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Online physical exercise and the neuropsychiatric symptoms in patients with dementia:
a cross-sectional study during the COVID-19 pandemic

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ABSTRACT. Social isolation is necessary during the COVID-19 pandemic but can be harmful to mental health, especially in people with neurocognitive disorders. Although physical exercise can alleviate neuropsychiatric symptoms and improve quality of life (QoL), sedentary behavior increased during the pandemic. Online interventions can contribute to improving physical activity and mental health. **Objective:** The objective of this study was to compare the neuropsychiatric symptoms and QoL of older adults with neurocognitive disorders who participated in an online physical exercise program with sedentary patients during the COVID-19 pandemic. **Methods:** In this cross-sectional study, 25 older patients with neurocognitive disorders (control group=11; online exercise group=14) were evaluated based on Neuropsychiatric Inventory (NPI) and the Quality of Life in Alzheimer's Disease (QoL-AD) scale. **Results:** There were differences between the two groups in the total NPI (U=36.50, p=0.025) and the nighttime behavior disturbances item (U=38.00, p=0.033), both with large effect sizes (ES=-1.03, 95% confidence interval [CI]:-1.83 to -0.16 and ES=-1.06, 95%CI -1.86 to -0.19, respectively). In terms of QoL-AD, a difference was identified only in the memory subitem (U=20.00, p=0.005), with a large ES (1.59, 95%CI 0.59–2.48). **Conclusions:** Older adults with neurocognitive disorders who participated in an online physical exercise program, during the COVID-19 pandemic, showed fewer neuropsychiatric total symptoms, fewer nighttime disturbances episodes, and better subjective memory, compared to their physically inactive counterparts. Randomized controlled trials should be performed to better understand the effect of physical exercise in neuropsychiatric symptoms in dementia patients during periods of social isolation.

Keywords: SARS-CoV-2; Dementia; Cognitive Dysfunction; Mental Health; Exercise.

EXERCÍCIO FÍSICO *ONLINE* E SINTOMAS NEUROPSIQUIÁTRICOS EM PACIENTES COM DEMÊNCIA: UM ESTUDO DE CORTE TRANSVERSAL DURANTE A PANDEMIA DE COVID-19

RESUMO. O isolamento social é necessário na pandemia de COVID-19, mas pode impactar a saúde mental, especialmente em idosos com demência, dada a alta prevalência de sintomas neuropsiquiátricos. Apesar da prática de exercícios físicos contribuir para a redução desses sintomas e a melhora da qualidade de vida, houve um aumento de comportamento sedentário durante a pandemia. **Objetivo:** Comparar os sintomas neuropsiquiátricos e a qualidade de vida de idosos com distúrbios neurocognitivos que participaram de um programa de exercícios físicos *online* voltado a pacientes sedentários durante a pandemia de COVID-19. **Métodos:** Neste estudo de corte transversal, 25 idosos diagnosticados com transtorno neurocognitivo (controle=11; exercícios *online*=14) foram avaliados por meio do inventário neuropsiquiátrico (INP) e da escala de qualidade de vida na doença de Alzheimer (QV-DA). **Resultados:** Observou-se diferença entre os grupos no INP total (U=36,50, p=0,025), com tamanho de efeito grande (effect size [ES]=-1,03, intervalo de confiança — IC95% -1,83 a -0,16), e no subdomínio sono (U=38,00, p=0,033), com tamanho de efeito grande (ES=-1,06, IC95% -1,86 a -0,19), favoráveis ao grupo fisicamente ativo. Na QV-DA, houve diferença entre os grupos apenas no subitem memória (U=20,00, p=0,005), com tamanho de efeito grande (ES=1,59, IC95% 0,59 a 2,48), não houve diferença na pontuação total (U=45,5, p=0,277). **Conclusões:** Idosos submetidos a rotina de exercícios físicos com supervisão *online* na pandemia de COVID-19 apresentam menos sintomas neuropsiquiátricos, melhor qualidade de sono e memória quando comparados aos fisicamente inativos. Estudos randomizados controlados devem ser feitos para a melhor compreensão dos efeitos do exercício físico nos sintomas neuropsiquiátricos de pacientes com demência durante períodos de isolamento social.

Palavras-chave: SARS-CoV-2; Demência; Disfunção Cognitiva; Saúde Mental; Exercício Físico.

This study was conducted by the Group of Neuroscience of the Exercise, Institute of psychiatry, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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INTRODUCTION

Government recommendations for social distancing were implemented during the COVID-19 pandemic to protect the public, particularly older adults at higher risk of serious complications or death due to SARS-CoV-2 infection[1,2]. Although the primary purpose of social isolation is to reduce infection rates, studies have also shown the negative impacts of prolonged quarantine periods on aspects of mental health, such as increased anxiety (*Odds Ratio* [OR]=2.92, 95% confidence interval [CI] 2.43–3.51) and depressive symptoms (OR=4.55, 95%CI 3.82–5.41) in the general population[3]. In particular, studies in elderly people with neurocognitive disorders have revealed positive associations between social isolation and worsening of mental health during the COVID-19 pandemic[4,5]. A multicenter national survey conducted in 89 centers for cognitive disorders and dementia in Italy investigated the impact of quarantine after 45 days of social isolation on 4,913 patients with dementia. This study revealed a worsening of cognition in 55% of the sample, as well as neuropsychiatric symptoms of irritability (40%), apathy (35%), and agitation (31%)[5]. A review study on the experience of people with neurocognitive disorders in dealing with the COVID-19 pandemic indicated a worsening of neuropsychiatric and cognitive symptoms as well as an increase in caregiver burden during this period[6].

Neuropsychiatric symptoms have an impact on a patient's quality of life (QoL) and a caregiver's burden and well-being, contributing to early institutionalization[7-9]. Behavioral and psychological symptoms of dementia are more associated with QoL than cognition and functionality[10]. Recently, Dourado et al.[11] verified that mood, functionality, and awareness of morbidity are predictors of QoL in patients with Alzheimer's disease (AD). In acute situations, psychotropic drugs can be used to treat symptoms that endanger the safety of the patient or caregiver[12]. The administration of this treatment should be performed for the shortest possible time, since these drugs are associated with potential side effects. Antipsychotics are associated with an increased risk of sudden death and cardiovascular events[13], and the use of selective serotonin reuptake inhibitors and venlafaxine as antidepressants is associated with an increased risk of hyponatremia[14]. Exercises, beyond effectiveness in multidomain in AD, showed cost-effectiveness to behavioral and psychological symptoms[15,16]. Therefore, if possible, neuropsychiatric symptoms should be managed through non-pharmacological measures[7].

Studies have shown that therapeutic activities accompanied by music[18] and physical exercise[19,20] have beneficial effects on neuropsychiatric symptoms in the elderly. In particular, studies have indicated the positive effects of physical exercise on neuropsychiatric and depressive symptoms and QoL in people with cognitive impairment[20]. Physical exercise improves the QoL in elderly people with neurocognitive disorders[21]. A study conducted in patients with dementia in a long-term institution showed that participation in combined exercises was associated with an improvement in QoL compared to the control group[22]. In the general population, it is known that strategies incorporating physical exercise have a favorable effect on mental health since a positive correlation is observed between the level of habitual physical activity and the feeling of mental well-being during quarantine[23,24] combined with fewer symptoms of depression and anxiety[25].

