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COVID-19 Associated Cognitive Dysfunction

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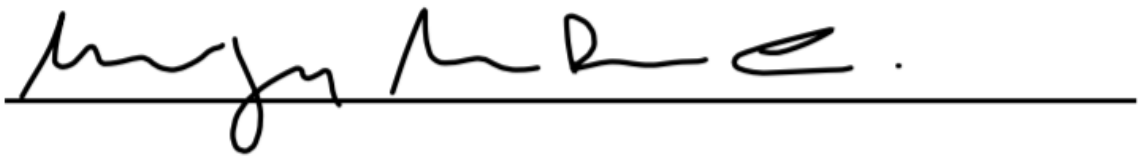

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Dedicatória

Para meu Isidro, que acreditou indubitavelmente em mim até ao seu último dia.

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Resumo

Introdução: O surto de SARS-CoV-2, que se iniciou em dezembro de 2019, rapidamente se tornou uma ameaça à saúde pública, tendo sido decretada pandemia pela Organização Mundial de Saúde em março de 2020. As queixas mnésicas e os défices cognitivos objetivos são frequentes pós *Coronavirus Disease 2019* (COVID-19). No entanto, poucos são os estudos que se debruçaram especificamente sobre o défice cognitivo a longo-prazo e os seus preditores.

Objetivos: O presente estudo tem como objetivos principais: 1) identificar a presença de sintomas persistentes 12 meses após a infeção por SARS-CoV-2 com ênfase no défice cognitivo e nas queixas cognitivas e 2) explorar variáveis demográficas e clínicas preditivas de défice cognitivo objetivo e de queixas cognitivas.

Métodos: Cem indivíduos com diagnóstico de COVID-19 entre março e novembro de 2020 participaram numa breve avaliação neurológica e neuropsicológica cerca de 12 meses após a infeção.

Resultados: Foram registadas alterações de desempenho cognitivo numa bateria breve composta por três testes neuropsicológicos em 43% dos indivíduos e foram classificados com défice cognitivo significativo e objetivável (alteração em pelo menos 2 dos 3 testes cognitivos) em 9% dos participantes. Os testes com maior frequência de défice medem aprendizagem e memória visual e verbal. Verificou-se que a baixa escolaridade e a insónia de novo aquando da infeção são fatores de risco de défice cognitivo um ano após COVID-19. O sexo feminino e o surgimento de distúrbio do sono aquando da infeção estão associados a mais queixas cognitivas, a mais sintomas de ansiedade, depressão e fadiga e a pior qualidade de vida a longo prazo. Apesar de estarem relacionados com mais queixas cognitivas subjetivas, o sexo feminino e os sintomas psicopatológicos não foram preditivos de défice cognitivo significativo e objetivável.

Conclusão: Os resultados do estudo documentam a persistência quer de défice cognitivo significativo quer de queixas cognitivas um ano após a infeção, suportando a noção de que uma percentagem de individuos desenvolve *Long-COVID*. A exploração dos possíveis preditores da função cognitiva quer objetiva quer subjetiva aponta para um efeito protetor da reserva cognitiva, enquanto distúrbio do sono de novo durante a fase aguda da COVID-19 parece ser um fator de risco para dificuldades cognitivas a longo-prazo. Ainda não é clara a relação entre o desenvolvimento de *Long-COVID* e a vacinação e reinfeção.

Palavras-chave: COVID-19, disfunção cognitiva, distúrbio do sono, reserva cognitiva

Abstract

Background: The SARS-CoV-2 outbreak that started in December of 2019 rapidly became a public health threat and in March 2020 a pandemic was declared by the World Health Organization. Cognitive complaints and cognitive deficits are frequent after Coronavirus Disease 2019 (COVID-19). However, there are few studies that dwell specifically on long-term cognitive deficit and its predictors.

Objectives: The main goals of the present study are: 1) to identify the presence of persistent symptoms 12 months after SARS-CoV-2 infection with focus on cognitive deficit and complaint and 2) to explore demographic and clinic predictors of objective cognitive deficit and cognitive complaint.

Methods: A hundred individuals with diagnosis of COVID-19 between March and November of 2020 participated in a brief neurologic and neuropsychological evaluation around 12 months after infection.

Results: Abnormal cognitive performance in at least one of the three neuropsychological tests was recorded in 43% of the individuals. Cognitive dysfunction (i.e., abnormal performance in at least 2 of the 3 cognitive tests) was found in 9% of the participants. The two tests with highest frequency of deficit measure visual and verbal learning and memory. Lower education levels and new-onset insomnia during the infection were found to be risk factors of cognitive dysfunction one year after COVID-19. The female gender and sleep disturbance during the infection were associated with more cognitive complaints, more symptoms of anxiety and depression, greater fatigue, and overall poorer long-term quality of life. Although being more related to subjective cognitive complaints, neither female gender nor psychopathology symptoms were predictive of cognitive dysfunction.

Conclusion: The study results document the persistence of significant cognitive deficits and complaints one-year post-infection, providing support to the notion that a subset of individuals develops Long-COVID. The exploration of possible predictors of both objective and subjective cognitive functioning points to the protective effect of cognitive reserve, whereas new-onset sleep disturbance during the acute phase of the COVID-19 infection appears to be a risk factor for long-term cognitive difficulties. It is unclear how the development of Long-COVID may be affected by variations in the virus, the availability of vaccines and the occurrence of reinfections.

Keywords: COVID-19, cognitive dysfunction, sleep disturbance, cognitive reserve

List of Abbreviations

ACE-2 – Angiotensin-Converting Enzyme-2

BBB – Blood-Brain Barrier

BICAMS – Brief International Cognitive Assessment for Multiple Sclerosis

BMI – Body Mass Index

BVMT-R – Brief Visuospatial Memory Test – Revisited

COPD **–** Chronic Obstructive Pulmonary Disease

CSF – Cerebrospinal Fluid

COVID-19 -Coronavirus Disease 2019

CVLT-II – California Verbal Learning Test

DM – Diabetes Mellitus

HADSA – Hospital Anxiety and Depression Scale - Anxiety

HADSD – Hospital Anxiety and Depression Scale - Depression

MFIS – Modified Fatigue Impact Scale

MMSE – Mini Mental State Examination

WHO – World Health Organization

CFQ – Cognitive Failure Questionnaire

RT-PCR – Real Time – Polymerase Chain Reaction

CNS – Central Nervous System

SDMT – Symbol Digit Modalities *Test*

ICU – Intensive Care Unit

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Introduction

The SARS-CoV-2 outbreak, that began in December of 2019, rapidly became a threat to public health and in March 2020 the World Health Organization (WHO) declared it a pandemic [(1)]. In 24 months, the pandemic has counted with over 400 million cases of Coronavirus Disease 2019 (COVID-19) and about 6 million deaths [(2)]. Nearly 10 billion vaccines have been administered [(2)].

The SARS-CoV-2 virus is an RNA-virus that belongs to the beta-coronavirus family, which is also the family of SARS-CoV and MERS-CoV, responsible for previous outbreaks [(3)]. This virus possesses a spike protein (1273 aminoacids), made of two trimeric fusion subunits – S1 and S2 [(4, 5)]. This protein is responsible for the connection of SARS-CoV-2 to the Angiotensin Converting Enzyme-2 (ACE-2), present in the membranes of the host's cells [(1, 3, 6-9)]. ACE-2 is expressed in arteries, oronasal mucosa, pulmonary epithelium, bone marrow, spleen, skin, heart, kidney, adipose tissue, reproductive system, brain, and intestinal mucosa [(3, 6, 7, 9)]. This protein makes the cells that possess ACE-2 the main targets of the virus and determines the extension, phenotype, and virulence of SARS-CoV-2 [(3)]. High levels of ACE-2 are associated with a variety of consequences as vasoconstriction, renal failure, heart disease, oxidative processes, and apoptosis that speed aging and brain degeneration [(8)]. After connecting to ACE-2 in the respiratory epithelium and blood vessels, SARS-CoV-2 triggers an excessive production of inflammatory cytokines, leading to an acute phenomenon called cytokine storm [(6, 10, 11)], which is marked by increased levels of interleukine-1, interleukine-6, and tumoral necrosis factor. This increase promotes vascular permeability, edema and generalized inflammation with consequent damage to cellular metabolism and protein production, as well as small ischemic infarctions on brain tissue, that in long-term may be associated with neurologic deficits [(8, 12)]. ACE-2 also modulates blood pressure, therefore its interaction with coronaviruses can induce an increase in blood pressure, that is itself a promotor for cerebral ischemic and hemorrhagic events, partially justifying the higher mortality among COVID-19 patients that present comorbidities such as high blood pressure, high Body Mass Index (BMI) and diabetes [(12)].

