

Investigating the Impact of COVID-19 on Cognitive Functions Through Event-Related Potentials Analysis

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ABSTRACT

Introduction: COVID-19 infection affects many systems, particularly the central nervous system. These effects are observed at different levels across various age groups. Although there are studies in the literature examining the negative effects of COVID-19 infection on cognitive functions, research including neurophysiological tests supporting these effects is limited. The aim of this study is to demonstrate the effect of COVID-19 infection on cognitive functions according to age through neurophysiological parameters.

Methods: This prospective study was conducted at the COVID-19 clinic from June 2020 to June 2021. Inclusion criteria comprised PCR-confirmed mild to moderate COVID-19 patients aged under 50 and over 65, as well as a PCR-negative control group comprised of individuals aged under 50 and over 65. Exclusion criteria included individuals under 18 years old, and participants from both the patient and control groups were selected without conditions such as dementia that could influence cognitive functions, as well as severe clinical presentations of COVID-19. In hospitalized patients, N200/P300 latencies and N2P3 amplitudes were measured on the first day of admission and again on the 60th day

post-discharge for those with positive COVID-19 PCR tests. For PCR-negative patients, measurements were taken only once on the first day of admission.

Results: The study encompassed a cohort of 48 COVID-19 PCR-positive patients alongside 47 PCR-negative subjects (constituting the control group). Statistically significant differences were observed between the COVID-19 PCR-positive and negative groups ($p < 0.05$). Additionally, significant differences in event-related potentials were found between the PCR-positive groups aged under 50 and those over 65 years ($p < 0.05$). After discharge, significant improvement was observed on the 60th day in the group under 50 years of age ($p < 0.05$), while no statistically significant improvement was detected in the group over 65 years ($p > 0.05$).

Conclusion: Our study demonstrated that COVID-19 has a negative impact on cognitive functions, which becomes more pronounced with advancing age.

Keywords: Cognition, COVID-19, event-related potentials, N200, P300

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INTRODUCTION

As of March 10, 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 117 million confirmed cases and 2.6 million fatalities from coronavirus disease 2019 (COVID-19) globally (1). Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness (2).

Coronavirus (COVID-19) infection can affect the central nervous system as well as the respiratory tract, resulting in neurological symptoms. Initially, clinical findings predominantly highlighted respiratory tract involvement. However, it was later understood that the disease impacts not only the respiratory tract but also manifests neurological signs and symptoms in 30-35% of patients (3).

Throughout the acute phase of COVID-19 infection, a wide variety of neurological complications have been reported, including symptoms such as headaches, loss of smell (anosmia), altered taste (dysgeusia), dizziness, agitation, confusion, diminished consciousness, and acute

strokes. A recent meta-analysis focused on the prevalence of ongoing symptoms occurring 12 weeks or more after acute COVID-19 found that about 22% of participants exhibited either subjective or objective

Highlights

- In this study, ERPs were measured in patients with Covid-19 infection.
- COVID-19 impairs cognitive functions, with severity increasing with age.
- It was observed that cognitive effects might persist into the post-COVID period.
- The severity of the disease has a negative impact on cognitive functions.

cognitive impairments. Within the PACS patient group, headaches and cognitive issues stand out as the most common neurological symptoms, although many other neurological manifestations have also been observed (4).

In recent years, in addition to neuropsychological tests, event-related potentials such as N200 and P300 have been frequently used in research laboratories for the assessment of cognitive functions. Electrophysiological markers of cognitive functions, such as these Event-Related Potentials (ERPs), are extensively utilized in scientific research for assessing and monitoring cognitive processes (5). The N-200 potential typically appears following tasks involving physical or semantic discrimination. Physical discrimination tasks involve passive attention, while semantic discrimination tasks require selective attention. These potentials are closely linked with pattern recognition and the classification of stimuli (6).

