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Auditory cognitive assessment in post COVID-19 patients: a case control study

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Abstract

Background There is increasing evidence suggesting that individuals with coronavirus disease 2019 (COVID-19) may experience symptoms that persist beyond the initial acute phase commonly referred to as "Long COVID." Cognitive deficits were among the frequently reported long-lasting symptoms post-COVID-19. Consequently, the study was designed to evaluate cognitive-communicative abilities in post COVID-19 patients focusing on auditory memory and auditory attention and to study the effect of different variables on these abilities in post COVID-19 patients.

Methods Eighty adult subjects were divided equally according to the presence or absence of a history of COVID-19 infection into the study and control group, respectively. All subjects were submitted to thorough history taking, basic audiological evaluation, auditory cognitive psychophysical tests including Auditory Continuous Performance test, Speech Intelligibility in Noise, Recognition memory, Memory for content and for sequence tests, digit span forward and backward tests, and electrophysiological auditory event-related potential (P300).

Results Post COVID-19 group showed significantly lower scores compared to the control group in all psychophysical auditory cognitive tests for attention and memory and significantly prolonged P300 wave latency and smaller amplitude. None of the variables measured (including duration passed from infection, severity, and number of infection) showed significant relations to test results except a significant negative correlation between the number of infections and memory for sequence results.

Conclusion Single infection with COVID-19 can have a prolonged impact on auditory cognitive abilities which were not related to the degree of severity of COVID-19. Thus, patients recovered from COVID-19 should receive auditory cognitive evaluations to detect even mild cognitive deficits that can affect quality of life.

Keywords COVID-19, Auditory attention, Auditory memory, P300

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 as the cause of a respiratory illness designated as coronavirus disease 2019 (COVID-19) [1], while patients with COVID-19 frequently suffered from respiratory symptoms; Neurologic and neuropsychiatric complications have been increasingly reported [2, 3].

COVID-19 is a short-term illness, and in general, the patients return to their usual state of health 12–14 days after receiving a positive test result [4]. However, it has been reported that some patients still have symptoms for weeks or even months after acute infection. The term "Chronic COVID" or "Long COVID" describes symptoms persisting for more than 12 weeks after infection [5]. Symptoms may be new onset following initial

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recovery from an acute COVID-19 episode or persist from the initial illness period [6].

Persistent cognitive impairments with memory and attention difficulties were increasingly reported in a large proportion of patients for several months after their recovery from COVID-19 [7]. Neuroimaging and EEG have shown structural and functional abnormalities, often in the frontal, temporal, and limbic regions [8]. These support the hypothesis that COVID-19 may contribute to cognitive impairment [9].

The specific pathological mechanisms underlying cognitive impairment associated with COVID-19 remained unclear. However, there are several proposed mechanisms for the central nervous system (CNS) affection including direct viral invasion to neurons and crossing the blood–brain barrier [10], inflammatory response, impaired clearance of brain metabolites including beta-amyloid peptides which was associated with Alzheimer's disease [11, 12]. Furthermore, hypoxemia and thrombo-inflammatory response induced by COVID-19 can cause transitory ischemia [13].

Cognitive impairments in COVID-19 patients were increasingly reported as a common complication of COVID-19 which can significantly impact daily functioning [14]. Our study focused mainly on the cognitive abilities related to the auditory modality only which were not exclusively examined in the previous studies on cognitive deficits post-COVID-19. Thus, we aimed to investigate the long-term consequences of COVID-19 on cognitive communicative abilities focusing on auditory memory and auditory attention and to study the effect of different COVID-19-related variables on cognitive communicative abilities.

Methods

This case control study was conducted from March 2022 till October 2023 in Audiology Unit, at Ain Shams University Hospital. The study was approved by the research ethical committee of the Faculty of Medicine, at Ain Shams University (FMASU MS 135/2022).

Forty subjects with past history of COVID-19 infection served as the study group and were selected according to the following criteria: age ranged from 18 to 50 years old, normal hearing thresholds, diagnosed as COVID-19 infection (by a positive result on real-time polymerase chain reaction PCR test), and recovered for at least 3 months from COVID-19. Patients with complaints of cognitive dysfunction prior to COVID-19 infection were excluded. The study group was compared to a control group which constituted of 40 normal-hearing subjects with no history of COVID-19 infection or any cognitive affection. In both groups, subjects with neurological or systemic disorders that could affect cognitive functions were excluded.