Systemic symptoms of COVID-19 infection resulting from the original virus and early variants (prior to the beginning of vaccination) typically began about five days after the first contact with the virus [(13)] and included fever, chills, cough, dyspnea, fatigue, myalgia, headaches, anosmia/dysgeusia, odynophagia, nasal congestion and nausea/vomit [(6, 9)]. Neurological manifestations were commonly anosmia/hyposmia and dysgeusia [(3)]. In the context of COVID-19, cases of encephalitis [(6, 14)], acute disseminated encephalomyelitis [(6, 14)], myelitis [(14)] and

Guillain-Barré Syndrome [3, 6] have also been described. Vascular cerebral disease related to COVID-19 [6, 14] had an estimated incidence of 1,4% according to a systematic review of Nannoni et al., being more frequent among individuals with cardiovascular risk factors prior to the infection and severe disease [15]. On a psychiatric and neuropsychiatric level, anxiety, depression, cognitive deficits, and sleep disturbance have been reported [16]. Possible causes for the neurological and neuropsychiatric symptoms related to COVID-19 include direct cortex and adjacent subcortical neuronal structures damage and indirect effects due to the systemic inflammatory activation and psychological trauma [17].

According to Koyuncu et al., all viruses are capable of reaching the Central Nervous System (CNS) under the right conditions, depending on viral factors (e.g., mutations in virulent genes) or host factors (e.g., immunodepression, age, comorbidities) [18]. It is known that several respiratory viruses, including coronaviruses, are neuroinvasive and neurotropic, with potential neuropathological consequences in vulnerable populations [19]. Coronaviruses have been associated to the physiopathology of neurodegenerative and neuroimmune diseases after viral particles of coronaviruses and antibodies anti-coronavirus were identified on the Cerebrospinal Fluid (CSF) of patients with Parkinson's Disease and Multiple Sclerosis [20-22]. The direct invasion of SARS-CoV-2 can occur in two ways: transneuronal pathway or hematogenic pathway [8]. The invasion theory by the transneuronal pathway through the cribriform plaque is supported by the existence of structural alteration in the olfactive tract, bulb and cortex found on Magnetic Resonance Imaging examination of COVID-19 patients [23, 24]. This alteration may be partially explained by the role of ACE-2, given its high density in the oronasal mucosa and its contribution to the development of symptoms in the senses of smell and taste [12]. Direct neuron infection with subsequent intracellular signaling change and cell death can alter neuronal connectivity [25]. SARS-CoV-2 may also reach the brainstem and lead to the impairment of respiratory centers [17] and to pain syndromes, that may persist in the post-infection phases [26]. However, direct infection is held as an unlikely neurological damage mechanism when it comes to COVID-19 [6].

The indirect effects that might be subjacent to the development of neurological alterations include neuroinflammation, cytokine storm, post-infectious autoimmunity, and hypercoagulability state [10, 12, 23, 27]. Neuroinflammation is a well-defined process that is involved in the development of psychiatric disturbances and is known to cause hypercoagulability states (which can provoke ischemic vascular events and other vascular manifestations) [12] and accelerate neurodegenerative processes [8]. On the other hand, neuroinflammation is also considered a secondary damage mediator due to cytokine and neurotropic factors secretion. Consequently, microglia, which is the CNS first line defense mechanism [28], is responsible for

inflammatory or immunomodulated responses of the cerebral tissue and may provide short-term neuroprotection, but can also lead to the development of neurodegenerative processes in the long-term, depending on the balance between inflammatory and anti-inflammatory cytokines produced in response to viral infection[19], being frequently a marker of neuroinflammation [8]. The cytokine storm provoked by SARS-CoV-2 infection, as previously explained, can trigger small ischemic infarctions in cerebral territory as well as damage to the blood-brain barrier (BBB) [8, 10]. The disruption of the BBB increases the microvascular permeability and contributes to the neuroinflammation process [6].

Viral infections can induce demyelination events in the CNS and may be involved in the pathogenesis of a common demyelinating syndrome – Multiple Sclerosis [29]. It has been suggested that cognitive difficulties associated with COVID-19 may share similarities with demyelinating diseases such as Multiple Sclerosis [12].

Hippocampus seems to be particularly vulnerable to infections by coronaviruses, increasing the likelihood of memory impairment after infection as well as acceleration of neurodegenerative processes like Alzheimer's Disease [17]. Hypoxia, which is a common cause of neuropsychiatric alterations seen in acute respiratory stress syndromes, is associated to brain atrophy and ventricle enlargement, being hypoxia's duration related to cognitive functioning levels, namely in attention, memory and executive functions [17, 30].

The impact of COVID-19 on cognitive function in patients who have recovered from viral infection and its association with inflammatory profile have been studied. Literature suggests that cognitive impairment seen in recovered COVID-19 patients may be associated to the inflammatory process subjacent to the infection [31]. There is also growing evidence that patients with severe COVID-19 show more frequently cognitive deficits than patients with non-severe COVID-19 [32-34]. One of the proposed mechanisms for the decline of cognitive function, especially memory capacity, is based in hypoxia, given that certain brain regions associated with cognitive functions, such as hippocampus, are susceptible to neuronal damage induced by hypoxia. Other explanatory mechanisms include chronic and systemic inflammation as well as immune dysregulation, causing damage to brain tissue. Studies have suggested that higher levels of education are protective of cognitive function in patients with severe COVID-19, mitigating the impact of the pathology on clinical expression, although schooling may not protect from the development of neurodegenerative disease [32].

Despite growing evidence that SARS-CoV-2 infection may have a significant impact on the cognitive capacity of infected people, existing studies explored a relatively short interval

between infection and cognitive evaluation (usually <6 months). Recent studies suggest that cognitive changes arising from COVID-19 can be persistent in time and may be part of a new syndrome called Long-COVID [35-37].

Methods

Subjects

In this study 100 individuals who had COVID-19 in 2020 were included. Of these, 98 were randomly selected from a sample of 732 patients evaluated in the project *COVID-19 Neurological Phenotypes: The Virus, The Host or Both?*, and had diagnosis of COVID-19 made in the University Hospital Center of Porto (CHUP) between March and June 2020 (from 06-03-2020 to 29-06-2020). Two individuals received diagnosis of COVID-19 between October and November 2020. SARS-CoV-2 infection in all individuals was confirmed using RT-PCR (Real Time – Polymerase Chain Reaction). Time between diagnosis of COVID-19 and presential follow-up evaluation was on average 343 days (180 to 421 days).

Procedures

A semi-structured interview of the participants was used to collect the following demographic and clinical variables: gender, age, education, comorbidities prior to COVID-19 (e.g., Hypertension, Diabetes, Renal Disease, Cardiovascular Disease, and Neurological Disease), and symptoms during acute infection by SARS-CoV-2. Symptoms during acute infection by SARS-CoV-2 were divided in neurological symptoms (i.e., headaches, vertigo, sleep disturbance, sensitive symptoms, and visual symptoms) and systemic symptoms (fever, dyspnea, hyposmia/anosmia, hypogeusia/dysgeusia, respiratory failure and myalgia). The persistence of these symptoms at follow-up was also investigated. During the presential consultation, a neurological examination was performed.

All participants were submitted to a short neuropsychological evaluation, which included the Mini Mental State Evaluation (MMSE) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Additionally, the Hospital Anxiety and Depression Scale (HADS), the Broadbent's Cognitive Failure Questionnaires (CFQ), the Modified Fatigue Impact Scale (MFIS) and the Short-Form Health Survey (SF-36) were applied individually. HADS, CFQ, MFIS and SF-36 are self-report questionnaires.

MMSE is a widely used screening test, that was initially created to evaluate quantitively the severity of cognitive deficit and document long-term cognitive changes [38]. This test is composed of several questions divided in components: orientation, retention, attention and calculus, verbal recall, language, and constructive abilities. The maximum score is 30 points. The

5th percentile for a given education level (Morgado et al., 2009) was used as a cut point of cognitive deterioration.