Sutton et al. (1965) first described the P300, which remains one of the most extensively studied Event-Related Potential (ERP) components. It is typically elicited in the oddball paradigm, where a random sequence of stimuli is presented. These stimuli can be categorized into two groups, and the task involves classifying them either by counting or by responding with a button press to stimuli from a specific category. When stimuli from one category are infrequent, known as 'oddballs,' they evoke a P300 response (7).

When we evaluate the studies in the literature that investigate the effects of COVID-19 on cognitive functions, we see a lack of research examining event-related potentials such as P300 and N200, which are neurophysiological parameters of cognitive functions. Additionally, there is a shortage of studies evaluating the direction and duration of cognitive function impairment in both young and elderly populations.

Our primary objective in this study is to evaluate the influence of Covid-19 on cognition through the analysis of N200 and P300 potentials. Our second aim to investigate potential differences in this impact between younger and older age groups. Additionally, third objective of our study is to determine the direction of changes in cognitive functions between the acute- subacute phase of COVID-19 and the post-COVID period.

METHODS

Patients

The prospective study was conducted in the COVID-19 clinic between June 2020 and June 2021. Inclusion criteria for the study comprised PCR-confirmed mild to moderate COVID-19 patients under 50 years old and over 65 years old, as well as PCR-negative control groups under 50 years old and over 65 years old. The exclusion criteria included individuals under the age of 18, and participants were selected from both patient and control groups devoid of conditions such as dementia, which could potentially impact cognitive functions, as well as severe COVID-19 clinical presentations. Additionally, participants were not undergoing any form of treatment (e.g., B-12 replacement therapy) for memory-related concerns. Written informed consent was obtained from all participants. By defining these inclusion and exclusion criteria, the study aimed to ensure that participants fell within a specific age range and possessed a confirmed diagnosis of COVID-19. This approach contributes to the validity of the study and allows for a more targeted analysis of the cognitive effects of COVID-19 within this specific population.

COVID-19 PCR-confirmed patients were categorized into two subgroups based on the severity of the disease: mild and moderate cases. Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have

shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO₂) \geq 94% on room air at sea level (2).

Methods

This prospective study encompassed patients undergoing inpatient care from June 2020 to June 2021. The patient group in our study consisted of individuals evaluated for COVID-19 in the hospital's outpatient clinic, where PCR samples were collected, and who were subsequently admitted to the ward for inpatient treatment. PCR analysis results were available, on average, within 4 hours after sample collection. Following the release of the PCR test results, ERP measurements were conducted on the first day of hospitalization for patients whose vital signs had been medically stabilized and who were deemed suitable for testing.

Patients whose general condition was unsuitable for testing were excluded from the study. For patients with fever, ERP measurements were performed after their fever was reduced with antipyretic medications (paracetamol) as part of the routine treatment for the illness. During the ERP measurements, patients' body temperatures were below 37 degrees Celsius. During the study period, while the Omicron variant's BA.1 subtype was more prevalent in the Republic of Turkey, information regarding COVID-19 variants was not included in the study's dataset.

An important point to emphasize is that the center where the study was conducted operated as a COVID-19 clinic within the neurology department due to pandemic conditions, with the neurophysiology laboratory located within the clinic. Data acquisition occurred through direct interactions within the electroneurophysiology laboratory. In the hospital's electroneurophysiology laboratory, which was repurposed as a COVID-19 facility amidst the pandemic, N200/P300 latencies and N2P3 amplitudes were measured in COVID-19 PCR- positive patients at two time points: during treatment initiation and on the 60th day post-discharge. Conversely, in the cohort under surveillance for suspected COVID-19, yielding PCR- negative outcomes, N200/P300 latencies and N2P3 amplitudes were assessed solely once. COVID-19 PCR samples were collected using specialized swabs from the nasopharyngeal and oropharyngeal regions. Participants suspected of having COVID-19 were isolated in separate rooms, and PCR tests were repeated 3 days after initial negative results for those who remained PCR-negative. Participants who continued to test negative were included in the study's PCR-negative group. Event-related potentials of PCR-negative participants were evaluated separately from those of PCR-positive participants, using different rooms and devices. All methods were performed in accordance with the relevant guidelines and regulations.

