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Covid-19 affects Cognitive Functions and can leave Permanent Sequelae

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Abstract

COVID-19 has affected more than two hundred thousand people since 2019. Research worldwide has investigated the transmission of the disease, treatments, drugs, vaccination and the consequences of the pandemic and the social imprisonment that COVID-19 has caused. This study was conducted at the Heart Institute of the University of São Paulo-FMUSP and investigated cognitive dysfunctions caused after COVID-19. Volunteers, who had COVID-19 and physically recovered were evaluated. The digital game MentalPlus® was used for neuropsychological evaluation. The results show that the most impaired neuropsychological functions were short-term memory (62.7%), alternate attention (43.2%), executive function (83.6%) and visuoperception (92.4%). The study concludes that COVID-19 may lead to cognitive dysfunction after remission and may last for an indefinite period.

Keywords: MentalPlus®, cognitive dysfunction, COVID-19, neuropsychological evaluation

Introduction

COVID-19 have affected many people since late 2019 (Dryhurst et al., 2020). This virus has been researched since and brought some challenges to the scientific medical community and has proved increasingly intriguing (Velavan & Meyer, 2020). People's behaviour has changed since the beginning of the pandemic that overwhelmed the world (Cucinotta & Vanelli, 2020). The panic brought chaos, uncertainty and instated social, economic and political problems in several countries (Daniel, 2020). These problems led to unemployment, public disorder and health insalubrity (Pfefferbaum & North, 2020). Many countries closed their borders; others went into a calamity state; others started campaigns of isolation and closing businesses to contain the virus's spread (Watkins, 2020). It is known that the entrance route of the coronavirus is by the airways. However, it compromises several other organic systems; one is the central nervous system (CNS) (Filatov et al., 2020). There are two forms of transmission of COVID-19, the direct transmission by droplets of saliva, propagated by air when the contaminated person coughs, sneezes, directly in the direction to the other unprotected person. The indirect form of virus transmission is the most difficult to occur. It is unknown how long the virus would live, and on which surfaces it could live for longer. Brazil and some countries have initiated drug therapy protocols to minimize the spread, severity, and contraction of COVID-19.

Chloroquine, Hydroxychloroquine, Ivermectin were used among several other medications that are still being tested. All of them have already been published, and the result showed that they are not effective in combating, preventing COVID-19 (Beigel et al., 2020). There are hypotheses that some blood types are more likely to contract COVID-19 than others (Muñiz-Diaz et al., 2020; Zhao et al., 2020). Currently, the efficacy of many vaccines is being studied, and some of several laboratories are already in use in partnerships with renowned universities such as Oxford in England and São Paulo Medical School in Brazil (Graham, 2020; Lurie et al., 2020; Thanh Le et al., 2020). According to the World Health Organization, since the pandemic started, more than 200 million people have died because of COVID-19.

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Method

One hundred five patients were studied at the Heart Institute of the University of Sao Paulo-INCOR-FMUSP. The study was approved by the ethics committee - FMUSP. After the clinical examination and the collection of socio-demographic data and symptoms, the volunteers signed their own free and spontaneous consent and started the MentalPlus® digital game's cognitive evaluation. The study registered in the Brazil Platform under the number CAAE: 30430720.0.0000.0068 entitled "The use of the MentalPlus® digital game to evaluate and rehabilitate the cognitive function after remission the symptoms of COVID-19". The study's inclusion criteria were to have contracted the COVID-19 and to be cured of the virus on the day of the evaluation; age between 08 and 88 years; have a basic technological notion of handling a cell phone or tablet; have enough visual acuity to see the screen and motor dexterity to touch the screen of these electronic devices during testing. The exclusion criteria were; the insufficient capacity to understand rules or handle the electronic device; have upper limbs compromised that prevent hand movements during the cognitive testing; still, be positive for the PCR-RT test for COVID-19, and fever above 37.8°. For the cognitive evaluation, the digital game MentalPlus® used a validated and standardized cognitive test to assess mnemonic, attentional, executive, language, and visuoperceptive functions.

For this study, the Mentalplus® platform had the demographic data collection part altered so that we could attach medication used in addition to the persistent symptoms after COVID-19.