BICAMS is a brief screening battery designed to detect cognitive dysfunction in Multiple Sclerosis. BICAMS is composed by three tests: Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test – Revisited (BVMT-R), and California Verbal Learning Test (CVLT-II). SMDT evaluates working memory and processing speed, BVMT evaluates the ability to recall new visuospatial information, and CVLT-II evaluates the capacity to learn new verbal information. Scores in each of these tests were adjusted to the demographic characteristics of each individual (age and/or education), in accordance to regression norms built for the Portuguese population [39]. Raw scores were transformed in T-Scores. The normative average T-score for a certain combination of demographic characteristics is 50 and its standard deviation is 10.

$$SDMT\ T\text{-}SCORE = 10.511 + (0{,}007 \times age^2) + (-0.966 \times schooling) + (4.138 \times adjusted\ value)$$

$$CVLT - II\ T\text{-}SCORE = 3.195 + (0.006 \times age^2) + (3.761 \times adjusted\ value)$$

$$BVMT - R\ T\text{-}SCORE = -8.004 + (0.514 \times age) + (3.833 \times adjusted\ value)$$

The percentile corresponding to each raw score converted in standardized score was identified. For the evaluation of the population in this study, a T-Score $\leq$ 37 was indicative of abnormal cognitive performance. A T-Score $\leq$ 37 matches approximately the percentile 10 of a normative sample. Participants with T-Score $\leq$ 37 at least in 2 of the 3 BICAMS tests (SDMT, CVLT-II, BVMT-R) were considered to have cognitive dysfunction (i.e., significant and objective cognitive deficit).

HADS Questionnaire is a screening instrument of depressive and/or anxiety states [40, 41]. The scale is formed by 14 items (7 to evaluate anxiety and 7 to evaluate depression). Each question has 4 answer possibilities, graded from 0-3. The total score of each component (anxiety – HADSA and depression – HADSD) range from 0 to 21, being higher scores related to higher states of anxiety and depression. The version used in this study is the Portuguese version, whose validation has been published [42]. The HADS Manual suggests that a score between 0-7 is normal, between 8-10 is mild, 11-14 is moderate and 15-21 is severe for both anxiety and depression subscales.

CFQ Questionnaire is a self-reported measurement of failures in perception, memory and motor function [43]. It was initially elaborated by Broadbent et al (1982). It is composed of 25 questions with 5 answer possibilities grading from 0 to 4. The questionnaire has 4 subscales (memory, distraction, daily mistakes, and name evocation). The questionnaire score is given by the sum of scores in each question, grading from 0 to 100. The bigger the score, the bigger the frequency of cognitive failures, as there are no defined cut-off points.

MFIS scale evaluates fatigue. The scale is built by 21 questions with 5 answer possibilities graded from 0 to 4. It is possible to divide the scale into 3 subscales or components: physical, cognitive, and psychosocial. The total score of the questionnaire matches the sum of each components score. There are no defined cut-off points for the interpretation of total scores in this scale. However, it is known that the bigger the score, the bigger the impact of fatigue on the individual's life.

SF-36 Questionnaire is widely used for its ability to compare the health status of a group of individuals with distinct chronic diseases and the health status of individuals of the same disease group but with different severity levels. In the context of this study, SF-36 was applied as a measurement of quality of life in individuals that had COVID-19. This questionnaire was used in the Portuguese version, and it is made of 36 questions covering eight quality of life dimensions (physical function, physical performance, bodily pain, general health, vitality, social function, emotional performance, and mental health). These dimensions were aggregated in two components: physical and mental. The physical component encompasses physical function, physical performance, bodily pain, and general health. The mental component encompasses mental health, emotional performance, social function, and vitality. Both the validation of the eight dimensions in the Portuguese version [44, 45] and the validation of both components in the Portuguese version [45, 46] have been published and used as mean of evaluation and scoring of this scale in this sample of this study. After calculating each component, its value is transformed into a scale with average 50 and standard deviation of 10. The physical component measures for the Portuguese population are 52,34 [44,51 ; 57,40] and the mental component measures are 52,23 [44,12 ; 57,64] (45). When it comes to interpretation of results, the lower the score, the lower the quality of life of the individual.

Statistical Analysis

Characteristics of the sample are expressed through descriptive statistics. Qui-Square Test or Fisher's Exact Test (when appropriate) and Mann-Whitney Test were used to compare groups. The level $p<0,05$ of significance was used. Multiple logistic regressions were used to

explore predictors of cognitive dysfunction. Pearson Correlations and multiple linear regressions were used to study predictors of CFQ. The backward method of variable selection (p>0,100) was used in logistic and linear regressions. Data was analyzed using IBM SPSS Statistics 26.0.0.0 software (IBM, New York, USA)

Results

Sample Characteristics

The sample consisted of 100 individuals with diagnosis of COVID-19 between March and November 2020. The demographic data are shown in Table I. The evaluated sample was predominantly female (56%), with an age ranging between 19 and 65 years, and with number of years of education varying between 3 and 23 years. Most common comorbidities were Hypertension (28%), Diabetes (13%), and Neurologic Disease (13%) (Table II). The reported neurologic disease included headaches, epilepsy, and transient ischemic attacks.

Clinical characteristics of infection are displayed in Table III. Most common reported symptoms were myalgia (n=80%), hyposmia/anosmia (69%), hypogeusia/dysgeusia (68%), fever (66%), headaches (54%) and sleep disturbance (44%). Sixteen individuals reported respiratory failure during acute COVID-19 (16%).

When questioned about cognitive symptoms/complaints, 53 of the 100 patients answered affirmatively (53%). Of these, 27 were females (50,9%), 27 reported mnestic complaints during and after infection (50,9%), 19 reported symptoms only during acute infection (35,8%), and 7 reported cognitive symptoms after infection (13.2%).

During the follow-up evaluation, the participants reported the following persistent neurological symptoms: headaches (32%), hyposmia (19%), dysgeusia (14%), sleep disturbance (10%), sensitive symptoms (4%) and visual symptoms (2%). No persistent vertigo was reported (0%).

Cognitive Deterioration and Cognitive Dysfunction

Eight patients (8%) presented cognitive deterioration according to their performance on the MMSE. No significant associations between cognitive deterioration and demographic characteristics, comorbidities or symptoms during infection were found (p>0,05).

Regarding BICAMS, abnormal performance (t-score $\leq$37) was recorded in 2% of individuals on SDMT, 15% on CVLT-II (15%), and 35% on BVMT (35%). Abnormal test performances (i.e., at least in one of the three BICAMS tests) were recorded in 43% of

participants. Cognitive dysfunction (i.e., at least two of three BICAMS measurements with abnormal performance) was detected in 9% of participants.

As seen in Table I, cognitive dysfunction in BICAMS was associated with lower education levels (p=0,021). No statistically significant differences were found between patients with or without cognitive dysfunction regarding gender, age, and comorbidities (Table I and Table II). No differences were found regarding the time interval between infection and follow-up (p=0,918).

The relationship connecting cognitive dysfunction recorded through BICAMS on follow-up evaluation and symptoms during COVID-19 infection was explored (see Table III). A statistically significant association between cognitive dysfunction and sleep disturbance (p=0,041) was found. Seven of the nine (77,8%) individuals with cognitive dysfunction reported sleep disturbance during acute infection in contrast with 40,7% of individuals without cognitive dysfunction. No other significant associations regarding cognitive dysfunction and COVID-19 symptoms were identified, including hyposmia/anosmia and hypogeusia/dysgeusia.

The sleep disturbance was characterized as initial type insomnia in 6/7 (85,7%) and terminal insomnia in 1/7 (14,3%) individuals with cognitive dysfunction. Each of the 7 individuals reported that the disruption in sleep began during the acute infection phase and 5 maintained at the follow-up evaluation. Fewer years of education (adjusted OR = 0,817; CI [0,684 ; 0,975]; p=0,025) and sleep disturbance (adjusted OR = 5,618; CI [1,047 ; 30,157], p=0,044) remained as significant predictors of cognitive dysfunction when analyzed as covariates.

Regarding the new-onset sleep disturbance in individuals without cognitive dysfunction (n=37), 11 (29,7%) had only initial type insomnia, 7 (18.9%) had only intermedium insomnia, 1 (2.7%) had only final insomnia, 1 (2.7%) had initial plus intermedium insomnia, 3 (8.1%) reported initial and final insomnia, 1 (2.7%) had only sleep fragmentation, 2 (5.4%) had sleep fragmentation and initial type insomnia, 4 (10.8%) had only hypersomnolence, 2 (5.4%) had hypersomnolence and initial plus intermedium insomnia, 3 (8.1%) had non-repairing sleep and 2 (5.4%) reported unspecific sleep complaints. Of these 37 individuals, 33 (89%) reported persistence of sleep disturbance at follow-up evaluation.