Measurements

Event-Related Potentials (ERPs)

ERPs were acquired within a neurophysiological laboratory utilizing a standardized protocol and the Medelec EMG-EP apparatus (Oxford Instruments Co., Surrey, UK) (8). Subjects underwent ERP recordings in a serene environment with eyes closed to minimize extraneous influences. Electrode placement adhered to the 10-20 system, targeting specific midline points—Fz, Cz, and Pz—while a ground electrode was stationed at Fpz and reference electrodes at the mastoids to establish the recording configuration. Additionally, an infraorbital (IO) channel was employed to mitigate potential artifacts from ocular movements.

"Electrode impedance was maintained below 5 K Ω to ensure precise signal capture. Signal processing was configured with a filter bandwidth of 0.5 to 50 Hz to eliminate undesired frequency components. The ERP analysis window spanned 1000 ms to enable thorough scrutiny of the

brain's reaction to auditory stimuli, with sound intensity set 40 dB above the established threshold, generally at 80 dB, tailored individually for participants based on observed variations.

Adhering to this standardized recording regimen aimed to procure consistent and dependable ERP datasets, facilitating a comprehensive assessment of auditory stimulus-induced cerebral responses. To ensure participants' comprehension and readiness, a one-minute counting task preceded the test. Employing an auditory oddball paradigm, ERPs were elicited, with participants exposed to two types of auditory stimuli: frequent (3000 Hz) non-target and rare (2000 Hz) target stimuli, both at an average intensity of 80 dB, delivered at a frequency of 0.7 Hz to both ears.

Participants were instructed to tally target tones (2000 Hz) while non-target tones (3000 Hz) were interspersed. Target tones were presented randomly at a 20% rate, with non-target tones comprising the remaining 80%. Across the recording session, 40 averages of target tones devoid of artifacts were collected, and the test was repeated twice to ensure data robustness and consistency.

For potential analysis, amplitude measurement spanned from the N200 to P300 peaks, referred to as N200/P300 amplitude, while latencies of the N200 and P300 potentials were computed relative to their midpoints. Statistical scrutiny was conducted using recordings from the Cz electrode (CZ-A1 channel), positioned along the midline according to the 10-20 system

Statistical Analysis

In the present study, statistical analysis was executed using the IBM SPSS Statistics 26 software package, widely recognized for its application across diverse research domains. A significance threshold (alpha) of 0.05 was adopted to ascertain statistical significance. For categorical data examination, encompassing variables like gender or treatment grouping, frequencies and percentages were computed to depict data distribution. Descriptive statistics, encompassing measures such as mean, standard deviation, minimum, and maximum values, were generated for numerical data to encapsulate central tendency and dispersion.

To evaluate dependent variable data, such as P300 and N200 latencies during and post-treatment (60 days after discharge), as well as N2P3 amplitudes, a 'Paired-Samples T Test' was employed. Before conducting the T-test, the normality of the data distribution was assessed by examining skewness and kurtosis values to ensure adherence to a normal distribution.

A two-way ANOVA was conducted to examine the differences in ERP values among COVID-19 positive and negative groups across different age categories (under 50 and over 65 years). The analysis aimed to assess the main effects of two independent variables: COVID-19 status (positive/negative) and age category (under 50/over 65) on ERP values, as well as the interaction effect between these variables.

Before conducting the two-way ANOVA, the normality of ERP values in each group was evaluated using the Shapiro-Wilk test. The results indicated that all groups had a p-value > 0.05, suggesting that the data followed a normal distribution. Thus, the assumption of normality required for the two-way ANOVA was satisfied.