In this study, we investigated the neuropsychiatric symptoms and QoL in elderly people with neurocognitive disorders during the social isolation period caused by the COVID-19 pandemic, to compare the differences between physically inactive patients with those who participated in a remotely supervised physical exercise program.

METHODS

Study design and participants

This cross-sectional case-control study was conducted between August and November 2020. All subjects were outpatients being followed up at the Alzheimer's Disease Center of the Institute of Psychiatry of the Universidade Federal do Rio de Janeiro (Brazil). The diagnosis was previously made by medical staff based on a structured clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[26] and the criteria of Petersen[27].

Elderly men and women aged over 65 years with a clinical diagnosis of a major neurocognitive disorder, such as AD (n=14), vascular disease (n=1), Lewy bodies (n=1), frontotemporal dementia (n=1) or unspecified (n=5), or mild neurocognitive disorder (n=2), were invited to participate with their caregivers. The exclusion criteria were as follows: history of severe heart disease, acute or chronic musculoskeletal injuries that prevent exercise, severe cognitive decline, and other mental disorders.

A priori sample calculation was performed using G*Power software, version 3.1.9.2. It was found an effect size (ES) of 1.46, a power of 0.95 (95%), and a type error α=0.05 (5%), which suggested a sample size of 22 individuals (11 in each group). The ES calculation was based on means and standard deviations (SDs)

suggested by Stella et al.[28] (control: M=43.3; SD=18.4 and physical activity group: M=16.9; SD=17.6), which evaluate the effect of a physical activity program on the neuropsychiatric symptoms of older adults with AD[26].

The exercise group comprised patients who already exercised before the pandemic and maintained the routine exercises throughout a remotely supervised physical exercise program. The online tool used to provide the program was Zoom's platform. The remotely supervised physical exercise routine consisted of a structured program of aerobic (stationary and varied walks), strength (standing up and sitting down, elbow flexion), coordination, flexibility and balance (one-foot support, plantar flexion) activities, as well as cognitive engagement dual-tasks (performing two concomitant tasks, motor/cognitive, as answering questions during the movement, trail guided by letters or colors) lasting 60 min. The activities were performed twice a week for at least 3 months in online groups of a maximum of 10 patients and their caregivers, always supervised by a physical education professional. Accessories including a plastic bottle filled with water or earth, towels, and cushions were adapted to meet the needs of each patient. The activities were of mild to moderate intensity and modified according to the capacity of each individual. The control group comprised other patients who were in outpatient follow-up and did not perform any type of exercise during the evaluation period.

This study was approved by the Ethics Committee (CAAE: 35449820.0.0000.5263), and all patients provided informed consent to participate via an online form before the beginning of the evaluations.

Procedures and measures

Evaluation of global cognitive capacity was performed at the time of the patient's initial evaluation by medical staff at the Alzheimer's Disease Center using the Mini-Mental State Examination[29], the Verbal Fluency Test[30], and the Clinical Dementia Rating[31]. This information was obtained through accessing medical records. The patient was interviewed through telephone contact via the main caregiver. The assessment included an evaluation of anamnesis and a structured questionnaire designed to collect sociodemographic data (e.g., sex, age, education, and marital status) and details of the patient's psychological symptoms and QoL. The evaluation was performed 6 months after the onset of quarantine and 3 months after starting the online exercise program.

Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (NPI)[32], which comprises a questionnaire delivered by the caregiver, consisting of 12 domains (i.e., hallucinations, delusions, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and sleep and eating disorders), each evaluated in terms of frequency and intensity, with scores ranging from 0 to 144 points[33].

The QoL of patients was assessed according to the Quality of Life in Alzheimer's Disease (QoL-AD) scale based on the answers provided by the main caregiver. The QoL-AD scale contains 13 items (i.e., physical health, energy, mood, living situation, memory, family, marriage, friends, ability to do chores, ability to do things for fun, self, money, and life as a whole), and scores ranging from 13 to 52 are directly proportional to a better QoL[34,35].

Statistical analysis

A descriptive analysis of the demographic data was conducted. The Kolmogorov-Smirnov and Levene's tests were applied to verify normal distribution and homoscedasticity of the data, respectively. The demographic characteristics and NPI and QoL scores were compared between groups (remotely supervised physical exercise×control group) using Student's *t*-test (parametric variables), the Mann-Whitney U tests (nonparametric variables), and χ^2 test (categorical variables). Cohen's coefficient was used to assess ES magnitude as small (>0.20), moderate (>0.50), or large (>0.80), with 95%CI[36]. All statistical analyses were performed using SPSS® version 26.0 and GraphPad® version 5.01. The value of $p \leq 0.05$ was considered statistically significant.

RESULTS

The final sample consisted of 25 patients: 11 patients in the control group and 14 patients in the exercise group (remotely supervised physical exercise). The details of the sociodemographic characteristics, cognitive characteristics, neuropsychiatric symptoms, and QoL-AD of the study participants are presented in Table 1.

The total NPI score in the exercise group (median=4.5, range=0–25) was lower than that in the control group (median=22.0, range=0–42), indicating that elderly patients with neurocognitive disorders who participated in the online supervised exercise program had significantly fewer neuropsychiatric symptoms (U=36.50, p=0.025). In the individual evaluation of the NPI scale items, there was a statistically significant difference between the groups only in the nighttime behavior disturbances item (U=38.00, p=0.033), showing that those who participated in the online supervised exercise had better sleep quality than those in the inactive group. The Mann-Whitney U-test analysis revealed that there were no significant

Table 1. Demographic and clinical characteristics by groups.

		Total (n=25)	Control group (n=11)	Physically active (n=14)	F/χ^2 (p-value)
Age (years)[a]		78.0 (4.0)	77.3 (7.5)	78.6 (7.9)	-0.40 (0.69)
Disease duration (years)[a]		6.0 (4.0)	6.5 (3.4)	5.7 (4.3)	0.43 (0.67)
Sex	Male (%)	52	45.5	57.1	0.33 (0.56)
	Female (%)	48	54.5	42.9	
Marital status, n (%)	Married	12 (50)	5 (50)	7 (50)	0.17 (0.91)
	Divorced	4 (16.7)	3 (30)	5 (35.7)	
	Widower	8 (33.3)	2 (20)	2 (14.3)	
Education (%)	0–4 years	24.0	27.3	21.4	5.21 (0.15)
	5–9 years	32.0	27.3	35.7	
	10–12 years	32.0	18.2	42.9	
	>12 years	12.0	27.3	0.0	
MMSE (score)[a]		22.2 (3.6)	20.7 (3.7)	23. (3.3)	-1.85 (0.07)
Verbal fluency (score)[a]		14.2 (7.4)	14.6 (8.8)	14.0 (6.4)	0.20 (0.83)
CDT (score)[b]		2.0 (0–5)	1.0 (0–3)	2.5 (0–5)	35.50 (0.04)*
CDR (score)[b]		1.1 (0–2)	1.2 (0–2)	1.0 (0.5–2)	57.00 (0.53)
NPI total (score)[b]		15.0 (0–42)	22.0 (0–42)	4.5 (0–25)	36.50 (0.02)*
QoL total (score)[b]		31.0 (15–39)	29.0 (15–39)	32.5 (22–37)	45.50 (0.26)