When BICAMS tests were evaluated separately, we verified that abnormal scoring on BVMT (35% of total sample) was more frequent in individuals with fewer years of education (median: 12 vs. 9 years of school, p=0,002) and in those who reported sleep disturbance (35,4% vs. 60,0%, p=0,018). Low education (adjusted OR = 0,850; CI [0,767 ; 0,943]; p=0,002) and sleep disturbance (adjusted OR = 2,980; CI [1,202 ; 7,388], p=0,018) remained as significant predictors

of abnormal performance on BVMT when analyzed as covariates. Anormal performance on CVLT (15% of total sample) was significantly related with fewer years of education (median: 12 vs. 9 years of school, p=0.012), but not with sleep disturbance (p=0,430). No significant associations were found between anormal performance on SDMT (2% of total sample) and demographic characteristics or sleep disturbance.

Participants with cognitive dysfunction (≥2 anormal BICAMS tests) reported lower levels of quality of life, according to scores on mental component of SF-36 (median: 36 vs. 49, p=0,035). Individuals with cognitive dysfunction also tended do have more cognitive complaints, as reflected by higher CFQ scores, though the difference did not reach the threshold for statistical significance (median: 53 vs. 30, p=0,079). No significant associations connecting cognitive dysfunction and HADS - Anxiety (p=0,928), HADS - Depression (p=0,482), or MFIS (p=0,561) were found. Within those who presented cognitive dysfunction (n=9), 7 had cognitive symptoms/complaints at the time of the follow-up evaluation.

Among participants with sleep disturbance during infection, the persistence of this symptom in the follow-up appointment was not associated with a higher frequency of cognitive dysfunction (p=0.649). Interestingly, among participants with headaches during COVID-19, cognitive dysfunction was only found in participants without persistent headaches (21.9% vs. 0%, p=0.033). No significant associations between cognitive dysfunction and other persistent symptoms, such as hyposmia (p>0,999), dysgeusia (p=0,575), sensitive symptoms (p=0,289) or visual symptoms (p>0,999), were found.

Cognitive Complaints

Female participants presented with more cognitive complaints at the follow-up consultation measured by the CFQ (median: 45 vs. 25, p<0,001). Individuals that had fever (median: 34 vs. 26, p=0,023), headaches (median: 46 vs. 25, p<0,001), or sleep disturbance (median: 42 vs. 27, p=0,001) during infection had higher scores on CFQ. No other statistically significant associations between cognitive complaints and other COVID-19 symptoms or comorbidities were found (p>0,050).

Score on CFQ had a negative correlation with years of education (r=-0,331, p=0,001) and with physical (r=-0,566, p<0,001) and mental (r=-0,579, p<0,001) components of SF-36. Strong positive correlations were found between CFQ scores and HADS anxiety (r=0,603, p<0,001) and depression (r=0,652, p<0,001) subscales, and between CFQ scores and MFIS scores (r=0,752, p<0,001). The relationship between CFQ scores and age is relatively modest (r=0,205, p=0,043).

Multiple linear regression analyses, in which demographic variables such as gender, age and education were considered as covariates, CFQ scores remained related to fever (ß=5,677; CI [-0,921 ; 12,275]; p=0,091; adjusted r^2 =0,306), headaches (ß=13,400; CI [7,723 ; 19,077]; p<0,001; adjusted r^2 =0,420), sleep disturbance (ß=10,497; CI [4,607 ; 16,388]; p<0,001; adjusted r^2 =0,368), physical (ß=-0,497; CI [-0,774 ; -0,219]; p=0,001) and mental components (ß=-0,708; CI [-0,969 ; -0,447]; p<0,001) of SF-36 (adjusted r^2 =0,621), anxiety (ß=0,872; CI [-0,005 ; 1,748]; p=0,051) and depression subscales (ß=1,986; CI [1,067 ; 2,905]; p<0,001) of HADS (adjusted r^2 =0,520) and MFIS (ß=0,622; CI [0,484 ; 0,760]; p<0,001; adjusted r^2 =0,635). In all these analyses, gender and education remained in the final regression model (com p<0,05), whereas variable age was always removed from the model through the backward method for selecting variables (p>0,100).

Among individuals with sleep disturbance associated to COVID-19, the persistency of this symptom during follow-up was associated to higher CFQ scores (49 vs. 25, p=0,021). Persistent headaches during follow-up were also associated to more cognitive complaints, however this difference did not reach the threshold for statistical significance (median: 52 vs. 34, p=0,075). No other significant associations between persistence of neurologic symptoms and CFQ scores were found (p>0,05). Neither persistent sleep disturbance nor persistent headaches remained statistically related to cognitive complaints when demographic characteristics (gender, age, and education) were considered as covariates.

Sleep disturbance

Sleep disturbance during infection tends to be more frequent in females (p=0,077) but is not related to age or education or comorbidities. Sleep disturbance during infection occurred more frequently in individuals who also reported dyspnea (p=0,015), anorexia (p=0,008), abdominal pain (p=0,019), headaches (p<0,001) and sensitive symptoms (p=0,011). No other significant associations with COVID-19 symptoms were found (p>0,05).

Individuals with sleep disturbance during infection, independently from their performance in BICAMS, had more symptoms of anxiety (median: 10 vs. 7, p=0,001) and depression (median: 6 vs. 4, p=0,004) on HADS, more symptoms of fatigue on MFIS (median: 38 vs. 22, p=0,005), and lower score on the mental component of SF-36 (median: 44 vs. 53, p=0,003) during follow-up evaluation.

Among individuals who had sleep disturbance, the persistency of this symptom was associated with more anxiety on HADS (p=0,014), more fatigue symptoms on MFIS (p=0,028), and worst quality of life on the physical component of SF-36 (p=0,025).

Discussion of Results

Results of this study revealed that about one year after COVID-19 infection, 43% of individuals had abnormal cognitive performance in BICAMS tests and 9% were classified with cognitive dysfunction (i.e., a significant and objective cognitive deficit) due to abnormal performance on at least 2 of 3 BICAMS tests. Learning and memory were the most affected cognitive domains. This finding is consistent with a large study comprising 740 individuals evaluated on average 7,6 months after the infection [47].

The available literature on the long-term cognitive deficits related to COVID-19 is scarce and commonly focuses on hospitalized patients during acute phase of the infection, suggesting moderate to severe disease. Cognitive dysfunction after critical disease is a common finding, observed previously for prolonged hospitalizations in Intensive Care Units (ICU) [48]. A study that included 78 individuals (with diagnosis of COVID-19 between March and April 2020, 12% with hospitalization) identified cognitive deficit in 10% of individuals [49]. These results were obtained 4 months after infection and are consistent with the data in our study one year after COVID-19. These studies point to the presence of cognitive deficits in some patients after infection.

The persistency of symptoms after SARS-CoV-2 has been reported frequently and has led to the concept of Long-COVID or Post-COVID Syndrome [35, 50], which may occur even in individuals with mild disease. Initial studies (prior to vaccination) estimated that about 80% of those infected with SARS-CoV-2 could develop symptoms of this syndrome [51]. The persistent symptoms are mostly unspecific [52]. In a cohort study that evaluated 1733 individuals 6 months after infection by SARS-CoV-2, fatigue, anxiety, depression, and sleep alterations were the most frequent persistent symptoms [52]. For a more adequate clinical response, it is important to identify risk factors for development of Long-COVID, including brain fog [36, 52-54].

Low education revealed to be a risk factor for cognitive dysfunction and more cognitive complaints (as measured by CFQ) at the follow-up evaluation one year post infection. These results suggest that education may have a protective role on cognitive functioning after COVID-19 and further supports the notion that cognitive reserve may modulate the clinical expression of neurological diseases. Evidence of the importance of cognitive reserve has been documented in several neurological diseases, including Alzheimer's Disease and Multiple Sclerosis [55, 56].

No significant associations connecting cognitive measures (objective and subjective) and individuals' age or comorbidities prior to COVID-19 were found. Some possible explanations for the non-rejection of the null hypothesis include relatively young age of the sample (median age of 49 years and age limit of 65) and identification of abnormal cognitive performance after

adjusting to the demographic characteristics of each individual according to existing normative data. It shall be referred that the normalization of BICAMS to the Portuguese population [39] was made on a sample of 60 individuals between 17 and 69 years of age and with an average age of 36 years. These characteristics of the normative sample can limit the detection capacity of cognitive deficit in older individuals. Therefore, the negative findings regarding age and comorbidities must be interpreted with reservations.