The two-way ANOVA was used to analyze the main effects of both COVID-19 status and age category on ERP values, as well as the interaction effect between these two factors. The analysis examined whether COVID-19 status had a significant effect on ERP values, whether age category (under 50 vs. over 65) influenced ERP values, and whether there was an interaction between COVID-19 status and age in affecting ERP values.

After obtaining significant differences from the ANOVA, the Tukey HSD post-hoc test was applied to determine which specific groups differed from one another. This test identified which groups exhibited statistically significant differences.

Moreover, linear regression analysis was conducted to explore the relationship between age and measurement values, as well as between disease severity and measurement values. Linear regression serves to model the relationship between a dependent variable (in this context, measurement values) and one or more independent variables (such as age and disease severity), aiming to determine whether this relationship is linear.

RESULTS

Sociodemographic Characteristics: The study encompassed a cohort comprising 48 COVID-19 PCR-positive patients alongside 47 PCR-negative subjects (constituting the control group). The mean age of the participants was recorded at 48.9 (± 20) years. The mean age of the PCR-positive patient group aged over 65 was 67.8 (± 3.1), while the mean age of the PCR-positive patient group aged under 50 was 30.4 (± 9.2). The mean age of the PCR-negative control group aged over 65 was 68.5 (± 3), while the mean age of the PCR-negative control group aged under 50 was 31.2 (± 10). There was no significant difference in mean age between the COVID PCR-positive and PCR-negative groups among participants over 65 years old ($p > 0.05$). Similarly, there was no significant difference in mean age between the two groups under 50 years old ($p > 0.05$). Of the participants, 50.5% (48) were male, while 49.5% (47) were female. In the PCR-positive groups, there were 50% (12) males in the under 50 age group and 54% (13) males in the over 65 age group. In the PCR-negative groups, there were 47% (11) males in the under 50 age group and 50% (12) males in the over 65 age group. Comprehensive details regarding participants' age and gender distribution can be found in Table 1 for reference.

Alterations in event-related potentials between the treatment period and the 60th day: In patients under 50 years of age with COVID-19 PCR positivity, prolonged P300 (328 ms) and N200 (227.6 ms) latencies, as well as reduced N2P3 (10.1 μ V) amplitudes, were observed on the first day of hospitalization compared to the community average ($p < 0.05$). When this

Table 1. Demographic data

Variables	Total (n = 95)	PCR-positive group under 50 years of age (n = 24)	PCR-negative group under 50 years of age (n = 23)	PCR-positive group over 65 years of age (n = 24)	PCR-negative group over 65 years of age (n = 24)
Age, years, Mean \pm SD	48.9 (20)	30.4 (9.2)	31.2 (10)	67.8 (3.1)	68.5 (3)
Gender, male n (%)	48 (50.5)	50 (12)	47 (11)	54 (13)	50 (12)

Mean \pm SD: Mean \pm standard deviation

Table 2. Event-related potential values on the first day of hospitalization and at the second month

		Event-related potentials					
		P-300		N-200		N2P3	
		First day (ms) (mean±SD)	P value	First day (ms) (mean±SD)	P value	First day (µV) (mean±SD)	P value
		Second month (ms) (mean±SD)		Second month (ms) (mean±SD)		Second month (µV) (mean±SD)	
PCR-positive groups	PCR-positive group under 50 years of age	328±6	<0.05	227.6±6.2	<0.05	10.1±0.9	<0.05
		321±5.1		222±5.4		11.4±0.8	
	PCR-positive group over 65 years of age	334±4	0.141	233.2±4	0.132	9±0.6	0.212
				232±4		9.1±0.4	

SD: standard deviation, ms: millisecond, µV: microvolt

Table 3. HCorrelation between main groups and event-related potentials at the first day of hospitalization