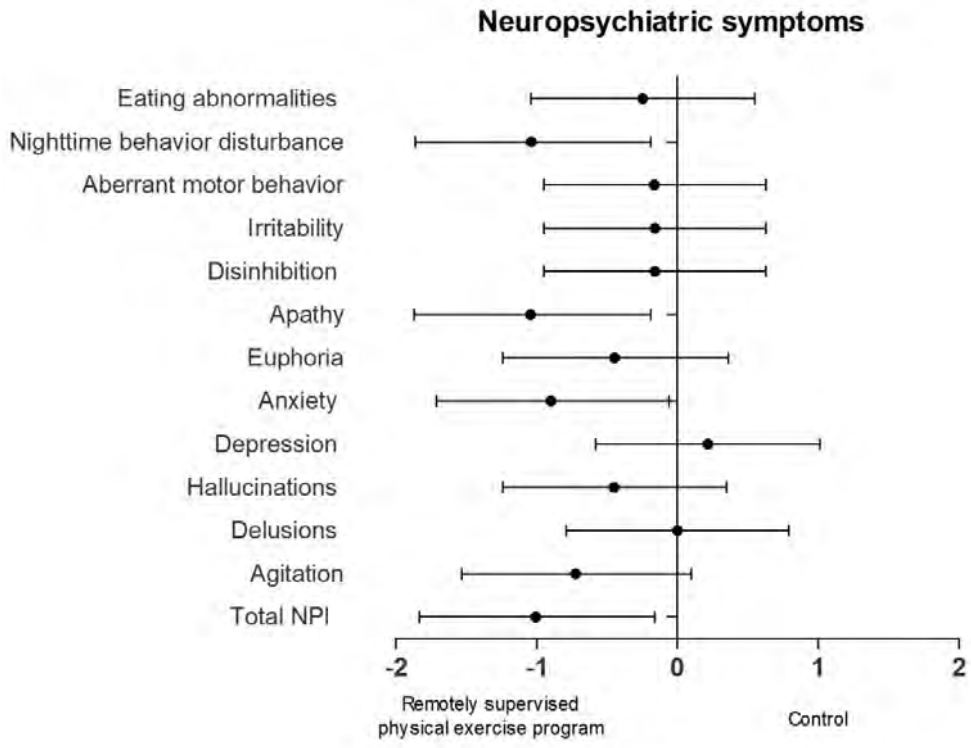
MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test; CDR: Clinical Dementia Rating; NPI: Neuropsychiatric Inventory; QoL: quality of life; *p<0.05; [a]Parametric (mean and standard deviation); [b]Non-parametric (median, minimum, and maximum).

differences between the groups in terms of the other NPI scale items.

The NPI ES magnitude analyses (Figure 1) revealed large effects between exercise and control group on the total NPI total scores (ES=-1.03, 95%CI -1.83 to -0.16), nighttime behavior disturbances (ES=-1.06, 95%CI -1.86 to -0.19), anxiety (ES=-1.06, 95%CI -1.71 to -0.06), and apathy (ES=-1.07, 95%CI -1.87 to -0.19). Moreover, a moderate ES was observed for agitation (ES=-0.75, 95%CI -1.53–0.1). Furthermore, we observed a small but favorable effect on delusions (ES=0.0, 95%CI -0.79–0.79), hallucinations (ES=-0.46, 95%CI -1.24–0.35), euphoria (ES=-0.46, 95%CI -1.24–0.36), disinhibition (ES=-0.16, 95%CI -0.95–0.63), irritability (ES=-0.16, 95%CI -0.95–0.63), aberrant motor behavior (ES=-0.17, 95%CI -0.95–0.63), and eating abnormalities (ES=-0.25, 95%CI -1.04–0.55). The only subitem for which a worst NPI score was detected in the exercise group was depression, although the ES was small (ES=0.22, 95%CI -0.58 to -1.01).

Regarding patient's QoL (Figure 2), there was a significant difference between groups only in the memory subitem (U=20.00, p=0.005), with a large ES (1.59, 95%CI 0.59–2.48), showing that caregivers evaluate better domain memory of people who performed physical exercise. There were no significant differences between the two groups in terms of the total QoL-AD (U=45.5, p=0.277) and other subitems.

The ES analysis revealed a moderate improvement in the total QoL-AD (ES=0.6, 95%CI -0.27 to 1.44), life as a whole (ES=0.64, 95%CI -0.23 to 1.47), and living situation (ES=0.76, 95%CI -0.13 to 1.60) subitems in the exercise group compared with the control group. The large ES in the money subitem (ES=0.85, 95%CI -0.05 to 1.69) in the exercise group indicated fewer financial concerns as assessed by the caregivers in



Negative results indicate fewer neuropsychiatric symptoms compared with the control group.

Figure 1. Effect sizes of neuropsychiatric symptoms by subdomain.

the exercise group compared with the control group. In addition, the small ES in the family (ES=0.48, 95%CI -0.38–1.31) and friends (ES=0.35, 95%CI -0.5–1.18) subitems revealed greater satisfaction in terms of interactions with family and friends in the exercise group compared with the control group. There was also a small effect on the self subitem of the QoL-AD scale (ES=-0.3, 95%CI 1.20–0.49). However, exercise had only negligible effects on physical health, marriage, mood, ability to do chores, and ability to do things for fun subitems (ES<0.20) compared with the control group.

DISCUSSION

In this study, we investigated the neuropsychiatric symptoms and QoL of patients with neurocognitive disorders who maintained a routine of remotely supervised physical exercise during the COVID-19 pandemic compared to those who were physically inactive. We showed that people with neurocognitive disorders who maintained a physical exercise routine during this period presented significantly fewer neuropsychiatric symptoms and better sleep than those who did not remain physically active. However, there was no difference in QoL between groups.

Social isolation caused by the COVID-19 pandemic has been indicated as a factor in increasing neuropsychiatric symptoms[37]. Lara et al. reported a significant increase in the total NPI score (p=0.028) in elderly people with mild cognitive impairment (MCI) and AD after 5 weeks of lockdown in Spain. Anxiety and apathy were the most frequently reported symptoms in the MCI group, while the AD group reported apathy and agitation. Recent studies have shown a relationship between exercise and mental well-being during the period of isolation during the COVID-19 pandemic[23-25]. A Brazilian study showed that those who practiced remotely supervised exercise presented fewer depressive symptoms than those who did not practice physical activity[38]. However, patients with dementia were not included in these studies. The results are in agreement with previous studies showing better neuropsychiatric symptoms in patients with dementia who participated in an exercise program[20,39,40]. In a recent meta-analysis, Dauwan et al.[41] also observed a positive effect of physical exercise on depressive symptoms in patients with AD.