Both groups were subjected to the following:

- Full history taking: providing information about their socio-demographic data, otological, medical history, history of COVID-19 infection including (onset, duration of illness, symptoms, severity, investigations done for diagnosis and management) and cognitive complaints related to post COVID-19 symptoms including attention and memory problems.
- Basic audiological evaluation using pure tone audiometry to confirm normal hearing threshold (250, 500, 1000, 2000, 4000, and 8000 Hz)

Auditory cognitive assessment tests including the following:

a. Arabic subjective psychophysical tests performed on two-channel audiometer Model MADSEN Astera 2.

   - Speech discrimination in noise test (SPIN) for adults [15]: to test selective auditory attention ability. The stimulus was presented monaurally at a level of 50 dBSL (regarding SRT) with a signal-to-noise ratio (SNR) equal zero dB. Scoring was done by calculating the number of % correct words out of the total.
   - Auditory continuous performance test (ACPT) [16]: to test sustained auditory attention ability. Speech test materials were delivered through a loudspeaker at a presentation level of 50 dB SL. The response was considered wrong, whenever the subject did not raise his hand corresponding to the target word or when he raised his hand corresponding to any of the non-target words.
   - Recognition memory test [16]: speech test materials were delivered through a loudspeaker at a presentation level of 50 dB SL. Scoring for each list was done by subtracting wrong responses from eleven. Final scoring is reached by calculating the mean of the five lists.
   - Memory for content test [16]: the test materials were delivered through a loudspeaker at a presentation level of 50 dB SL. The subject was instructed to repeat the whole list regardless of its sequence. The highest number of words the candidate could memorize was taken as his score.
   - Memory for sequence test [16]: the subject was instructed to repeat the whole list in the same order he had just heard. The list sequence

was considered wrong, with any wrong word arrangement.

- Digit span test [17]: The test was done in a quiet situation. Each digit is said in a monotone live voice, one second apart. The subject was informed to repeat them as heard in ascending order in digit span forward and in reverse order in digit span backward (this variation requires the participant to hold the digits longer in their working memory). The Digit Span score is the length of the longest correct sequence that the subject could repeat.

b. Objective Auditory evoked event-related potential P300 on evoked potentials system Model (interacoustics ECLIPSE EP25) using oddball paradigm with the frequent stimulus 1000 Hz tone burst and the deviant stimulus 2000 Hz tone burst. The stimuli were presented binaural at an intensity of 80 dB SPL through a loudspeaker in a silent sound-treated room.

Statistical plan

The collected data was tabulated and statistically analyzed using the SPSS program (Statistical Package for Social Sciences) software version 26.0. Data was presented and suitable analytical tests were accordingly used; comparisons between both study and control groups were done for quantitative non-parametric data using Mann–Whitney *U*. Correlation analysis (using Spearman's method): to assess the strength of association between two non-parametric quantitative variables. The level of significance was taken at *P* value < 0.05 is significant, otherwise is non-significant.

Results

This study was conducted on two groups (study and control group) matched in age, gender, and educational level ($P > 0.05$). The study group ages ranged from 22 to 50 years with a mean age of 33.75 ± 8.80 years, with a female to male distribution of 1.5:1, and most of the group (57.5%) achieved a bachelor's degree, while the control group age ranged from 19 to 49 years with mean age 32.45 ± 8.58 years and female to male distribution of 0.8:1 and the majority (67.5%) also achieved a bachelor's degree.

The study group had statistically significantly worse scores in all subjective tests and objective tests for auditory cognitive abilities ($p < 0.05$) with absent P300 wave in five patients Tables 1, 2 and 3.

Effect of variables

None regarding duration passed from COVID-19 infection, number of infections, and severity of infection showed a significant effect on the results of auditory cognitive assessments ($P > 0.05$) (Tables 4 and 5, Fig. 1) except for the significant negative correlation between number of infections and memory for sequence score.

Discussion

The present study aimed to investigate persistent specific auditory cognitive functions impacted by COVID-19, after recovery from infection.

Half of the patients (50%) in the study group complained of memory and attention deficits after COVID-19. These agreed with many studies which identified similar deficits, including problems with short-term memory, long-term memory, and attention [18–20]. Similarly, Krishnan et al. [21] and Herrera et al. [22] found that patients who experienced COVID-19 reported difficulties with auditory attention.