	Event-related potentials					
	P300		N200		N2P3	
	Mean±SD (ms)	P value	Mean±SD (ms)	P value	Mean±SD (µV)	P value
PCR-positive group under 50 years of age	328±6	<0.05	227.6±6.2	<0.05	10.1±0.9	<0.05
PCR-positive group over 65 years of age	334±4		233.2±4		9±0.6	
PCR-positive group under 50 years of age	328±6	<0.05	227.6±6.2	<0.05	10.1±0.9	<0.05
PCR-negative group under 50 years of age	320±5.4		219.8±4.9		12±0.7	
PCR-negative group under 50 years of age	320±5.4	0.722	219.8±4.9	0.658	12±0.7	0.705
PCR-negative group over 65 years of age	322.4±4.8		222.7±4.4		11.6±0.9	
PCR-positive group over 65 years of age	334±4	<0.05	233.2±4	<0.05	9±0.6	<0.05
PCR-negative group over 65 years of age	322.4±4.8		222.7±4.4		11.6±0.9	

SD: standard deviation, ms: millisecond, µV: microvolt

group was re-evaluated for event-related potentials on the 60th day, it was found that the P300 (321 ms) and N200 (222 ms) latencies had significantly shortened, and the N2P3 (11.4 µV) amplitudes had significantly increased ($p < 0.05$) (Table 2).

In patients over 65 years of age with COVID-19 PCR positivity, prolonged P300 (334 ms) and N200 (233.2 ms) latencies, as well as reduced N2P3 (9 µV) amplitudes, were observed on the first day of hospitalization compared to the community average ($p < 0.05$). When re-evaluated on the 60th day, although there were improvements in the values (in order: 332 ms; 232 ms; 9.1 µV), the changes were not statistically significant ($p > 0.05$) (Table 2)

Comparison of event-related potentials between main groups:

When comparing the two main groups under 50 years of age, the PCR-positive group showed a statistically significant prolongation in N200/P300 latencies and a significant reduction in N2P3 amplitudes compared to the PCR-negative group (in order: 227 ms vs. 219 ms; 328 ms vs. 320 ms; 10.1 µV vs. 12 µV) ($p < 0.05$) (Table 3).

When comparing the two main groups over 65 years of age, the PCR-positive group exhibited a statistically significant prolongation in N200/P300 latencies and a significant reduction in N2P3 amplitudes compared to the PCR-negative group (in order: 233 ms vs. 222 ms; 334 ms vs. 322 ms; 9 µV vs. 11.6 µV) ($p < 0.05$) (Table 3).

When comparing the PCR-positive main groups, the group over 65 years of age exhibited a statistically significant prolongation in N200/P300

latencies and a significant reduction in N2P3 amplitudes compared to the group under 50 years of age (in order: 233.2 ms vs. 227.7 ms; 334 ms vs. 328 ms; 9 µV vs. 10.1 µV) ($p < 0.05$) (Table 3).

When comparing the PCR-negative groups, no statistically significant differences were observed in N200/P300 latencies and N2P3 amplitudes between the two main groups under 50 years of age and over 65 years of age (in order: 219.8 ms vs. 222.7 ms; 320 ms vs. 322.4 ms; 12 µV vs. 11.6 µV) ($p > 0.05$) (Table 3).

Additionally, as a significant point, when we examined the relationship between disease severity and event-related potentials, we observed that disease severity negatively impacts cognitive functions. The results of the regression analysis for the effect of Disease Severity on P300 latency indicated an R^2 value of 0.228, signifying that 22.8% of the variance in P300 latency is explained by the Severity variable. The ANOVA results revealed $F(1, 46) = 13.598$ and $p = 0.001$, confirming that the model is statistically significant. Examining the coefficients, the constant (Const) was determined to be 321.836, and the Severity coefficient was observed as 5.878, indicating a positive effect of Disease Severity on P300 latency. Similarly, the regression analysis for the effect of Disease Severity on N2P3 amplitude was conducted, yielding an R^2 value of 0.213. This indicates that 21.3% of the variance in N2P3 amplitude is explained by Disease Severity. The ANOVA results showed $F(1, 46) = 12.433$ and $p = 0.001$, demonstrating that the model is significant. In terms of coefficients, the constant was found to be 11.045, while the coefficient for Disease Severity was -0.902, indicating that an increase in Disease Severity is associated with an average decrease in N2P3 amplitude (Figure 1,2).