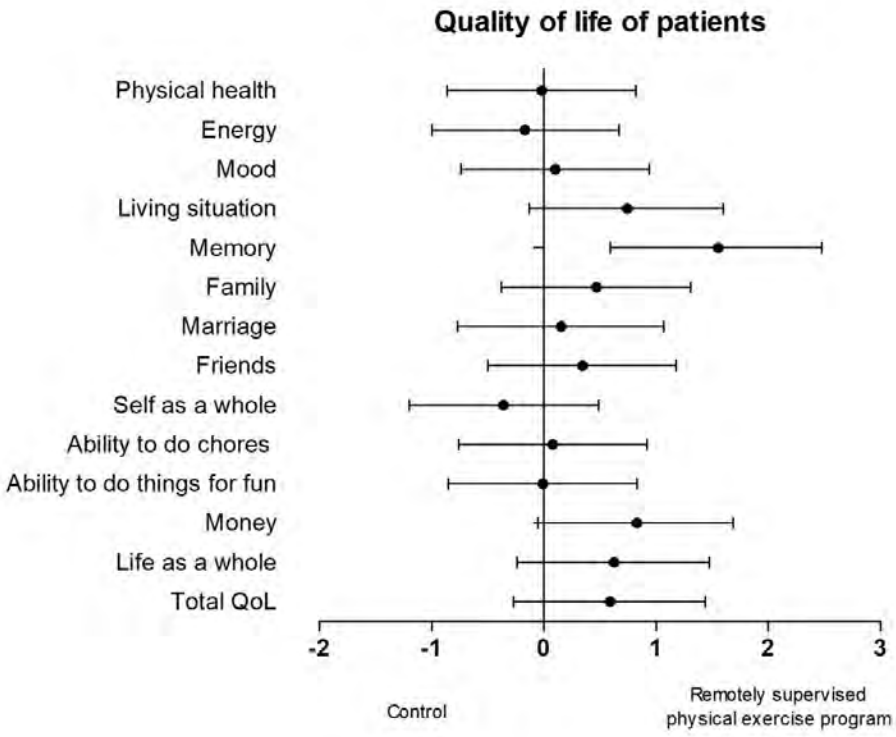


Figure 2. Quality of life effect sizes by subdomain.

The results reported in this study highlight the value of remotely supervised physical exercise as a possible alternative intervention to promote mental health in patients with neurocognitive disorders during the COVID-19 pandemic.

Sleep was the only subdomain among the NPI items for which a significant difference was identified between the exercise and control groups (p=0.03), with a large effect detected for the remotely supervised physical exercise group (ES=-1.06). This finding follows the report suggested by McCurry et al.[42], in which sleep improvement was observed in patients with dementia following a combined intervention of sleep hygiene, exposure to light, and walking. In addition, multimodal exercise was found to attenuate sleep disturbance in AD patients[43]. The potential mechanisms by which sleep disturbance is alleviated by the exercise program include changes in core body temperature, the release of neurotransmitters that regulate sleep, increased energy consumption, changes in heart rate variability and autonomic function, and reduced inflammation[44]. As expected, we found a large ES for the anxiety and apathy subdomains, showing that people with neurocognitive disorders who participated in the online physical exercise program had fewer symptoms than those in the control group. Among the possible mechanisms associated with the anxiolytic and antidepressant effects of physical exercise, it is expected an increase in neurotransmitters and trophic factors, neurogenesis, and angiogenesis, as well as an increased activation of the opioid and endocannabinoid systems[21].

In this study, we found that there was no difference in the total QoL-AD scores of the exercise and control groups. However, the scores in the exercise group were similar to those observed in previous studies of the QoL of people with neurocognitive disorders before the COVID-19 pandemic[11,34]. The relatively low QoL-AD scores in the control group may be associated with the effects of the pandemic and social isolation, which corroborate the findings of reduced QoL in cognitively healthy elderly individuals and those with neurocognitive disorders[45,46]. Moreover, reports on the effects of physical exercise on the QoL of people with neurocognitive disorders are inconsistent[47], which may be due to the multifactorial characteristics of the evaluation or variability in the instruments used. In general, studies have demonstrated the benefits of exercise on the QoL

of elderly who are cognitively healthy[48] and those with depression[47,49], as well as people with neurocognitive disorders, even dementia types[20,21,41,50]. However, the evidence is scarce and the level of evidence is low. In our QoL evaluation, memory was the only subitem for which significant difference was detected between the two groups, with a large ES identified in the group of patients who participated in the online exercise program.

This study has some limitations that need to be considered, such as the cross-sectional design and the small number of subjects. Moreover, the participants were not evaluated before and after the intervention; thus, a causal role for the intervention cannot be inferred from our data. Therefore, it is not possible to infer that those who had milder symptoms previously could be in the exercise group because they are more predisposed to perform exercises. In addition to the limitations of this study, there are barriers to implementing online interventions in dementia patients, namely, the presence of the caregiver, caregiver's support by the teacher, interest in doing online activities, and the difficulty of digital inclusion.

Randomized controlled trials are required to further clarify the potential benefits of a remotely supervised exercise program in people with neurocognitive disorders.

Elderly people with neurocognitive disorders who participated in a remotely supervised program of physical activities had significantly better sleep quality, subjective memory, and fewer neuropsychiatric symptoms. This type of intervention seems to be a feasible option for reducing sedentary behavior and improving behavioral symptoms in people with neurocognitive disorders during the COVID-19 pandemic. However, randomized controlled trials should be performed to better understand the effect of physical exercise in dementia patients during the periods of social isolation.

Authors' contributions. CDN: conceptualization, investigation, methodology, writing – original draft. JDL: methodology, software, visualization, writing – original draft, writing – review & edit. IAT: conceptulization, methodology, writing – review & edit. FOS: methodology, software, supervision, project administration, writing – review & edit. JSD: investigation, data curation. FCM: investigation, writing – review & edit. MCND: conceptualization, methodology, writing – review & edit. VM: conceptualization, writing – review & edit. ACD: conceptualization, funding acquisition, investigation, methodology, project administration, visualization, supervision, writing – original draft, and writing – review & editing.

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Dysphagia in Alzheimer's disease:
a systematic review

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ABSTRACT. Dysphagia is described as a highly relevant comorbidity of Alzheimer's disease (AD). However, there is a scarcity of studies aiming at the characteristics and progression of dysphagia. Objective: The objective of this study was to identify the specific characteristics, progression, and prevalence of dysphagia in AD. Methods: Publications were searched in the PubMed (MEDLINE), EBSCO, ScienceDirect, and BASE databases. Critical appraisal and evidence-level analysis were conducted using the Joanna Briggs Institute and Effective Public Health Practice Project's (EPHPP) tools. Results: A total of 26 studies were reviewed. Symptoms begin in the early stage of AD, as oral phase impairments, and progress to pharyngeal symptoms and swallowing apraxia in the later stages of AD. Dysphagia progresses, as AD, along a *continuum*, with severity depending on individual variability. There were no studies found on prevalence. Conclusions: Dysphagia is a complex and important comorbidity in AD that impacts the quality of life. No recent publications on prevalence may imply that is not being coded as a potential cause for pneumonia deaths in AD.

Keywords: Deglutition Disorders; Alzheimer Disease; Disease Progression; Prevalence.