Regarding symptoms during the period of infection, significant associations were found between sleep disturbance and cognitive dysfunction (i.e., significant, and objective cognitive deficit measured by BICAMS) and subjective cognitive deficit (self-perceived cognitive failures in everyday life according to CFQ). Sleep disturbance in individuals with cognitive dysfunction (n=7) was not present before COVID-19 and it was characterized mainly as initial type insomnia (6 of 7 individuals, 86%). In these cases, the sleep disturbance arose during COVID-19 infection, but only in 5 of these 7 patients (71%) did this symptom persisted at the one-year follow-up. The association between sleep disturbance and cognitive dysfunction after COVID-19 infection has not been described in literature until this point.

Persistent sleep disturbance, independently of cognitive performance, was related to more psychopathology, fatigue, and poorer quality of life. The relationship between sleep disturbance and psychological suffering is widely recognized in other populations [57, 58]. The results of the present study call attention to the necessity of clinical evaluation and symptomatic treatment of people with sleep disturbance following COVID-19.

The sleep disturbance described by individuals who had COVID-19 is mostly insomnia. Primary insomnia is considered one of the most common sleep disturbances [59]. However, in this study, insomnia referred by the participants should not be considered primary insomnia, as it arose after an infectious event. Insomnia in general is frequently related to cognitive dysfunction in other populations, with emphasis on attention [60-62] and episodic memory functions [62]. Though, the relationship between primary insomnia and cognitive impairment is less clear [63]. It is complex to differentiate sleep disturbance as a neurologic symptom or as arising from other causes, namely social isolation, anxiety, and depression, as these have been common in both infected and non-infected individuals during the pandemic.

Higher scores on CFQ were associated to female gender and more symptoms of anxiety, depression, and fatigue. This relationship between subjective perception of more cognitive failures on everyday life after COVID-19, female gender and psychopathologic symptoms is consistent with the results of a cohort study encompassing 1733 patients evaluated 6 months

after SARS-CoV-2 infection, in which the female gender was a risk factor for developing persistent symptoms of fatigue, depression and anxiety [52]. In our study, the pattern of associations observed for subjective cognitive complaints contrasts with results obtained for objective evaluation of cognitive function. No significant associations were found between cognitive dysfunction and female gender or anxiety symptoms, depression or fatigue. These results suggest a dissociation between self-reported cognitive difficulties and objective cognitive deficits, one year after COVID-19. Higher CFQ scores may represent a vulnerability factor and a reflection of poorer ability to respond to stress [43], which allied to the pandemic context, may have severe repercussions on the individuals' quality of life.

Both higher CFQ scores and objective cognitive dysfunction were associated with diminished quality of life. Unfortunately, the analyses of the SF-36 data were marked by missing responses. Self-completion failures resulted in the impossibility of calculating the physical and mental components of the SF-36 in 27 participants. These missing data limit the informative value of the study.

The generalization capacity of our results is limited by our sample size (n=100) and by the time period in which COVID-19 was diagnosed (98 individuals were diagnosed between March and June 2020 and 2 individuals between October and November 2020). The subsequent emergence of vaccines [64, 65] and the appearance of new and potentially less pathogenic variants of SARS-CoV-2 [66] may affect the development of Long-COVID. The present study results may not be representative of COVID-19 infections in the context of later SARS-CoV-2 variants and/or in vaccinated individuals.

The large number of comparisons performed in this study increases the risk of a type 1 statistical error, i.e., it increases the probability of rejecting the null hypothesis when it is true. This is another limitation of our study. Therefore, the results obtained should be considered exploratory.

Conclusion

In this study, we verified that low education and new-onset insomnia during COVID-19 infection are risk factors for cognitive dysfunction one year after COVID-19. Female gender and the onset of sleep disturbance during infection are associated to more long-term self-perceived cognitive difficulties, symptoms of anxiety, depression and fatigue, and overall poorer quality of life. Even though self-perceived cognitive difficulties were related to female gender and psychopathologic symptoms, these were not predictive of significant and objective cognitive

deficits. Future studies are necessary to confirm and explore the association between new-onset sleep disturbance related to COVID-19 and long-term cognitive difficulties.

Appendix

Table I – Demographic characteristics of the sample. Comparison between participants with and without cognitive dysfunction on BICAMS.

Variable	Total (n=100)	With dysfunction (n=9)	Without dysfunction (n=91)	p
Median age [IQR], y	49 [40 ; 57]	48 [42 ; 63]	49 [38 ; 57]	p=0,588
Gender				
Female, n (%)	56 (56,0%)	5 (55,6%)	51 (56,0%)	p>0,999
Male, n (%)	44 (44,0%)	4 (44,4%)	40 (44,0%)	
Median Education [IQR], y	12 [7 ; 16]	6 [4; 12]	12 [9 ; 16]	**p=0,021**

Data is presented in frequencies (%) and medians (percentile 25 and 75). Fisher's Exact and Mann-Whitney Tests were used for comparison of groups. IQR- Interquartile Range

Table II – Comorbidities prior to infection. Comparison between participants with and without cognitive dysfunction on BICAMS.

Pre-morbid variables	Total (n=100)	With dysfunction (n=9)	Without dysfunction (n=91)	p
Hypertension	28 (28,0%)	2 (22,2%)	26 (28,6%)	p>0,999
Diabetes	13 (13,0%)	2 (22,2%)	11 (12,1%)	p=0,331
Renal Disease	7 (7,0%)	1 (11,1%)	6 (6,6%)	p=0,494
Neurological	13 (13,0%)	1 (11,1%)	12 (13,2%)	p>0,999
Cardiovascular	8 (8,0%)	0 (0%)	8 (8,8%)	p>0,999

Data is presented in frequencies (%). Fisher's Exact Test was used for comparison of groups.

Table III – Non-neurologic and neurologic manifestations during infection. Comparison between participants with and without cognitive dysfunction on BICAMS.

Symptoms during infection	Total (n=100)	With dysfunction (n=9)	Without dysfunction (n=91)	p
Fever	66 (66,0%)	6 (66,7%)	60 (65,9%)	p>0,999
Dyspnea	41 (41,0%)	5 (55,6%)	36 (39,6%)	p=0,481
Respiratory Insufficiency	16 (16,0%)	2 (22,2%)	14 (15,4%)	p=0,633
Myalgia	80 (80,0%)	8 (88,9%)	72 (79,1%)	p=0,683
Anorexia	51 (51,0%)	5 (55,6%)	46 (50,5%)	p>0,999
Diarrhea	53 (53,0%)	7 (77,8)	46 (50,5%)	p=0,167
Nauseas/Vomits	30 (30,0%)	2 (22,2%)	28 (30,8%)	p=0,720
Abdominal pain	23(23,0%)	4 (44,4%)	19 (20,9%)	p=0,205
Hyposmia/Anosmia	69 (69,0%)	5 (55,6%)	64 (70,3%)	p=0,453
Hypogeusia/Dysgeusia	68 (68,0%)	5 (55,6%)	63 (69,2%)	p=0,462
Headaches	57 (57,0%)	7 (77,8%)	50 (54,9%)	p=0,293
Vertigo	14 (14,1%)[1]	1 (11,1%)	13 (14,4%)	p>0,999
Sleep Disturbance	**44 (44,0%)**	**7 (77,8%)**	**37 (40,7%)**	**p=0,041**
Sensitive symptoms	26 (26,0%)	2 (22,2%)	24 (26,4%)	p>0,999
Visual symptoms	23 (23,0%)	2 (22,2%)	21 (23,1%)	p>0,999

[1] total number of evaluated individuals for vertigo is 99 (n=99, 9 of these with cognitive deficit).

Fisher's Exact Test was used for comparison of groups.