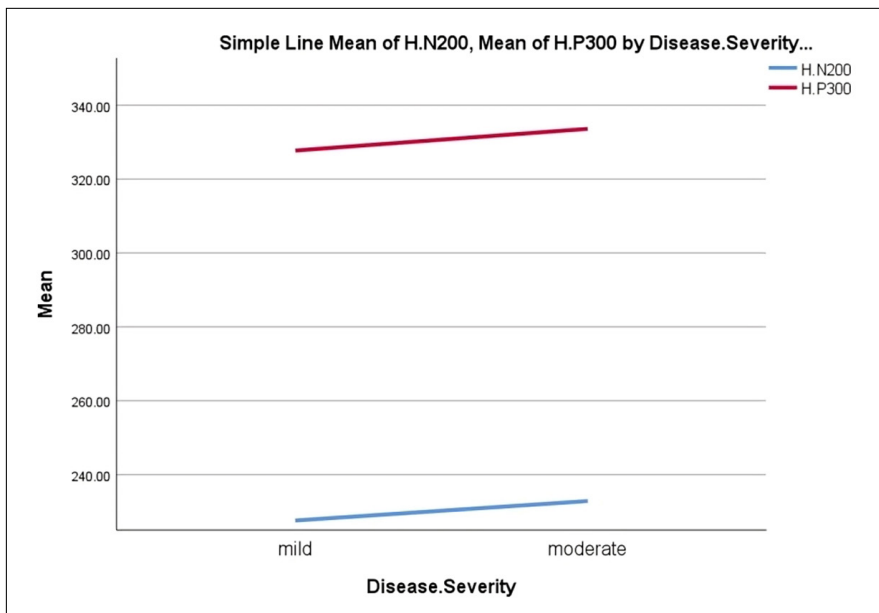


Figure 1. Linear regression analysis showing the effect of disease severity on N200 and P300 latencies. *The severity of disease has negative effect on the cognition.

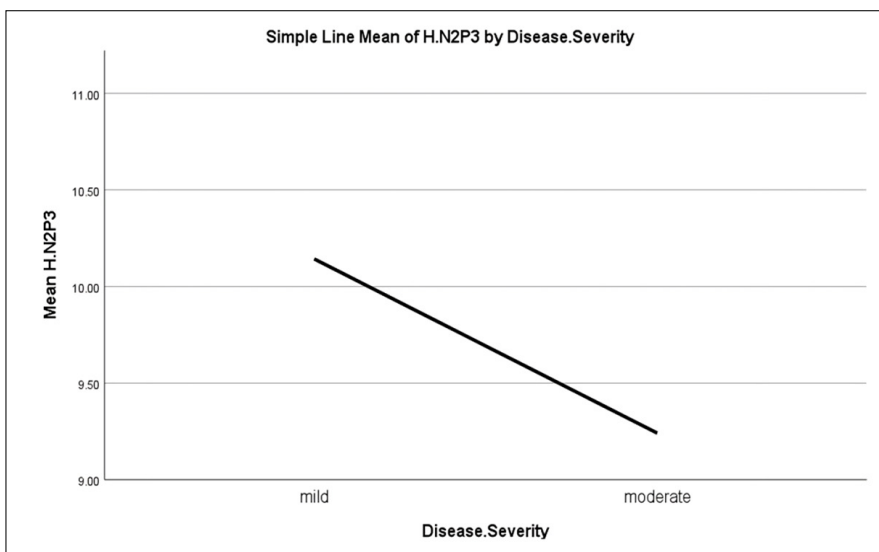


Figure 2. Linear regression analysis showing the effect of disease severity on N2P3 amplitudes. *The severity of disease has negative effect on the cognition.