A DISFAGIA NA DOENÇA DE ALZHEIMER: UMA REVISÃO SISTEMÁTICA

RESUMO. A disfagia é uma comorbidade relevante da doença de Alzheimer (DA). No entanto, existem poucos estudos sobre as suas características e progressão. Objetivo: Identificar as características específicas, a progressão e a prevalência da disfagia na DA. Métodos: Pesquisa conduzida nas bases PubMed (*Medical Literature Analysis and Retrieval System Online* — MEDLINE), EBSCO, ScienceDirect e BASE. Avaliação crítica e análise do nível de evidência foram conduzidas usando as ferramentas do Joanna Briggs Institute e do Effective Public Health Practice Project (EPHPP). Resultados: Incluíram-se 26 estudos. Os sintomas iniciam-se no estádio inicial da DA, como alterações de fase oral, progredindo para alterações faríngeas e apraxia de deglutição no estádio grave. A disfagia progride, como a DA, num *continuum*, com a gravidade dependendo da variabilidade individual. Não foram encontrados estudos de prevalência. Conclusões: A disfagia é uma comorbidade complexa e importante que tem impacto na qualidade de vida. A escassez de publicações atuais de prevalência pode indicar que não é considerada como potencial causa de morte por pneumonia na DA.

Palavras-chave: Transtornos de Deglutição; Doença de Alzheimer; Progressão da Doença; Prevalência.

INTRODUCTION

Alzheimer's disease (AD) was first described by Alois Alzheimer in 1907, which is a neurodegenerative disease[1] that accounts for 60–70% of all cases of dementia[2]. Clinically, AD is characterized by behavioral and cognitive decline[1,3] that typically results in symptoms originating from hippocampal and bilateral parietal-temporal dysfunction[2]. The progressive cognitive, behavioral, and neuropsychiatric symptoms have significant impacts on the affected individual's autonomy[3].

Prevalence of dysphagia

The high prevalence of dysphagia among individuals with dementia is the result of

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age-related changes to sensory and motor functions, in addition to those produced by neuropathology[4]. The prevalence of dysphagia in moderate to severe AD is from 84 to 93%[5-7]. Ironically, dysphagia remains an overlooked symptom, even when its complications can lead to longer hospitalizations and increased health care costs[8].

In AD, swallowing impairments are the leading cause for a progressive reduction in solid and liquid food intake[6]. Given that swallowing impairments directly affect food consumption, dysphagia may lead to weight loss, malnutrition, and dehydration[9-11].

Cortical deficits regarding dysphagia in Alzheimer's disease

Cortical regions involved in normal swallowing are affected by AD, including the insula/inferior frontal gyrus, pars opercularis, anterior cingulate cortex, and anterior medial temporal lobe[12]. As AD progresses, individuals experience a significant deterioration in the swallowing mechanism[6]; although some studies report swallowing impairments in the early stages of AD, it is more pronounced in the later stages[9].

Dysfunctions in cortical regions that control swallowing render the act of eating and drinking extremely effortful and may have devastating implications, such as increased risk for tracheal penetration and aspiration of foods, liquids, or even saliva, which can lead to aspiration pneumonia or death[10,12,13]. In AD, 70% of all deaths are related to pneumonia[14].

Dysphagia progression

In the early stages of AD, dysphagia undergoes a prolonged oral stage characterized by reduced lingual movement and delayed swallowing reflex[14,15]. This extended oral stage has been correlated with a longer duration for meal completion and, consequently, a risk of malnutrition[16]. The most frequent symptoms are oral residue after swallowing, mastication inefficacy, coughing or choking when consuming solid and/or liquid foods, and the need for verbal cues to initiate the swallowing reflex[17]. Some neurocognitive factors are associated with greater swallowing impairments, such as the inability to visually recognize foods, tactile and oral agnosia, and swallowing apraxia[18].

Moderate AD stages are characterized by difficulties in bolus preparation, airway clearance, upper esophageal sphincter opening, and visible aspiration when conducting Fiberoptic Endoscopic Evaluation of Swallowing (FEES)[19], where pharyngeal impairments can lead to aspiration before, during, or after swallowing[18].

In the severe stage, swallowing difficulties are severe and significantly impinge on the individual's quality of life[6,9]. At this stage, individuals with AD may experience swallowing apraxia[20].

Speech and Language Therapists' role

Speech and language therapists (SLTs) have a fundamental role in the assessment and intervention of dysphagia, collaborating with diverse medical and nursing specialties in a variety of contexts[21,22]. Interventions by SLTs should be evidence-based and tailored to a unique set of difficulties of the person with dysphagia[23].

The notable association between swallowing pattern, nutritional status, and general health status highlights the need for the specialized skills of SLTs in the effective management of dysphagia. Successful interventions help increase solid and liquid food intake, maintain nutritional status, and prevent morbidities such as pneumonia[10].

The most frequent interventions used by SLTs are compensatory interventions (e.g., modification of diet consistency and/or postures), although their effects on the prevention of aspiration are variable[24]. The implementation of compensatory interventions is somehow related to the safety of oral food consumption, and their failure supports the use of acute alternative sources of nutrition[7].

Enteric nutrition

Enteric nutrition (percutaneous endoscopic gastrostomy [PEG] or nasogastric tube) in patients with AD or other dementias should only be administered in acute situations (e.g., cases of aspiration pneumonia or severe dysphagia). Generally, artificial nutrition yields no benefit on survival rates or decreasing the risk of aspiration in patients in the most advanced stages of dementia[18].

Aim

The primary aim of this review was to identify and describe the specific characteristics and symptom progression of dysphagia in AD in recent literature. The secondary aim was to investigate the available evidence on the prevalence of dysphagia in AD patients.

METHODS

Search strategy and selection criteria

In March 2020, two researchers independently conducted a search of publications between 2010 and 2020 by following a predefined protocol. This literature search was conducted on the PubMed, EBSCO, Science Direct, and BASE databases to identify studies on the characteristics of dysphagia in AD and its progression and prevalence. Reference lists of relevant articles were also reviewed. To ensure a thorough search, a protocol

based on the PRISMA statement was designed, and combinations of search terms were determined (e.g., dysphagia, swallowing disorders, deglutition disorders, AD, prevalence, evolution, and progression). The inclusion criteria comprised peer-reviewed primary studies written in English, French, Spanish, or Portuguese published between 2010 and 2020.

Critical appraisal and level of evidence

A critical appraisal and an evidence-level analysis were performed with the Joanna Briggs Institute Critical Appraisal Tools and the Effective Public Health Practice Project's (EPHPP) "Quality Assessment Tool for Quantitative Studies."

The Joanna Briggs Institute Critical Appraisal Tools[25] were applied to each study according to its design and methodology. These tools allowed us to determine construct and internal validity, the sample establishment criteria, the risk of bias (in studies and by researchers), and the validity of the statistical tools chosen. Therefore, each critical appraisal tool allowed researchers to analyze the included studies independently. A consensus of critical appraisal was compiled in a table according to the study design. Of note, no study was excluded from the sample following the critical assessment.

Later, the process of assessing the level of evidence within the studies was conducted. To this end, the "Quality Assessment Tool for Quantitative Studies" tool, from the EPHPP, was used[26]. This tool analyzes the bias in the selection of the sample, study design, confounding variables, the knowledge of individuals regarding the objectives and/or procedures, methods of data collection, exclusions and/or withdrawals, integrity of the intervention, and analysis of the results; as a result, studies are assigned as possessing a strong, moderate, or weak level of evidence. The levels of evidence are attributed based on the application of the criteria listed in the tool's appendix. The level assigned to each domain being studied is then reflected in the overall assessment of a given study. Three levels can be assigned: level 1 is "strong," level 2 is "moderate," and level 3 is "weak." As no significant discrepancies were found in the application of the tool and in the levels of evidence established, a consensus on the level of evidence was reached.