Statistical Analysis

The study's statistical analysis was performed using the MentalPlus® digital game results for cognitive evaluation. The study shows that the patients who contracted COVID-19 have had a cognitive deficit. For this comparison was used the control group's data that validated and standardized the Mentalplus® digital game. The qualitative characteristics were described using absolute and relative frequencies within the association between the groups; the quantitative characteristics were verified using the chi-square test. The results of cognitive functions evaluated by the MentalPlus® digital game were described using summary measurements (mean, standard deviation, median, minimum and maximum) and compared between groups using t-Student or Mann-Whitney tests (Kirkwood and Sterne, 2006). The IBM-SPSS for Windows version 20.0 software was used to perform the analyses, and the Microsoft Excel 2003 software was used for data tabulation. The tests were performed with a 5% significance level.

Results

The average age of the volunteers evaluated was 45(11;81) years, the schooling was higher than 12 years of studies prevailing in 144(77.8) % of the volunteers. The systemic arterial systolic pressure and the diastolic pressure remained high 128± (90; 186); 89± (60; 120) even after the remission of the symptoms of COVID-19. The mean heart rate was also high 88.6±15.8. The mean oxygen saturation was below the ideal 96.53±2. For blood type, type A+ prevailed with 37.84% of the sample, (Table 1).

Table 1. *Personal and clinical characteristics description according to groups and statistical test results*

Variable	Group		p
	Control MP (n=163)	COVID-19 (n=185)	
Age (years)	51,1±16,2	44,6±13,9	<0,0001
mean±SD	53(18;80)	45± (11;81)	
median (min.; max.)			
Schooling, n (%)			
Elementary	14(8,6)	16(8,6)	0,106*
Middle	36 (22,1)	25(13,5)	
High	113 (69,3)	144(77,8)	
College or >			
SBP			0,006
mean±SD	124,5±12,8	129,3±17,9	
median (min.; max.)	120 (110; 167)	128± (90; 186)	
DBP			<0,0001
mean±SD	77,4±8,5	88,4±11,3	
median (min.; max.)	80 (53; 95)	89± (60; 120)	
RH			<0,0001
mean±SD	82,1±13	88,6±15,8	
median (min.; max.)	80 (57; 115)	86± (59; 121)	
Oxygen Saturation			
mean±SD		96,53±2	
median (min.; max.)		97(99; 90)	
ABO blood			
A+	37,84%		N=70
A-	4,32%		N=6
B+	12,43%		N=24
B-	1,62%		N=4
O+	30,27%		N=56
O-	5,41%		N=15
AB+	3,78%		N=9
AB-	0%		N=0

Note: ***t-Student Test; *Chi-square Test***

Abbreviations: Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Heart rate (HR). This table shows that only schooling did not show a statistically significant association between groups (p = 0.106). On the other results, the mean was statistically higher in patients who had Covid-19 (p <0.05).

Table 2. *Description of the results of the MentalPlus® domains according to groups and comparative test results.*