DISCUSSION

Central nervous system (CNS) involvement has been hypothesized, given the reported neurotropic nature of the virus toward the CNS (9). The systemic inflammation induced by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which underlies the disease, disrupts the blood-brain barrier, leading to GABAergic damage and neuronal degeneration in the brain (10). Consequently, the hypoxic conditions associated with pneumonia can affect the brain, causing heightened oxidative neuronal damage and inflammation (11).

The condition known as Long-COVID-19 or post-COVID-19 syndrome remains incompletely defined. However, symptoms such as fatigue, headache, dyspnea, and cognitive deficits are frequently reported among those affected (12). Emerging evidence indicates that certain patients experience symptoms like fatigue, 'brain fog,' or cognitive issues following the acute infection phase, often termed 'Long COVID.' A six-month study utilizing comprehensive data from the medical records of 73,435 COVID-19 patients demonstrated that beyond the initial 30 days of illness, individuals face heightened risks of mortality, increased healthcare resource utilization, and a greater burden from neurocognitive

disorders (13). The increased risk of thrombosis and stroke during the disease progression also contributes to cognitive impairment. Limited studies suggest that experimentally induced cerebral hypoperfusion may promote amyloid β deposition and activate tau and TDP-43 pathology (14). Furthermore, another study has reported that olfactory dysfunction, which can occur in COVID-19 patients with a homozygous ApoE e4 mutation, may trigger the onset of dementia (15). Similarly, numerous theories have been suggested to clarify the pathogenesis of PACS, including the possibility of persistent SARS-CoV-2 reservoirs in tissues, immune system dysregulation, autoimmunity, or microvascular injury (16). Research indicates that patients experiencing acute COVID-19 with neurological symptoms often show increased levels of cytokines and markers indicating neuronal damage. Furthermore, a correlation has been observed between elevated cytokines or neuronal damage markers and the emergence of post-acute sequelae of COVID-19 (17).

Neuroimaging investigations concerning PACS have produced inconsistent results: while some studies have reported a decrease in cortical thickness, gray matter volume, and cerebral blood flow in comparison to control groups, others have noted an increase in gray

matter volume in particular areas of the brain, such as the hippocampus and insula. Moreover, white matter hyperintensities have also been reported. Nonetheless, the overall significance of these findings and their link to the cognitive effects seen in PACS patients is still uncertain, and currently, there is no clear agreement on the pathogenic processes driving PACS (18).

In our study, the mean N200/P300 latencies and N2P3 amplitudes of the control group under 50 years old, who tested negative for COVID-19 PCR, were observed to be significantly shorter in latencies and significantly higher in amplitudes compared to the patient group of the same age who tested positive for COVID-19 PCR ($p < 0.05$). Similarly, the mean N200/P300 latencies and N2P3 amplitudes for the control group over 65 years of age who tested negative for COVID-19 PCR were significantly shorter in terms of latencies and significantly higher in terms of amplitudes when compared to those of the patient group in the same age cohort who tested positive for COVID-19 PCR ($p < 0.05$). These data indicate that COVID-19 infection has an adverse effect on cognitive functions.

When comparing the N200/P300 latencies and N2P3 amplitudes among different age groups of COVID-19 PCR-positive individuals, the values for the group under 50 years of age were found to be significantly shorter in latencies and significantly higher in amplitudes compared to those of the group over 65 years of age ($p < 0.05$). In contrast, when comparing COVID-19 PCR-negative participants by dividing them into under 50 and over 65 age groups, no significant differences were found in terms of N200/P300 latencies and N2P3 amplitudes ($p > 0.05$).

In our study, when comparing the event-related potential changes in COVID-19 PCR-positive patients during treatment and on the 60th day post-discharge, we found a statistically significant improvement in the group under 50 years of age ($p < 0.05$). However, this was not the case for the group over 65 years of age. While there was an observed improvement in event-related potentials on the 60th day post-discharge in the over-65 age group, this improvement was not statistically significant ($p > 0.05$).