Data extraction and reporting

The data collected from the sample studies were organized into a table, which included author(s), publication year, study design, sample, objectives, data collection instruments, most pertinent results, and broader implications.

For the qualitative processing and synthesis of the studies, we used WebQDA software that identifies itself as a qualitative data analysis software.

RESULTS

The initial search yielded 505 results from candidate studies that were screened by title and abstract. The screening process excluded 468 studies that failed to meet the inclusion criteria (e.g., heterogeneous sample, secondary or unrelated studies, studies in non-specified languages). After screening, both researchers proofread the remaining 37 studies and found that 11 of them were duplicated. Ultimately, 26 studies were included, as shown in Figure 1.

The level of evidence, which was determined by the EPHPP – Quality Assessment Tool for Quantitative Studies[26], stated that the majority of the studies (69%) included had a moderate level of evidence.

With respect to study design, the final sample included 6 experimental studies and 20 observational studies, more specifically, non-randomized clinical trials (n=6), a case–control study (n=1), cohort studies (n=9), a case study (n=1), and longitudinal studies (n=9). The greatest limitations were found to be the study design, sample characteristics (e.g., number of participants, selection criteria, nonspecific dementia samples), and nonuniversal nomenclature used to describe the swallowing disorders.

Later, results were analyzed and synthesized, allowing to outline broad patterns and general characteristics. The scope of the studies is outlined in Figure 2.

There were no epidemiological studies on prevalence published in the past 10 years, and the results presented

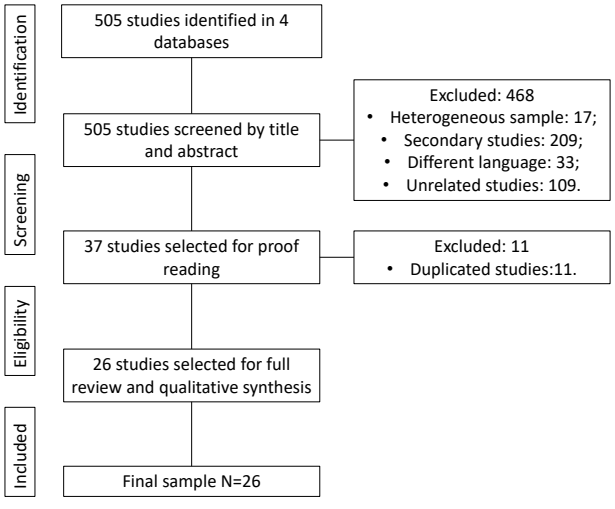

Figure 1. PRISMA flow diagram of the sampling process.

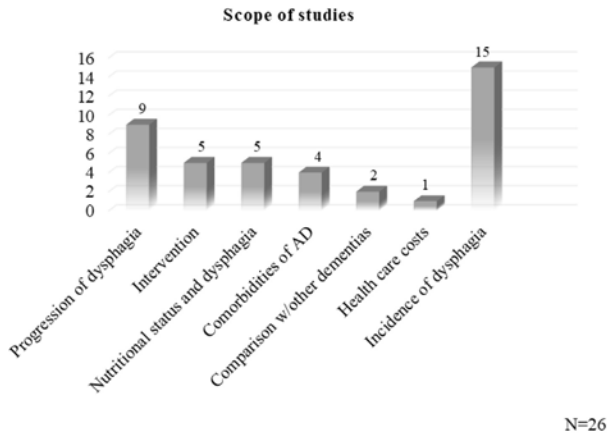

Figure 2. Scope of the sample studies.

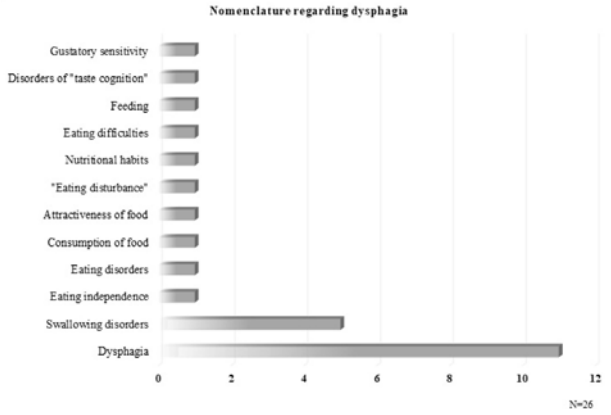

Figure 3. Nomenclature regarding dysphagia.

a broad variety of topics and nomenclature regarding dysphagia in AD. Studies were found on the evolution of dysphagia, the correlation between nutritional status and dysphagia, intervention methodologies, health care-associated costs, comparison of dysphagia symptoms and progression between dementias, and dysphagia as a comorbidity of AD. The lack of consensus in nomenclature and criteria used for incidence and description of symptoms is shown in Figure 3.

Regarding dysphagia symptoms and their progression, stratification in stages was most commonly found according to the clinical dementia rating (CDR). A compilation of the most frequent symptoms is shown in Table 1.

In the sample studies, the incidence of dysphagia varied from 2.4 to 100% (Table 2). The values shown were assessed by different methods and correspond to the AD population with different symptoms of dysphagia present in the samples of the studies included.

Therefore, the sample studies were analyzed and synthesized according to their relevance in dysphagia

Table 1. Dysphagia symptoms and progression according to clinical dementia rating.

Dysphagia symptoms	CDR1	CDR2	CDR3
Prolonged oral stage/phase	x	x	x
Reduced lingual movement	x	x	x
Mastication inefficacy/bolus preparation	x	x	x
Oral residue after swallowing	x	x	x
Delayed swallowing reflex	x	x	x
Coughing/airway clearance	x	x	x
Chocking	x	x	x
Upper esophageal sphincter opening		x	x
Visible aspiration (FEES)		x	x
Need for verbal cues to initiate swallow reflex		x	x
Oral agnosia			x
Swallowing apraxia			x

CDR: clinical dementia rating.

understanding and management in the clinical setting. Relevant topics that were shown in recent literature were added to the study, analyzed, and described.

DISCUSSION

The initial proposal for this study was to identify the specific characteristics of dysphagia in the different stages of AD. This was a goal rather challenging due to the design of the studies in recent literature. Designing and executing an experimental study in a target population with great individual variability as AD (clinical, neuropsychological, and cognitive-behavioral) may affect the quality and accuracy of study results. This may explain the abundance of studies in the literature with non-specified samples (i.e., dementia without any other specification), which were excluded from this study. The sample used in our own systematic review, which used observational (n=20) and experimental (n=6) studies, is not exempt from these challenges.

Dysphagia characteristics and symptom progression

Dysphagia symptoms in early AD are centered around a longer oral phase with reduced lingual movement and delayed swallowing reflex. Understanding whether there would be functional changes in the cerebral

Table 2. Incidence of dysphagia in sample studies.