Table 1 Comparison between study and control groups regarding SPIN and ACPT

		Study group ($n = 40$)	Control group ($n = 40$)	^{Z}MWU	*P*-value
SPIN Right ear	**Mean ± SD**	92.8 ± 3.7	96.25 ± 2.13	5.160	**< 0.001**
	Median	94.0	96.0		
	Range	76.0–98.0	90.0–100.0		
SPIN Left ear	**Mean ± SD**	92.25 ± 5.27	96.25 ± 1.82	5.237	**< 0.001**
	Median	93.0	96.0		
	Range	72.0–98.0	94.0–100.0		
ACPT	**Mean ± SD**	18.90 ± 1.35	19.97 ± 0.16	4.505	**< 0.001**
	Median	20.0	20.0		
	Range	16.0–20.0	19.0–20.0		

P-value < 0.05 is significant, *P*-value < 0.01 is highly significant

SD standard deviation, ^{Z}*MWU* Mann–Whitney *U* test

Table 2 Comparison between the study and control groups regarding memory and digit span tests

		Study group ($n=40$)	Control group ($n=40$)	^{Z}MWU	*P*-value
Recognition memory score	**Mean ± SD**	9.57 ± 1.24	10.55 ± 0.5	4.211	**< 0.001**
	Median	10.0	11.0		
	Range	5.0–11.0	10.0–11.0		
Memory for content score	**Mean ± SD**	4.77 ± 0.73	5.82 ± 0.75	5.301	**< 0.001**
	Median	5.0	6.0		
	Range	3.0–6.0	4.0–7.0		
Memory for sequence score	**Mean ± SD**	4.13 ± 0.72	4.85 ± 0.53	4.557	**< 0.001**
	Median	4.0	5.0		
	Range	3.0–6.0	4.0–6.0		
Digit span score forward	**Mean ± SD**	5.48 ± 1.11	6.03 ± 0.97	2.085	**0.037**
	Median	6.0	6.0		
	Range	3.0–7.0	4.0–8.0		
Digit span score backward	**Mean ± SD**	4.03 ± 0.97	4.60 ± 0.96	2.579	**0.010**
	Median	4.0	5.0		
	Range	3.0–6.0	3.0–8.0		

P-value < 0.05 is significant, *P*-value < 0.01 is highly significant

SD standard deviation, ^{Z}*MWU* Mann–Whitney *U* test

Table 3 Comparison between the study and control groups regarding P300 latency and amplitude

		Study group ($n=40$)	Control group ($n=40$)	^{Z}MWU	*P*-value
P300 latency in ms	**Mean ± SD**	365.94 ± 57.32 ($n=35$)	315.98 ± 23.04	4.288	**< 0.001**
	Median	358.0	310.0		
	Range	300.0–530.0	250.0–378.0		
P300 amplitude in µV	**Mean ± SD**	3.91 ± 2.47 ($n=35$)	6.97 ± 1.88	5.746	**< 0.001**
	Median	3.70	6.53		
	Range	0.95–11.77	4.50–12.37		

P-value < 0.05 is significant, *P*-value < 0.01 is highly significant

SD standard deviation, ^{Z}*MWU* Mann–Whitney *U* test

In the current study, significant impairment in cognitive abilities involving auditory memory, auditory selective, and sustained attention was demonstrated in patients with past history of COVID-19 by subjective psychophysical test results and objective test (p300) in the form of prolonged latencies and small amplitude reflecting abnormalities in auditory cognitive processing and attention resource allocation (Tables 1, 2 and 3). These findings agreed with Cian et al. [23] who showed a significant difference between COVID-19 patients and the control group in memory tests particularly in free and delayed verbal recall, recognition, and working memory using digit span backward test. Additionally, a systematic review by Bertuccelli et al. [24] reported memory, attention, and executive functions (including sustained and selective attention) to be the most affected cognitive domains, highlighting a potential effect of previous post-COVID-19 infection on cognitive impairments. These were further proven by neuro-imaging studies where there was a greater loss of gray matter in several brain areas mainly in the orbitofrontal cortex and parahippocampal gyrus [25], structural alterations in white matter tracts, reduced cortical thickness and decreased cerebral blood flow with many of the areas related to auditory processing [26].