Upon reviewing the literature, while studies specifically evaluating the impact of COVID-19 on cognitive functions using event-related potentials like N200/P300 are scarce, there is extensive research focusing on the assessment of cognitive functions more broadly. In the study conducted by Amalakanti et al., it was found that cognitive outcomes in patients with COVID-19 PCR positivity were lower in individuals over 50 years compared to their younger counterparts ($p < 0.05$), a finding that is similar to the results of our study. However, unlike our study, they did not observe a significant difference in overall cognitive outcomes between the control and patient groups ($p > 0.05$) (19).

It has been mentioned in studies by Hosp and colleagues that evaluated MoCA scores and found a decrease in cognitive outcomes in COVID-19 patients, which is similar to the findings in their own study (20). Méndez et al.'s study assessing cognitive functions in COVID-19 patients post-discharge shares similarities with our study. They evaluated patients' cognitive functions neuropsychologically post-discharge and recorded outcomes that similarly showed deterioration, akin to our findings. However, unlike our study, their research did not assess cognitive impairment during the acute-subacute phase pre-discharge (21).

In their study, Negrini et al. observed a deterioration in MMSE (Mini Mental State Examination) test scores among severe COVID-19 cases in the acute phase. While their study aligns with ours in evaluating cognitive outcomes, it differs by focusing specifically on patients with severe COVID-19 (22).

Crivelli et al.'s meta-analysis, similar to our study, demonstrated that cognitive impairment during the post-COVID period significantly

worsened in patients with moderate COVID-19 (23). In Bertuccelli et al.'s review study, it was noted that cognitive functions such as memory, attention, and executive functions were similarly adversely affected during the post-COVID period (24).

In Manera et al.'s study, when comparing cognitive impairment in COVID-19 patients across different age groups, they found that younger patients exhibited better outcomes in cognitive functions such as short- and long-term memory and orientation compared to older patients. These findings align with our study, indicating that older age groups tend to experience greater cognitive impairment (25).

When examining these studies, it was found that event-related potentials, which are neurophysiological parameters, were not evaluated. Our findings are consistent with the literature regarding the direction of cognitive impairment. The inclusion of N200/P300 potential research and the comparative evaluation of the effects of COVID-19 in the acute, subacute, and post-COVID periods enhance the reliability of this study. We believe that the current data will significantly contribute to the literature by revealing the effects on cognitive functions between elderly and young cohorts.

Among the limitations of our study, we would like to point out that although the PCR test results of the participants in the control group were confirmed to be negative upon retesting, the possibility of false negatives depending on the day the PCR was taken raises concerns about the actual health status of some individuals in the control group. Additionally, the absence of neuropsychological assessments, alongside the neurophysiological evaluations, is also considered a limitation of our study.

In our study, we determined that COVID-19 negatively impacts cognitive functions, with the severity of this effect increasing with age. Furthermore, it was observed that these effects might persist into the post-COVID period. Additionally, our study demonstrated that the severity of the disease has a negative impact on cognitive functions. Long-term follow-up and multicenter studies with a large number of patients are needed to determine whether cognitive impairment following COVID-19 persists over the years and whether this condition can be considered a risk factor for dementia.

Ethical approval: The ethics committee approval for the study was obtained from the Scientific Research Ethics Committee of the University of Health Sciences on 09.06.2020/2020-238.

Informed Consent: All participants furnished informed and voluntary consent by endorsing the informed consent form.

Peer-review: Externally peer-reviewed.

Author contribution: Conception: EE, ÖK; Design: EE, JS, ÖK; Supervision: EE, ÖK; Materials: ÖK; Data collection and/or Processing: EE, JS, AÖK, ÖK; Analysis-interpretation: AÖK, JS; Literature review: EE, JS, AÖK, ÖK; Writing: EE, JS, AÖK, ÖK; Clinical Review: EE, JS, AÖK, ÖK; Statistical analysis: JS, AÖK.

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