Year	Journal	Author(s)	Publication	Incidence of dysphagia (%) (samples)
2010	Arquivos Neuropsiquiatria	Correia et al [9]	Swallowing in moderate and severe phases of Alzheimer's disease	27.8–71.9
2012	Geriatrics Gerontology International	Edahiro et al.[37]	Factors affecting independence in eating among elderly with Alzheimer's disease	2.4–87.3
2013	European Psychiatry	Heun et al.[35]	Alzheimer's disease and comorbidity: increased prevalence and possible risk factors of excess mortality in a naturalistic 7-year follow-up	11
	Alzheimer's Disease Association Disorders	Tian et al.[36]	Health care utilization and costs among patients with AD with and without dysphagia	5.4
2014	Revista. Latino-Americana Enfermagem	Goes et al.[30]	Evaluation of dysphagia risk, nutritional status, and caloric intake in elderly patients with Alzheimer's disease	86
	Geriatrics Gerontology International	Sato et al.[14]	Detecting signs of dysphagia in patients with Alzheimer's disease with oral feeding in daily life	12.8–41
2015	Journal of Clinical Nursing	Chen et al.[28]	Effects of a feeding intervention in patients with Alzheimer's disease and dysphagia	100
	PLoS ONE	Kai et al.[38]	Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease	81.4
	Turkish Journal of Medical Sciences	Yildiz et al.[34]	Malnutrition is associated with dementia severity and geriatric syndromes in patients with Alzheimer's disease	5.4–36
2016	Journal of Nursing Home Research Sciences	Miranda et al [31]	Undernutrition in institutionalized elderly patients with neurological diseases: comparison between different diagnostic criteria	63
	Clinical Neurophysiology	Seçil et al.[20]	Dysphagia in Alzheimer's disease	75
	Medicine	Tang et al.[39]	Therapeutic efficacy of neuromuscular electrical stimulation and electromyographic biofeedback on Alzheimer's disease patients with dysphagia	100
2018	Dementia and Neuropsychologia	Mastroianni and Forgerini[40]	Drug administration adjustments for elderly patients with dysphagia	100
2019	Journal of Parenteral and Enteral Nutrition	Ozsurekci et al.[32]	Timing of dysphagia screening in Alzheimer's dementia	98.7
	Singapore Medical Journal	Shea et al.[41]	Chinese patients with Lewy body dementia had shorter survival and developed complications earlier than those with Alzheimer's disease	12.9

cortex responsible for swallowing in the early stages of the disease prior to the onset of symptoms of oropharyngeal dysphagia was found in a study by Humbert and colleagues[12]. This study focused on the assessment of deficits in cortical control of swallowing in the early stages of AD and may have important clinical implications for educating patients with AD and their caregivers, early assessment, diagnosis, and intervention to minimize risks, future complications, and health care costs[12].

The early-stage dysphagia symptoms have been correlated with a longer duration for meal completion and, consequently, a higher risk of malnutrition. The oral residue after swallowing, mastication inefficacy, coughing or choking when consuming solid and/or liquid foods, and the need for verbal cues to initiate the swallowing reflex are described in recent literature.

Dysphagia symptoms in moderate AD stages progress toward the pharyngeal phase where impairments can lead to aspiration before, during, or after swallowing. Difficulties in bolus preparation, airway clearance, upper esophageal sphincter opening, and visible aspiration when conducting FEES are the most common symptoms. Some neurocognitive factors are associated with greater swallowing impairments, such as the inability to visually recognize foods, tactile and oral agnosia, and swallowing apraxia.

The cortical deficits in the later stages of AD, oral, and pharyngeal phase difficulties were associated with difficulties in meal initiation, passivity, low attentional capacity, and refusal to eat. The decrease in speed and volume of intake relates to sensory-motor issues associated with cognitive changes resulting from AD[9]. In 2018, a study[27] corroborated these results, focusing on the importance of manipulating the consistency of the foods offered to minimize the risk of aspiration and malnutrition[27].

Swallowing difficulties in the later stage of AD are severe and greatly impair the quality of life. Also, patients with AD may experience swallowing apraxia at this stage.

A study by Seçil and colleagues in 2016[20] found the changes in the electrophysiological parameters of swallowing in 75% of their sample, although no symptoms were shown. The authors also observed the following changes in swallowing as the disease progresses: subclinical dysphagia (early stage), dysphagia (moderate stage), and apraxia of swallowing (severe stage). The concept of progressive deterioration of the swallowing reflex appears in all studies.

Some studies have correlated dysphagia to the individual's general nutritional status. For instance, studies[28-34] found the correlations between nutritional aspects and dysphagia. Ultimately, the studies converge on the following results: the more severe the dysphagia, the worse the individual's nutritional condition.

The evidence states unequivocally that AD comorbidities are interrelated[35]. The severity of dysphagia in the studies we sampled seems to directly influence nutrition, hydration, the presence of pressure ulcers, the presence and severity of respiratory infections, the severity of cognitive-behavioral changes, and the general health status of individuals with AD[34,35].

Prevalence and incidence of dysphagia in Alzheimer's disease

The studies in this review allowed only to partially answer the research question. There were no studies found in the past 10 years regarding the prevalence of dysphagia in AD and the lack of consensus in nomenclature, and criteria used for incidence and description of symptoms were considerable limitations. Incidence data were classified and stratified according to CDR, others to the degree of severity of dysphagia, risk of dysphagia, or even risk of malnutrition. The authors used terms such as "malnutrition," "low, moderate, high risk of dysphagia," "eating disorders," or "eating difficulties" that appear to indicate the incidence of swallowing disorders. Such nonspecific nomenclature is often used to describe issues associated with dysphagia, which has two potential explanations. First, clinicians are unable to determine where the physiological phenomenon of dysphagia begins, and the cognitive-behavioral phenomena associated with dementia end. The potential explanations provided suggest the presence of a vicious clinical circuit; the presence of AD disturbed intake, and the metabolic consequences worsening AD. Preclinical detection would be a valuable clinical goal that could influence early intervention, potentially slow down progression, and decrease health care cost. Second, the professional background of the researchers affects the nomenclature employed to describe the physiological phenomenon under study. The use of nonspecific nomenclature referring to swallowing disorders renders any generalizations dubious in validity. In addition, the frequency of a feature's references does not necessarily represent the real prevalence of that feeding characteristic. This is due not only to the level of evidence of the studies and their methodological limitations, but also to the studies' aims and to the instruments used to measure swallowing difficulties.

Regarding incidence, data were collected, analyzed, and summarized according to CDR. Incidence of dysphagia in the sample studies showed a major variation that ranged from 2.4 to 100%. The discrepancy of values could be explained by the differences in aim, samples, and assessment methods, and correspond to the AD population with different symptoms in the samples of the studies included. Researchers should aim for a consensual nomenclature (that does not depend on the researcher's professional background) as well as homogeneous samples in their studies. Therefore, a qualitative analysis of the most relevant topics in recent

literature should be conducted with clinical implications in managing dysphagia in AD.

FURTHER DISCUSSION

A study by Tian and colleagues[36] proved to be unique in the literature; they retrospectively studied two databases of North America's health care subsystems within a 4-year period and found that patients with AD and dysphagia use health services significantly more and at higher costs. This corroborates the idea that early intervention in dysphagia in AD may help to lower health care-related expenditures. Further research in this area could spur political and clinical decision-makers to fund early intervention.

Limitations

The main proposal of this study was to present a global and largely inclusive perspective on swallowing disorders in AD patients.

An effort was made to systematize the information into main categories; however, it might not have involved a consensual approach.

