken into consideration.

Statistical methodology

Data collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis performed using the Statistical Package of Social Science **(SPSS)** software version 22 in windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages of qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion of quantitative parametric data.

For quantitative parametric data:

Independent samples **t test** was used to compare quantitative measures between two independent groups. One -way **ANOVA** test used to compare quantitative measures between more than two independent groups of quantitative data. **Bivariate Sperman correlation test** to test the association between nonparametric quantitative variables. **Multiple linear regressions used** to test the association between quantitative dependent and independent variables and detection of risk factors. The **P-value< 0.05** was considered as statistically significant.

3. Results

The current study was conducted at Beni-Suef university hospital at NDRC (Neurodiagnostic and Research Centre) within 6 months in the period between April 2022 and December 2022 a total of 50 subjects recovered from COVID-19 infection (at least 8 weeks after recovery.

Table (1): Comparisons of post COVID-19 P300 parameters among cases.

Variables		P300 parameters		
		Reaction Time	P300 latency	P300 amplitude
		Mean± SD	Mean± SD	Mean± SD
CORAD degree				
3		362.2±0	308.8±0	12.4±0
4		434.3±82.3	438.3±84.6	7.4±3.1
5		460.9±96.03	471.6±72.3	5.6±2.7
P-value		0.4	**0.04***	**0.02***
COVID-19 severity				
Mild		431.5±86.5	415.8±78.9	8.2±3.3
Moderate		447.9±81.6	472.4±79.4	5.7±2.4
Severe		492.5±144.7	493.4±55.6	4.2±2.6
P-value		0.4	**0.03***	**0.006***
Respiratory support				
Oxygen	**No**	441.3±96.8	428.3±80.2	7.6±3.5
	Yes	447.9±81.6	472.4±79.4	5.8±2.4
P-value		0.8	0.06	0.06
MV	**No**	440.4±83.4	446.6±83.3	6.8±3.1
	Yes	492.5±144.8	493.5±55.6	4.2±2.6
P-value		0.4	0.2	0.4
Admitted in ICU				
No		437.9±82.6	443.7±81.8	6.8±3.1
Yes		504.4±128.2	510.2±61.01	4.9±2.7
P-value		0.2	0.08	0.3
Time of vaccination				
Vaccinated Before infection		440.1±78.2	433.7±86	7.04±3.3
Not vaccinated before infection		450.8±103.2	473.4±71.9	6.1±2.9
P-value		0.7	**0.08**	0.4

*Significance difference with p-value <0.05

The table illustrated that there was no statistically significant different in level of reaction time as regard ERP analysis among cases in different diseased cases.

As regards **P300 latency** there was a statistically **significant higher mean** among cases with severe degree of disease and those not vaccinated before infection with p-value <0.05 with no difference as regards other data

Finally, to **P300 amplitude** there was a statistically **significant lower mean** among cases with c CORAD 5 and with a severe degree of disease with p-value <0.05 with no difference as regards other variables.

Table (2): Correlation between P300 parameters among cases.

Variables	P300 parameters

	Reaction Time	P300 latency	P300 amplitude
	R P-value	R P-value	R P-value
Age	**0.25(0.01*)**	0.14(0.2)	-0.14(0.2)
Duration of COVID-19 infection	0.07(0.6)	0.11(0.4)	-0.08(0.6)
Duration of hospital stay	0.21(0.1)	**0.33(0.02*)**	-0.19(0.2)
Duration of mechanical ventilation	0.40(0.6)	0.40(0.6)	-0.20(0.8)
Duration of recovery from COVID-19 infection	-0.13(0.3)	-0.16(0.3)	0.10(0.5)

*Significance difference with p-value <0.05

The table illustrated that there was statistically significant **positive** correlation with p-value <0.05 between reaction time and age, and also between p300 latency and duration of hospital stay. On the other hand, there was no statistically significant correlation with p-value >0.05 between other different variables.

Table (3): Multivariate linear regression analysis to determine the power of different risk factors in prediction of P300 latency assessment.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	573.877	158.688		3.616	.001	253.400	894.353
Age	-.692	1.454	-.068	-.476	**.040**	-3.628	2.245
CORAD	-16.775	33.459	-.110	-.501	.619	-84.347	50.797
O2 support	55.658	37.010	.343	1.504	.140	-19.085	130.401
MV	-15.274	100.002	-.051	-.153	**.031**	-217.231	186.684
Admission ICU	83.638	81.320	.309	1.029	.310	-80.591	247.868
Time of Vaccination	-50.456	25.630	-.307	-1.969	.056	-102.21	1.304
Duration of illness	.037	1.068	.006	.034	.973	-2.120	2.193
Duration of hospital stay	1.931	1.979	.194	.976	.335	-2.065	5.927

The multivariate linear regression model analysis was conducted to explore the explanatory power of different risk factors in prediction of **P300 latency** measure it illustrated that there was statistical significance model with p-value 0.04 R= 0.51 and R2=0.26 with p-value 0.04 to patient age, and those needed Mechanical Ventilation.