Mini Mental State Examination (MMSE)

1. Orientação (1 ponto por cada resposta correcta)

Em que ano estamos? _____
Em que mês estamos? _____
Em que dia do mês estamos? _____
Em que dia da semana estamos? _____
Em que estação do ano estamos? _____

Nota:____

Em que país estamos? _____
Em que distrito vive? _____
Em que terra vive? _____
Em que casa estamos? _____
Em que andar estamos? _____

Nota:____

2. Retenção (contar 1 ponto por cada palavra correctamente repetida)

"Vou dizer três palavras; queria que as repetisse, mas só depois de eu as dizer todas; procure ficar a sabê-las de cor".
Pêra _____
Gato _____
Bola _____

Nota:____

3. Atenção e Cálculo (1 ponto por cada resposta correcta. Se der uma errada mas depois continuar a subtrair bem, consideram-se as seguintes como correctas. Parar ao fim de 5 respostas)

"Agora peco-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado volta a tirar 3 e repete assim até eu lhe dizer para parar".
27_ 24_ 21 _ 18_ 15_

Nota:____

4. Evocação (1 ponto por cada resposta correcta.)

"Veja se consegue dizer as três palavras que pedi há pouco para decorar".
Pêra _____
Gato _____
Bola _____

Nota:____

5. Linguagem (1 ponto por cada resposta correcta)

a. "Como se chama isto? Mostrar os objectos:
Relógio ____
Lápis_____

Nota:____

b. "Repita a frase que eu vou dizer: O RATO ROEU A ROLHA"

Nota:____

Figure 1 - Mini Mental State Examination

c. "Quando eu lhe der esta folha de papel, pegue nela com a mão direita, dobre-a ao meio e ponha sobre a mesa"; dar a folha segurando com as duas mãos.
Pega com a mão direita____
Dobra ao meio ____
Coloca onde deve____

Nota:____

d. "Leia o que está neste cartão e faça o que lá diz". Mostrar um cartão com a frase bem legível, "FECHE OS OLHOS"; sendo analfabeto lê-se a frase.
Fechou os olhos____

Nota:____

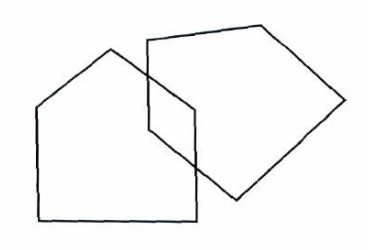
e. "Escreva uma frase inteira aqui". Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação.

Frase:

Nota:____

6. **Habilidade Construtiva** (1 ponto pela cópia correcta.)

Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar tremor ou rotação.



Cópia:

Nota:____

TOTAL(Máximo 30 pontos):____

Considera-se com defeito cognitivo:	• analfabetos ≤ 15 pontos • 1 a 11 anos de escolaridade ≤ 22 • com escolaridade superior a 11 anos ≤ 27

Figure 2 - Mini Mental State Examination

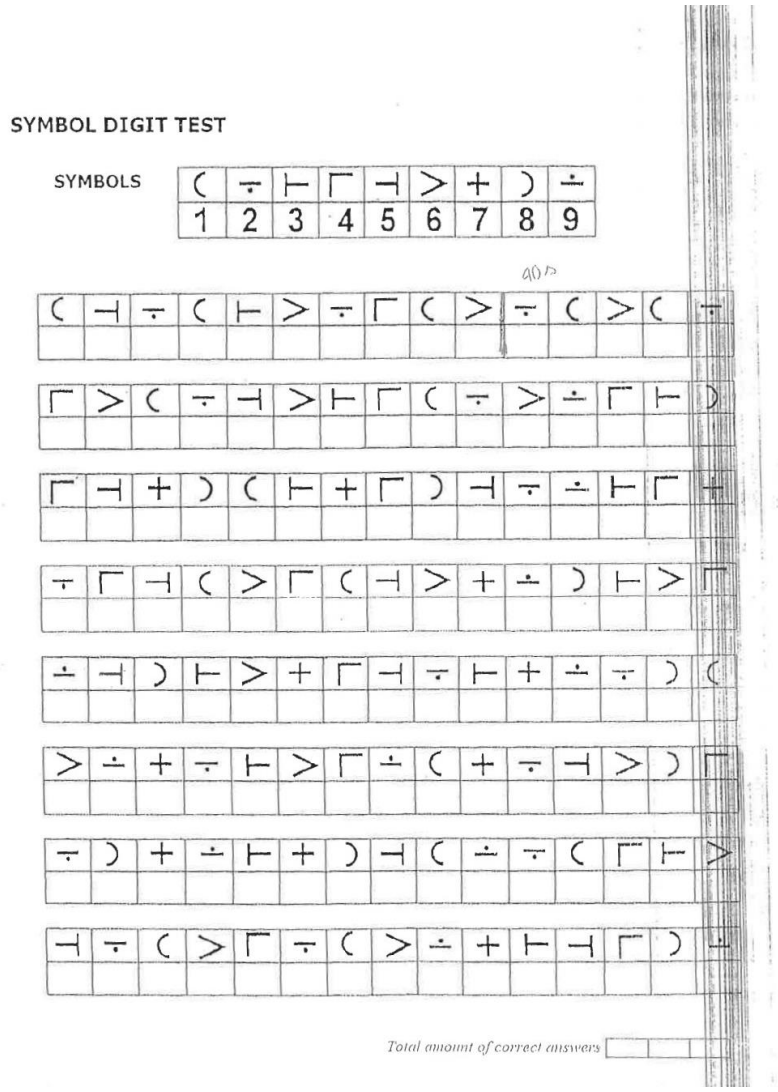


Figure 3 – SDMT – Symbol Digit Modalities Test

***Battery International Cognitive Assessment Multiple Sclerosis* (BICAMS)**

(validação BICAMS – Portugal)

***California Verbal Learning Test* (CVLT-II)**

(Versão experimental Portuguesa: Sousa, C., Neves M.R., Passos, A. & Sá, M. J.)

Instruções para os ensaios

Instrução (ensaio 1): Vou-lhe ler uma lista de palavras. Ouça com atenção porque quando eu terminar vou pedir-lhe que me diga o maior numero de palavras que conseguir. Pode dizê-las por qualquer ordem apenas diga tantas quanto conseguir. Está pronta (a)?

Instrução (ensaio 2-5): Vou ler de novo a mesma lista. Como há pouco, diga me o maior numero de palavras que conseguir, por qualquer ordem. Diga também as palavras da lista que me disse da primeira vez.

	1	2	3	4	5
Camião					
Fava					
Girafa					
Estante					
cebola					
Motorizada					
Armário					
Zebra					
Carro					
Quadro					
Alface					
Vaca					
Sofá					
Barco					
Esquilo					
Couve					

Figure 4 - CVLT-II- California Verbal Learning Test

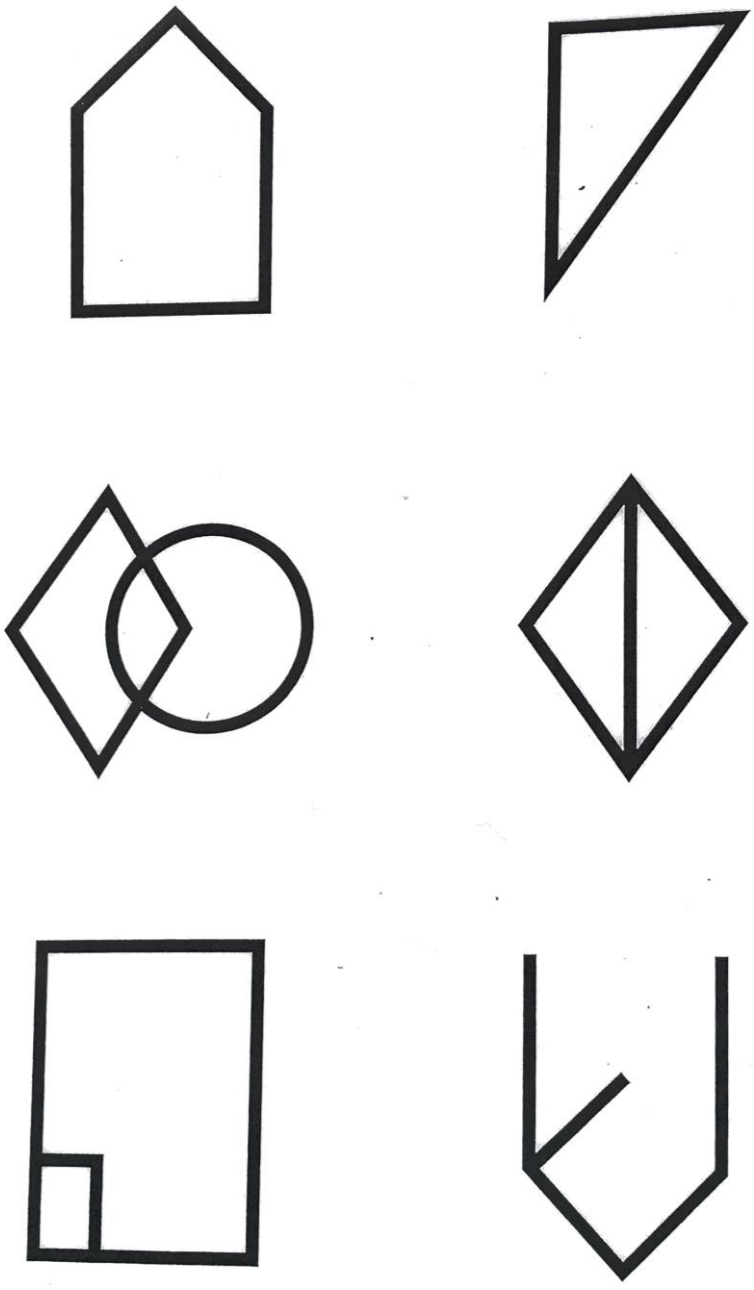


Figure 5 - BVMT-R – Brief Visuospatial Memory Test – Revisited

ID: _____

Escala de Ansiedade e Depressão Clínica

Este questionário foi construído para ajudar a saber como se sente. Pedimos-lhe que leia cada uma das perguntas e faça uma cruz **(X)** no espaço anterior à resposta que melhor descreve a forma como se tem sentido na última semana.