Cognitive Functions	Group		P
	Control MP (n=163)	COVID-19 (n=185)	
Executive Function-Inhibitory Control - Hit			<0,0001
mean±SD	22,4±5,7	19,3±8	
median (min.; max.)	22(10; 30)	21 (0; 30)	
Executive Function-Inhibitory Control - Error			<0,0001
mean±SD	3,46±3,82	8,26±12,12	
median (min.; max.)	2 (0; 16)	4 (0; 84)	
Executive Function-Inhibitory Control - Omission			<0,0001
mean±SD	5,51±4,57	10,74±8,04	
median (min.; max.)	4 (0; 16)	9 (0; 30)	
Long-Term Memory - Hit			0,036
mean±SD	10,6±1,8	10,3±2	
median (min.; max.)	11 (1; 15)	11 (0; 14)	
Long-Term Memory- Error			<0,0001
mean±SD	2,88±1,35	4,47±1,76	
median (min.; max.)	3 (0; 6)	4 (0; 16)	
Long-Term Memory - Omission			<0,0001
mean±SD	3,35±2,08	4,56±1,66	
median (min.; max.)	3 (0; 9)	4 (0; 10)	
Alternated Attention - Hit			0,192
mean±SD	29,6±9,6	26,1±5,6	
median (min.; max.)	27 (13; 62)	28 (0; 30)	
Alternated Attention - Error			<0,0001
mean±SD	1,34±1,75	3,72±3,4	
median (min.; max.)	1 (0; 9)	3 (0; 16)	
Alternated Attention - Omission			<0,120
mean±SD	1,88±2,18	1,98±3,49	
median (min.; max.)	1 (0; 10)	1 (0; 23)	
Selective Attention - Hit			<0,0001
mean±SD	29,7±2,2	26, ±6,3	
median (min.; max.)	30 (22; 34)	29 (0; 30)	
Selective Attention - Error			<0,0001
mean±SD	0,66±1,51	3,17±3,59	
median (min.; max.)	0 (0; 8)	2 (0; 19)	
Selective Attention - Omission			<0,0001
mean±SD	0,54±1,93	1,96±4,24	
median (min.; max.)	0 (0; 22)	0 (0; 26)	
Short-Term Memory- Hit			<0,0001
mean±SD	12,2±1,6	9,4±3,8	
median (min.; max.)	13 (7; 14)	10 (0; 14)	
Short-Term Memory- Error			<0,0001
mean±SD	1,55±1,13	2,9±2,49	
median (min.; max.)	1 (0; 5)	2 (0; 14)	
Short-Term Memory- Omission			0,551
mean±SD	0,82±0,88	1,52±2,87	
median (min.; max.)	1 (0; 3)	0 (0; 12)	
Visuoperception- Hit			<0,0001
mean±SD	34,9±4,5	24,7±10,4	
median (min.; max.)	35 (18; 44)	24 (0; 51)	

Note: Mann-Whitney Test; MP= MentalPlus®.

Table 2 shows the results of the neuropsychological evaluation. The groups are statistically different; the COVID-19 group presented a statistically lower score of hits in the executive function's inhibitory control, long-term memory, selective attention, short-term memory and visuoperception ($p < 0.05$); for errors and omissions the COVID-19 group tended to present higher scores. The only domain that

the COVID-19 group presented similar hit scores with the control group was the alternate attention ($p = 0.192$), but the error score in this domain was statistically higher in the COVID-19 group ($p < 0.001$).

The digital game evaluated the neuropsychological functions of the COVID-19 group for long- and short-term memory, selective and alternate attention, visuoperception and executive function. There is a cognitive dysfunction after remission of symptoms to short-term memory in 62.7% of the volunteers. One hundred and thirty-four volunteers had a good capacity for long-term memory (73.2%). More than half of the group presented dysfunction for alternate (56.8%) and selective (71.9%) attention function. The evaluation detected alterations in the visuoperceptive function after COVID-19 in almost all the volunteers, 171 patients. Moreover, the executive function presented cognitive dysfunction in 83.6% of the group COVID-19, (Table 3).

Table 3. *Neuropsychological functions of the COVID-19 group analyzed in a degree of impairment.*

Cognitive Functions	N	%
Short-Term Memory		
preserved	69	37,3
compromised	116	62,7
Long-Term Memory		
preserved	134	73,2
compromised	49	26,8
Alternate Attention		
preserved	105	56,8
compromised	80	43,2
Visuoperception		
preserved	14	7,6
compromised	171	92,4
Executive Function		
preserved	30	16,4
compromised	153	83,6
Selective Attention		
preserved	133	71,9
compromised	52	28,1

Note: Percentages of cognitive dysfunctions presented by the COVID-19 group in the evaluation phase of the MentalPlus® digital game.

During the initial manifestation of the virus, several medications were prescribed. Regarding the patients' reports, azithromycin was the most prescribed medication for COVID-19 (37%); followed by antipyretic (32%) and (11%) dipyrone and paracetamol, respectively. The other medications were prescribed according to the current symptomatology during the medical consultation or hospitalization. Prophylactic medication prescriptions were made, such as anti-flu drugs (4%), anticoagulants (4%), vitamin C (4%), (Table 4).

Table 4. *Medicines used during the initial manifestation of the disease.*

Total Patients	N	%
With Medicine	**135**	**76**
Without Medicine	**43**	**24**
No declared	**7**	**3,78**
Azithromycin	66	37
Dipyrone	57	32
Paracetamol	20	11
Oseltamivir	17	10
Ivermectin	15	8
Loratadine	14	8
Prednisone	13	7
Ceftriaxone	13	7
Dexamethasone	12	7
Hydroxychloroquine	10	6
Omeprazole	8	4
Vitamins	8	4
Anti-flu	7	4
Metformin	7	4
Chloroquine	7	4
Enoxaparin	6	3
Anticoagulant	6	3
Levothyroxine	5	3
Vitamin C	5	3

Note: Percentage and medicines used during the COVID-19 initial manifestations symptoms.