4. Discussion

SARS-CoV-2 infection has a potential long-term impact on the cognition of patients. As the COVID-19 pandemic is still raging in many countries and is expected to last for a long period, the long-term cognitive sequelae may become a major public health issue long after the pandemic has ended. Screening patients who have recovered from COVID-19 became obligatory for better understanding the long-term cognitive consequences of COVID-19, particularly in severe cases **[10].**

The aim of our work was to assess the cognitive function in patients recovered from COVID-19 infection, using P300. We collect our patients from three months to one year after recovery from covid-19 symptoms. The possible mechanisms underlying such cognitive impairment is the effect of systemic inflammation on the CNS in addition to the storm of intracranial cytokines **[11].** P300 amplitude represents the degree of information processing, attention and the level of superior cognitive function **[12].**

P300 latency reflects the process of selective attention and working memory. The prolongation of P300 latency or diminution in the P300 amplitude reflects bad cognitive performance **[13].** Cognitive decline was observed in our patients recovered from COVID-19 infection as significantly small P300 amplitude and delayed P300 latency was demonstrated in patients comparing to healthy controls. Our results revealed also significantly impaired cognitive function, delayed P300 latency and small P300 amplitude among severe cases.

We revealed significantly delayed P300 latency and small amplitude in hypoxic critically severe patients and this was supported by the research of **Nakata Hiroki et al., (2017)** who found that P300 latency at Fz was significantly delayed in hypoxic conditions **[14].** The long duration of hospital stay has a serious impact on cognitive performance Our results revealed a significant positive correlation between cognitive function, P300 latency, and duration of hospital stay. This agrees with **Tolson D et al., (1999**) who estimated that the prevalence of cognitive impairment in hospitalized adults ranges from 14% to 66% **[14]**. On evaluated the impact of vaccination on outcome, we found that patients who received vaccination before COVID-19 infection had less delay in P300 in comparison to those who did not receive vaccination.

5. Conclusion and Recommendations

Cognitive function in patients recovered from COVID-19 infection was significantly impaired. Such impairment can be detected clinically using psychometric tests and neurophysiologically as well. Patients who received vaccination before COVID-19 infection had better post COVID-19 cognitive function in comparison to those who didn`t receive vaccination. Also, age and hypoxia

were found to be significant predictors of post COVID -19cognitive impairment. Thus, studying the impact of post COVID-19 fatigue, sleep abnormalities, anxiety, and depression on post COVID-19 cognitive function is crucial and should be correlating with the cerebral micro and macrostructural changes using diffusion tensor imaging and brain volumetric imaging respectively.

References

1- *Afari N and Buchwald D (2003).* Chronic fatigue syndrome: a review. Am. J. Psychiatry*; 160: 221–236.*

2- *Weinberg A, Meyer A, Hale-Rude E, Perlman G, Kotov R, Klein D N& Hajcak G (2016).* Error-related negativity (ERN) and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. Psychophysiology; *53(3): 372– 385.*

3- *Sutton S, Braren M, Zubin J, John ER. (1965).* Evoked-potential correlates of Stimulusuncertainty. Science; *150:1187–8.*

4- *Polich J & Kok A (1995).* Cognitive and biological determinants of P300: an integrative review. Biological psychology; *41(2): 103-146.*

5- *Korkmaz O E, Aydemir O, Oral E A & Ozbek I. Y (2021).* Investigating the Effect of COVID-19 Infection on P300 Based BCI Application Performance. Traitement du Signal, *38(6).*

6- *Fischer C, Luaute J, Nemoz C, Morlet D, Kirkorian G, Mauguiere F (2006).* Improved prediction of awakening or non-awakening from severe anoxic coma using tree-based classification analysis. Crit Care Med; *34(5):1520–1524.*

7- *Nijboer F, Sellers, EW, Mellinger J, Jordan, M A, Matuz T, Furdea A & Kübler A(2008).* A P300-based brain–computer interface for people with amyotrophic lateral sclerosis. Clinical neurophysiology*;119(8): 1909-1916.*

8- *World Health Organization. Interim Guidance on Ending Isolation and Precautions for Adults with COVID-19.* March8, 2021.KAYAASLANET AL.6579.

9- *World Health Organization. Clinical management of COVID-19 2020: interim guidance, 27 May 2020.*

10- *Liu YH, Wang Y R, Wang Q H, Chen Y, Chen X, Li Y & Wang, Y J (2021).* Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. Molecular neurodegeneration*; 16: 1-10.*

11- *Hawkins M, Sockalingam S& Bonato S (2021*). A rapid review of the pathoetiology, presentation, and management of delirium in adults with COVID-19. J Psychosom Res*; 141:110350.*

12- *Fabiani M, Karis D, Donchin E (1990).* Effects of mnemonic strategy manipulation in a Von Restorffparadigm. Electroencephalogr Clin Neurophysiol*; 75:22–35.*

13- *Vecchio F& Maatta S (2011*). The use of auditory event-related potentials in Alzheimer's disease diagnosis. Int J Alzheimers Dis *:653173.*

14- *Nakata & Hiroki (2017)"*Effects of acute hypoxia on human cognitive processing: A study using ERPs and SEPs." Journal of Applied Physiology*; 123.5: 1246-1255.*

15- *Tolson D, Smith M & Knight P 15-(1999).* An investigation of the components of best nursing practice in the care of acutely ill hospitalized older patients with coincidental dementia: a multi-method design. J Adv Nurs*;30: 1127–113.*