Não demore muito tempo a pensar nas respostas. A sua reacção imediata a cada questão será provavelmente mais correcta do que uma resposta muito ponderada.

Por favor, faça apenas uma cruz em cada pergunta

1. Sinto-me tenso/a ou nervoso/a:
( ) Quase sempre
( ) Muitas vezes
( ) Por vezes
( ) Nunca

2. Ainda sinto prazer nas coisas de que costumava gostar:
( ) Tanto como antes
( ) Não tanto agora
( ) Só um pouco
( ) Quase nada

3. Tenho uma sensação de medo como algo terrível estivesse para acontecer:
( ) Sim e muito forte
( ) Sim, mas não muito forte
( ) Um pouco, mas não me aflige
( ) De modo algum

4. Sou capaz de rir e ver o lado divertido das coisas:
( ) Tanto como antes
( ) Não tanto como antes
( ) Muito menos agora
( ) Nunca

5. Tenho a cabeça cheia de preocupações:
( ) A maior parte do tempo
( ) Muitas vezes
( ) Por vezes
( ) Quase nunca

6. Sinto-me animado/a:
( ) Nunca
( ) Pouca vezes
( ) De vez em quando
( ) Quase sempre

7. Sou capaz de estar descontraidamente sentado/a e sentir-me relaxado/a:
( ) Quase sempre
( ) Muitas vezes
( ) Por vezes
( ) Nunca

8. Sinto-me mais lento/a, como se fizesse as coisas mais devagar:
( ) Quase sempre
( ) Muitas vezes
( ) Por vezes
( ) Nunca

9. Fico de tal forma apreensivo/a (com medo), que até sinto um aperto no estômago:
( ) Nunca
( ) Por vezes
( ) Muitas vezes
( ) Quase sempre

10. Perdi o interesse em cuidar do meu aspecto físico:
( ) Completamente
( ) Não dou a atenção que devia
( ) Talvez cuide menos que antes
( ) Tenho o mesmo interesse de sempre

11. Sinto-me de tal forma inquieto/a que não consigo estar parado/a:
( ) Muito
( ) Bastante
( ) Não muito
( ) Nada

12. Penso com prazer nas coisas que podem acontecer no futuro:
( ) Tanto como antes
( ) Não tanto como antes
( ) Bastante menos agora
( ) Quase nunca

13. De repente, tenho sensações de pânico:
( ) Muitas vezes
( ) Bastantes vezes
( ) Por vezes
( ) Nunca

14. Sou capaz de apreciar um bom livro ou um programa de rádio ou televisão:
( ) Muitas vezes
( ) De vez em quando
( ) Poucas vezes
( ) Quase nunca

MUITO OBRIGADO PELA SUA COLABORAÇÃO

Figure 6 - HADS - Hospital Anxiety and Depression Scale

Questionário de Falhas Cognitivas (Broadbent, Cooper, FitzGerald & Parkes, 1982)

As seguintes questões referem-se a pequenas falhas que todos nós temos de vez em quando, mas algumas delas acontecem mais frequentemente do que outras. O objetivo deste questionário é saber com que frequência aconteceram estas falhas nos últimos 6 meses. Por favor, assinale a sua resposta com um circulo no número correspondente.

	Muito Frequentemente	Frequentemente	Ocasionalmente	Raramente	Nunca
1. Quando lê alguma coisa, no final acha que não prestou atenção e que tem de ler tudo novamente?	4	3	2	1	0
2. Esquece-se porquê que se deslocou de um lado para outro da casa?	4	3	2	1	0
3. Na estrada ou na rua, não repara nas placas de sinalização?	4	3	2	1	0
4. Quando fornece indicações de direção, confunde a direita e a esquerda?	4	3	2	1	0
5. Esbarra com (vai de encontro a) outras pessoas?	4	3	2	1	0
6. Esquece-se se desligou a luz, apagou o fogão ou se fechou a porta?	4	3	2	1	0
7. Quando uma pessoa se apresenta ou lhe é apresentada, não presta atenção ao nome da pessoa?	4	3	2	1	0
8. Diz alguma coisa e só depois se apercebe que o que disse poderá ser visto como insultuoso?	4	3	2	1	0
9. Não ouve as pessoas a falar consigo, quando está a fazer outra coisa?	4	3	2	1	0
10. Perde a cabeça e depois arrepende-se?	4	3	2	1	0
11. Deixa por responder cartas importantes (mensagens ou e-mails) durante dias?	4	3	2	1	0
12. Esquece-se em que rua virar num caminho que conhece bem, mas que raramente usa?	4	3	2	1	0
13. No supermercado, não consegue encontrar o que procura (apesar do que procura estar lá)?	4	3	2	1	0
14. Numa conversa, de repente, dá por si a perguntar-se se usou uma palavra corretamente?	4	3	2	1	0

1

Figure 7 - CFQ - Cognitive Failures Questionnaire

Questionário de Falhas Cognitivas (Broadbent, Cooper, FitzGerald & Parkes, 1982)

	Muito Frequentemente	Frequentemente	Ocasionalmente	Raramente	Nunca
15. Tem dificuldade em decidir?	4	3	2	1	0
16. Esquece-se de compromissos?	4	3	2	1	0
17. Esquece-se onde deixa as coisas, como as chaves ou o telefone?	4	3	2	1	0
18. Acidentalmente deita fora o que quer manter e fica com aquilo que pretende deitar fora - por exemplo, deita fora a caixa de fósforos e guarda no bolso o fósforo usado?	4	3	2	1	0
19. Fica a sonhar acordado em vez de estar a ouvir algo?	4	3	2	1	0
20. Esquece-se do nome das pessoas?	4	3	2	1	0
21. Em casa, começa a fazer uma coisa, distrai-se e acaba por fazer outra coisa (não intencional)?	4	3	2	1	0
22. Não consegue lembrar-se de alguma coisa, apesar de "estar na ponta da língua"?	4	3	2	1	0
23. Quando vai às compras, esquece-se do que ia comprar?	4	3	2	1	0
24. Deixa cair coisas?	4	3	2	1	0
25. Tem dificuldades em pensar nalguma coisa para dizer?	4	3	2	1	0

Figure 8 - CFQ - Cognitive Failures Questionnaire

Escala de Impacto da Fadiga Modificada (MFIS) - versão portuguesa

Nº Processo: _____ Data: ____/____/____

INSTRUÇÕES: Em seguida será apresentado um conjunto de afirmações sobre como a fadiga pode afectar uma pessoa. A fadiga é uma sensação de cansaço físico e perda de energia que muitas pessoas sentem de tempos em tempos. Por favor, leia cada afirmação cuidadosamente e desenhe um círculo em volta do número que melhor indique como a fadiga o tem afectado durante as 4 últimas semanas. Se necessitar de ajuda para marcar as respostas, peça ao entrevistador, indicando o número que melhor corresponde à sua resposta. Por favor, responda a todas as questões. Se não tiver certeza sobre qual a resposta a seleccionar, escolha aquela que estiver mais próxima daquilo que descreve o que tem vindo a sentir. O entrevistador poderá explicar algumas palavras ou frases que não compreenda.

Por causa da minha fadiga durante as 4 últimas semanas....