In table 5, the physical, emotional, neurological and cognitive symptoms were presented by volunteers during the acute phase of COVID-19 and after remission of the disease. Dysgeusia was the most presented symptom in the COVID-19 group (101%), followed by 98 patients with anosmia (55%). Some symptoms, such as tiredness (29%), headaches (24%), shortness of breath (14%) were persistent after the COVID-19. Other symptoms that have compromised the daily activities of those affected by the COVID-19 was the memory loss (21%), attentional failures (19%), and failure in executive function (13%). Patients also presented symptoms such as anxiety (13%), irritability (10%), and depression (6%).

Table 5. *Symptoms presented by volunteers during the evaluation phase.*

Symptoms	N	%
With Symptoms	126	68.1
Without Symptoms	59	31.9
Dysgeusia	180	97.3
Anosmia	98	52.9
Tiredness	51	27.5
Headache	42	22.7
Memory failure	37	20
Attention failure	33	18
Myalgia	28	15.1
Respiratory failure	25	13.5
Anxiety	24	13
Executive function failure	24	13
Cacosmia	22	12
Irritability	18	10
Cough	16	8.6
Language failure	13	7
Depression	10	5.4
Fever	10	5.4
Coryza	9	5
Nausea	8	5
Sore throat	6	3.2
Muscle weakness	6	3.2

Note: Percentage of symptoms described during the phase of COVID-19 manifestation and after remission of the disease.

Discussion

COVID-19 leaves sequelae after its remission. The most investigated sequelae in some researches are the neurological ones, whereas the physical ones are by the numbers of cases and patients' complaints (Dubey et al., 2020). Neuropsychological and emotional dysfunctions have not yet been described in the scientific literature as causes and consequences of COVID-19 (Peteet, 2020). Cognitively evaluating a patient is not an easy task. It requires time, specialized professionals and validated and standardized neuropsychological tests. Several pathologies can present neuropsychological dysfunctions, such as clinics: diabetes, cardiovascular syndromes, hypertension, asthma; neurological, such as Alzheimer's, Parkinson's, multiple sclerosis; and psychiatric, such as schizophrenia, depression and anxiety (Bansal, 2020; Fang et al., 2020; Hornuss et al., 2020; Muniyappa & Gubbi, 2020; Vaira et al., 2020; Zheng et al., 2020). Neuropathologies or clinical pathologies after neuropsychological evaluation can receive conventional treatments for the rehabilitation of their cognitive functions. These treatments are conventional drugs and psychotherapies. There is an innovative treatment through digital games that enables cognitive rehabilitation of patients who present neuropsychological

dysfunction after these diseases. Digital games can be cognitive rehabilitator when well applied (Crespo et al., 2020). The digital game MentalPlus® is the only validated and standardized neuropsychological test that evaluates cognitive functions: attention, memory, executive, visuoperception and language. MentalPlus® is quick and easy to apply, requiring only 25 minutes of application for each assessment or rehabilitation phase (Pereira & Valentin, 2018). The instrument can be used as an assessment test or a neuropsychological rehabilitation game. The digital game MentalPlus® has 12 themes that can be used as follows; the first application as an assessment phase, ten themes that can be used to rehabilitate the patient and the last phase; or the twelfth theme phase re-evaluate the person being assessed (Valentin, 2017). MentalPlus® is registered in the Brazilian National Library, under patent number 915179377.

Conclusion

There are neuropsychological dysfunctions after COVID-19 that persist for a long and indefinite period. The primary neuropsychological dysfunctions found in this study were visuoperceptive, executive, attentional and mnemonic. Because only one neuropsychological test was used, this study may have biases. However, according to other research fields where these same protocols of Mentalplus® were used, it showed us how the cognitive stimulation profits the human cognition and already elucidated and reveals the consequences caused by COVID-19 and its benefits the pandemic that we are facing it.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial, or financial relationships construed as a potential conflict of interest.

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