On the other hand, Baseler et al. [27] did not find a significant impact of COVID-19 on memory in adults 18–24 years old which could be attributed to different tests used as he depended on questionnaires, also the age group was mainly young adults with expected

Table 4 Correlation between duration from COVID-19 infection on auditory cognitive abilities

	Time passed from COVID-19 infection	
	r	*P*-value
ACPT score	0.237	0.141
Recognition memory score	−0.049	0.763
Memory for content score	0.026	0.871
Memory for sequence score	0.097	0.550
SPIN (right ear)	0.113	0.489
SPIN (left ear)	0.106	0.515
Digit span score forward	−0.073	0.653
Digit span score backward	0.116	0.477
P300 latency in ms	0.211	0.223
P300 amplitude in μV	−0.217	0.212

P-value < 0.05 is significant, *P*-value < 0.01 is highly significant, *r* Spearman correlation

Table 5 Correlation between number of infection and auditory cognitive abilities

	Times of infection	
	r	*P*-value
ACPT score	0.030	0.853
Recognition memory score	−0.155	0.340
Memory for content score	−0.272	0.089
Memory for sequence score	−0.387	**0.014**
SPIN (right ear)	−0.069	0.673
SPIN (left ear)	−0.268	0.094
Digit span score forward	−0.073	0.654
Digit span score backward	−0.181	0.264
P300 latency in ms	−0.101	0.559
P300 amplitude in μV	0.133	0.440

P-value < 0.05 is significant; *P*-value < 0.01 is highly significant, *r* Spearman correlation

better performance. Also, Zhou et al. [28] showed no significant differences in digit span tests between the two groups. However, this study had a relatively small sample and the evaluation has been performed online.

Impairment in auditory cognitive abilities post COVID-19 can be attributed to direct viral entry to CNS through direct neuronal infection and axonal transport to CNS or through hematogenous spread by crossing the blood–brain barrier [10]. Furthermore, the inflammatory response initiated by COVID-19 can lead to endothelial lesions, leading to further compromise in the blood–brain barrier which can help viral infiltration and impair brain metabolites clearance, including beta-amyloid peptides, which are involved in Alzheimer's disease [29]. Lastly, hypoxemia and thrombo-inflammatory response can lead to transient ischemia affecting cognitive centers.

The severity of COVID-19 showed no significant effect on auditory cognitive abilities (Fig. 1). These results were in agreement with a study which examined COVID-19 patients with varying disease stages (mild, moderate, severe, and critical) and revealed that there was no correlation between disease severity and cognitive deficits [30]. These results were augmented by a metanalysis in 2022 concluding that there was no significant association between deterioration of cognitive function and severity of illness [31]. On the contrary, Alemanno et al. [18] reported that patients with more severe COVID-19 infection were found to have greater cognitive deficits 1 month after discharge, it is noteworthy that their study group was mainly elderly. Moreover, the difference observed could be attributed to the duration from infection, as illustrated by a study by Ferrucci et al. [32] which indicated that clinical illness variables (e.g., oxygen saturation) affected cognitive impairment in the short and medium term but not in the long term.

In the current study, although patients had recovered from COVID-19 (for 6 months to 2 and half years ago) (Table 6) complaints of memory and attention were still present and no significant improvement was observed over time (Table 4); this was in agreement with Miskowiak et al. [33] who identified clinically significant cognitive impairments in 48–56% of the patients 1-year post-COVID-19 infection and was comparable to the frequency of symptoms observed 3 months post-infection.

Infection with COVID-19 only once can be sufficient to affect auditory cognitive abilities as there were no significant correlations with auditory test results. There were negative correlations with all memory tests which reached significance in memory for sequence tests only (Table 5) indicating that recurrent infections by COVID-19 may have a cumulative effect on memory impairment.

To the authors' best knowledge, there were no published reports that have specifically addressed the impact of the frequency or number of COVID-19 infections on cognitive abilities deficits.

Conclusion

COVID-19 had a prolonged effect on auditory cognitive functions which were not related to the severity of COVID-19 and didn't show improvement over time. A single COVID-19 infection was sufficient to affect auditory cognitive abilities. Thus, patients recovered from COVID-19 should receive auditory cognitive evaluations to detect even mild cognitive deficits that can affect the quality of life.