		Nunca	Raramente	Algumas vezes	Muitas vezes	Quase sempre
1.	Eu tenho estado menos alerta.	0	1	2	3	4
2.	Eu tenho tido dificuldades em manter a atenção por períodos longos.	0	1	2	3	4
3.	Eu tenho sido incapaz de pensar claramente.	0	1	2	3	4
4.	Eu tenho andado desastrado e descoordenado.	0	1	2	3	4
5.	Eu tenho andado esquecido.	0	1	2	3	4
6.	Eu tenho tido necessidade de me moderar nas minhas actividades físicas.	0	1	2	3	4
7.	Eu tenho estado menos motivado para fazer qualquer coisa que exija esforço físico.	0	1	2	3	4
8.	Eu tenho estado menos motivado para participar em actividades sociais.	0	1	2	3	4
9.	Eu tenho estado limitado na minha capacidade para fazer coisas fora de casa.	0	1	2	3	4
10.	Eu tenho tido dificuldades em manter o esforço físico por períodos longos.	0	1	2	3	4
11.	Eu tenho tido dificuldades em tomar decisões	0	1	2	3	4
12.	Eu tenho estado menos motivado para fazer qualquer coisa que exija esforço mental.	0	1	2	3	4
13.	Os meus músculos têm estado fracos.	0	1	2	3	4
14.	Eu tenho estado fisicamente desconfortável.	0	1	2	3	4
15.	Eu tenho tido dificuldades em terminar tarefas que exijam esforço mental.	0	1	2	3	4
16.	Eu tenho tido dificuldades em organizar os meus pensamentos quando estou a fazer coisas em casa ou no trabalho.	0	1	2	3	4
17.	Eu tenho estado menos capaz de completar tarefas que exijam esforço físico.	0	1	2	3	4
18.	O meu pensamento tem estado mais lento.	0	1	2	3	4
19.	Eu tenho tido dificuldades de concentração.	0	1	2	3	4
20.	Eu tenho limitado as minhas actividades físicas.	0	1	2	3	4
21.	Eu tenho tido necessidade de descansar mais frequentemente ou por períodos mais longos.	0	1	2	3	4

Figure 9 - MFIS - Modified Fatigue Impact Scale

Processo:_____

A MINHA SAUDE

Para as perguntas 1 e 2 por favor coloque um círculo no número que melhor descreve a sua saúde.

1. Em geral, como diria que a sua saúde é:

Óptima.....1
Muito boa.....2
Boa.....3
Razoável.....4
Fraca.....5

2. Comparando com o que acontecia há um ano, como descreve, o seu estado geral actual:

Muito melhor.....1
Com algumas melhoras.....2
Aproximadamente igual.....3
Um pouco pior.....4
Muito pior.....5

3. As perguntas que se seguem são sobre actividades que executa no seu dia a dia. Será que a sua saúde o/a limita nestas actividades? Se sim, quanto?

(Por favor, assinale com um círculo um número em cada linha)

	SIM, MUITO LIMITADO/A	SIM, UM POUCO LIMITADO/A	NÃO, NADA LIMITADO/A
A. Actividades violentas, tais como correr, levantar pesos, participar em desportos violentos.....	1	2	3
B. Actividades moderadas, tais como deslocar uma mesa ou aspirar a casa.....	1	2	3
C. Levantar ou **carregar** as compras da mercearia.....	1	2	3
D. Subir vários lanços de escada.....	1	2	3
E. Subir um lanço de escada.....	1	2	3
F. Inclinar-se, ajoelhar-se ou abaixar-se.....	1	2	3
G. Andar **mais de 1 Km**.....	1	2	3
H. Andar **vários quarteirões**.....	1	2	3
I. Andar **um quarteirão**.....	1	2	3
J. Tomar banho ou vestir-me sozinho.....	1	2	3

Figure 10 - SF-36

Processo:_____

4. Durante as últimas quatro semanas teve no seu trabalho ou actividades diárias algum dos problemas apresentados a seguir como consequência do seu estado de saúde física?

(Por favor em cada linha ponha um círculo à volta do número 1 se a sua resposta for sim, ou à volta do número 2 se a sua resposta for não)

	SIM	NÃO
A. Diminuiu o **tempo gasto** a trabalhar, ou noutras actividades.....	1	2
B. Fez **menos** do que queria.....	1	2
C. Sentiu-se limitado no **tipo** de trabalho ou outras actividades.....	1	2
D. Teve **dificuldade** em executar o seu trabalho ou outras actividades (por exemplo, foi preciso mais esforço).....	1	2

5. Durante as últimas quatro semanas, teve com o seu trabalho ou com as suas actividades diárias, algum dos problemas apresentados a seguir devido a quaisquer problemas emocionais (tal como sentir-se deprimido/a ou ansioso/a)?

(Por favor em cada linha ponha um círculo à volta do número 1 se a sua resposta for sim, ou à volta do número 2 se a sua resposta for não)

	SIM	NÃO
A. Diminuiu o tempo gasto a trabalhar, ou noutras actividades	1	2
B. Fez menos do que queria.....	1	2
C. Não executou o seu trabalho ou outras actividades tão cuidadosamente como era costume.....	1	2

Para cada uma das perguntas 6, 7 e 8 por favor ponha um círculo no número que melhor descreve a sua saúde.

6. Durante as últimas 4 semanas, em que medida é que a saúde física ou problemas emocionais interferiram com o seu relacionamento social normal com a família, amigos, vizinhos ou outras pessoas?

Absolutamente nada.....1
Pouco.....2
Moderadamente.....3
Bastante.....4
Imenso.....5

7. Durante as últimas 4 semanas teve dores?

Nenhumas.....1
Muito fracas.....2
Ligeiras.....3
Moderadas.....4
Fortes.....5
Muito fortes.....6

Figure 11 - SF-36

Processo:_____

8. Durante as <u>últimas 4 semanas,</u> de que forma é que <u>a dor</u> interferiu com seu o trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

Absolutamente nada.....1
Um pouco.....2
Moderadamente.....3
Bastante.....4
Imenso.....5

9. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas nas últimas quatro semanas.
Para cada pergunta, coloque por favor um círculo à volta do número que melhor descreve a forma como se sentiu.
Certifique-se que coloca um círculo em cada linha.

Quanto tempo **nas últimas quatro semanas**	SEMPRE	A MAIOR PARTE DO TEMPO	BASTANTE TEMPO	ALGUM TEMPO	POUCO TEMPO	NUNCA
A. Se sentiu cheio/a de vitalidade?....	1	2	3	4	5	6
B. Se sentiu muito nervoso/a?.....	1	2	3	4	5	6
C. Se sentiu tão deprimido/a, que nada o/a animava?.....	1	2	3	4	5	6
D. Se sentiu calmo/a e tranquilo/a?....	1	2	3	4	5	6
E. Se sentiu com muita energia?.....	1	2	3	4	5	6
F. Se sentiu triste e em baixo?.....	1	2	3	4	5	6
G. Se sentiu estafado/a?.....	1	2	3	4	5	6
H. Se sentiu feliz?.....	1	2	3	4	5	6
I. Se sentiu cansado/a?.....	1	2	3	4	5	6

10. Durante as <u>últimas quatro semanas</u>, até que ponto é que a saúde física ou problemas emocionais limitaram a sua actividade social (tal como visitar amigos ou familiares próximos)?

Sempre.....1
A maior parte do tempo.....2
Algum tempo.....3
Pouco tempo.....4
Nunca.....5

Figure 12 - SF-36

Processo:_____

11. Por favor, diga em que medida são verdadeiras ou falsas as seguintes afirmações.

(Por favor assinale um número em cada linha)

	TOTALMENTE VERDADE	VERDADE	NÃO SEI	FALSO	TOTALMENTE FALSO
A. Parece que adoeço mais facilmente do que os outros.....	1	2	3	4	5
B. Sou tão saudável como qualquer outra pessoa...	1	2	3	4	5
C. Estou convencido/a que a minha saúde vai piorar.....	1	2	3	4	5
D.A minha saúde é óptima.....	1	2	3	4	5

12. Durante as últimas quatro semanas, com que frequência teve dificuldades

(Por favor, assinale um número em cada linha)

	SEMPRE	COM MUITA FREQUÊNCIA	FREQUEN-TEMENTE	COM POUCA FREQUÊNCIA	QUASE NUNCA	NUNCA
A. Em se concentrar e pensar?.....	1	2	3	4	5	6
B. Em manter a sua atenção numa actividade por um período longo de tempo?.....	1	2	3	4	5	6
C. Em raciocinar e resolver problemas (p.e., fazer planos, tomar decisões, aprender coisas novas)?....	1	2	3	4	5	6

13. Nas últimas quatro semanas, teve algumas dificuldades:

(Por favor, assinale um número em cada linha)

	SIM, BASTANTES	SIM, ALGUMAS	RARAS	NENHUMAS
A. De memória?.....	1	2	3	4
B. Com o seu discurso ou linguagem?.....	1	2	3	4

MUITO OBRIGADA PELA SUA COLABORAÇÃO.

Figure 13 - SF-36

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