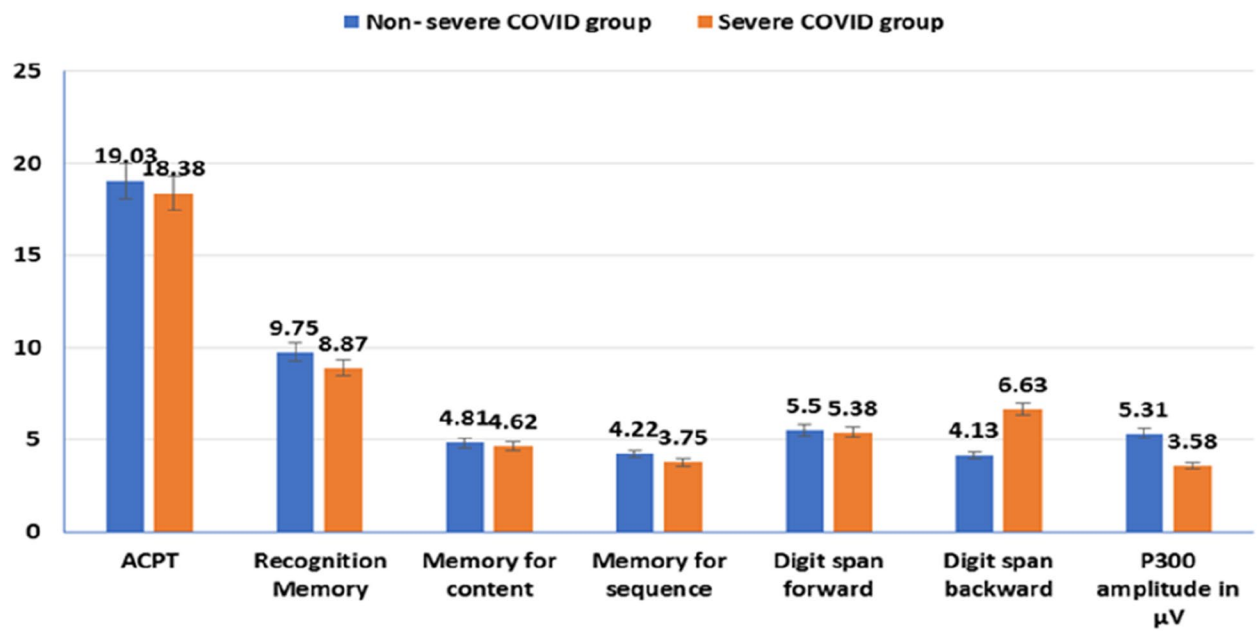

Fig. 1 Comparison between severe and non-severe groups regarding ACPT, memory tests, and P300 amplitude

Table 6 Clinical characteristics of COVID-19 in study group

		Study group ($n=40$)	
Duration from the COVID-19 infection till examination (in months)	**Mean ± SD**	16.48 ± 6.15	
	Median (IQR)	15.0 (12.0–19.0)	
	Range	6.0–32.0	
Numbers of times of infection with covid-19	**Once**	$n=34$	85.0%
	Twice	$n=4$	10.0%
	3 times	$n=2$	5.0%
Severity of COVID-19	**Non severe**	$n=32$	80%
	Severe	$n=8$	20%

20% of study group were severe cases according to WHO 2023 by having any of: oxygen saturation less than 90% on room air, severe pneumonia or signs of respiratory distress

Recommendation

This study's participants did not receive any auditory cognitive training so, a longitudinal study on post COVID-19 patients to assess the effect of remediation on auditory cognitive abilities as an effective therapeutic strategy for these patients was recommended.

Abbreviations

ACPT	Auditory Continuous Performance test
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNR	Signal-to-noise ratio
SPIN	Speech discrimination in noise test

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None.

Authors' contributions

RE formulated the research question, design of the work, and data analysis. HW conducted the design of the work and data analysis. AE conducted the data analysis and interpretations, helped in data acquisition, and revised the manuscript. HS conducted the acquisition and analysis of the data for the work and edited the manuscript. All authors gave their approval to the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the research ethical committee of the Faculty of Medicine, at Ain Shams University (FMASU MS 135/2022). Informed consent

was obtained from all subjects involved before testing after explaining the aim of the study and the procedures.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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