Several limitations should be borne in mind when interpreting our results. Selection bias may be present. To increase data collection, the identification of grey (unpublished) literature could offer new insights, although it is also a controversial procedure due to its unconventional format and a lack of a peer-reviewed process.

Another important source of bias in results comparison is the variety of the studies included. For example, there were a limited number of experimental studies and a significant number of observational studies, variation of protocols and outcome measures, and no assessment of the risk of bias. Furthermore, studies evaluating interventions and management were unable to blind direct care providers due to the nature of the intervention. The diversity of terms regarding dysphagia with a lack of consensus between authors was also a serious limitation to the data analysis, increasing the risk of bias.

Future directions

Although there is evidence in the literature that dysphagia is an important symptom in AD, no studies in the past decade were found on its prevalence or variations in prevalence as a function of disease progression. Future research is encouraged to focus on prevalence so that clinicians, politicians, and the public at large can be better informed about dysphagia, and better diagnostic tools can be developed.

Only a handful of studies showed that changes in the cortical swallowing network occur early in AD and may be correlated with early functional changes in swallowing; however, the neuropathophysiology of dysphagia in AD remains unclear. Therefore, future studies should focus on the neuropathophysiology of swallowing impairments in AD so that the association with functional changes and symptoms is brought to light.

Dysphagia presents itself as one of the most impactful comorbidities of AD, yet its supporting evidence is scarce. Although the literature indicates that dysphagia affects both the oral and pharyngeal stages of swallowing in AD, no studies were found on the esophageal stage of swallowing. Future research on the specific symptoms of each stage of swallowing in AD would improve assessment and intervention, as well as the quality of life.

The research team also found that most studies differ in their nomenclature on dysphagia, a problem that urgently needs a solution.

In addition, different methodologies were used to examine dysphagia in AD, with no specific and individualized swallowing assessment being consistently used. Also, few studies examined specific interventions for dysphagia in individuals with AD. Postural adjustments, food consistency modifications, electric or sensory stimulation, and motor training as intervention have been thoroughly studied in several neurodegenerative diseases, and future research should aim for the same standard to be applied in dysphagia interventions in AD.

In conclusion, dysphagia in AD is described in the literature as an important comorbidity due to its impact on the quality of life of individuals. It has a complex, multifaceted, and variable clinical presentation. Dysphagia, such as AD, progresses along a continuum of symptoms that decrease the individual's quality of life and increase the health care costs.

Long before symptoms appear, there are cortical changes in the neural networks responsible for swallowing. Dysphagia is linked to other comorbidities of AD unequivocally: more severe dysphagia leads to severe malnutrition and dehydration, severe respiratory infections, falls, pressure ulcers, cognitive-behavioral decline, and even the individual's death. This systematic review aims to impact clinicians in the assessment and diagnosis of dysphagia in AD and in the design of a specific and individualized therapeutic program that aims to prevent future clinical complications or even death.

Regarding the prevalence of dysphagia in AD, there are no epidemiological studies on the prevalence of this comorbidity in the literature in the past 10 years but only estimated data (with wide prevalence windows) from international health associations that (specifically) study the pathology and the comorbidities associated with it. It is considered imperative to

understand the real prevalence of dysphagia in AD so that policymakers and clinicians can converge toward early intervention and reducing the burden on health systems. No up-to-date study on the prevalence of dysphagia in AD could also mean that this comorbidity could be underdiagnosed and not noted as a leading cause of death from pneumonia in patients with AD.

As a partial answer to the research question, it is concluded that dysphagia is undeniably presented as an important, impactful, continuous disorder, often associated with the progression of AD. It evolves, like the disease, in a degenerative sense and contributes to the progressive decrease in the individual's quality of life and to the increase in access and associated costs in health (medication, hospitalization, among others).

The lack of a clear nomenclature, incidence data, and recent prevalence studies contributes to lessen the quality of dysphagia understanding and management in AD.

This review contributes to a global view of the phenomenon of dysphagia in AD and serves as a basis for future research.

Authors' contributions. AM: study design, methods, data collection and analysis, manuscript draft, and critical appraisal; RG: methods, data collection and analysis, and manuscript draft; ITR: study design, methods, critical appraisal, and supervision.

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Therapeutic role of memantine for the prevention of cognitive decline in cancer patients with brain metastasis receiving whole-brain radiotherapy:
a narrative review

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ABSTRACT. Brain metastases are the most common central nervous system tumors. The mainstay treatment for this tumor in low to middle income countries is whole brain radiation therapy. Irreversible cognitive decline is associated with the use of whole brain radiotherapy. Several pharmacologic and nonpharmacologic options have been employed in studies focusing on the prevention of cognitive decline following whole-brain radiation therapy. Memantine use has been shown to provide some benefit in reducing the rate of decline in cognitive function and time to cognitive failure. The objective of this review article is to provide a summary on available primary literature on the therapeutic role of memantine for the prevention of cognitive decline in cancer patients with brain metastasis receiving whole brain radiotherapy.

Keywords: Memantine; Radiotherapy; Brain neoplasms; Cognition.

PAPEL TERAPÊUTICO DA MEMANTINA NA PREVENÇÃO DO DECLÍNIO COGNITIVO EM PACIENTES COM CÂNCER COM METÁSTASE CEREBRAL RECEBENDO RADIOTERAPIA CEREBRAL TOTAL: UMA REVISÃO NARRATIVA

RESUMO. As metástases cerebrais são os tumores mais comuns do sistema nervoso central. O tratamento principal para este tumor em países de baixa e média renda é a radioterapia de cérebro inteiro. O declínio cognitivo irreversível está associado ao uso de radioterapia cerebral total. Várias opções farmacológicas e não farmacológicas têm sido empregadas em estudos com foco na prevenção do declínio cognitivo após radioterapia de cérebro inteiro. O uso de memantina demonstrou fornecer algum benefício na redução da taxa de declínio na função cognitiva e no tempo até a falha cognitiva. O objetivo deste artigo de revisão foi fornecer um resumo da literatura primária disponível sobre o papel terapêutico da memantina para a prevenção do declínio cognitivo em pacientes com câncer com metástase cerebral recebendo radioterapia cerebral total.

Palavras-chave: Memantina; Radioterapia; Neoplasias encefálicas; Cognição.

INTRODUCTION

Metastases to the brain are the most common central nervous system tumors. It occurs in 20–40% of all patients with malignant tumors (mostly from lung and breast cancers)[1]. There has been an increasing trend toward survival among these patients and this may be due to improved diagnostic modalities and improvement in treatment regimens. The incidence of brain metastasis is estimated to be about 17,000 per year in the United States, which is 10 times higher than the incidence of the most common primary brain tumors[2].

This study was conducted by the Memory, Aging and Cognition Center, Department of Neurology in coordination with the Department of Radiotherapy, Jose R. Reyes Memorial Medical Center, Manila, Philippines

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A study in 2016 revealed that the incidence of brain neoplasms in the Philippines is 2297, with 1969 deaths[3]. A retrospective study in 2015 done in a tertiary hospital showed metastatic brain disease accounted for 3.2% of all central nervous system neoplasms[4]. In our institution, a retrospective chart review identified 86 patients with metastatic brain disease. Currently, there are no existing national registries for brain tumors and attempts have been made at an institutional level.

METHODS

The records were searched until December 30, 2020, and identified through PubMed, Embase, ClinicalTrials.gov, ICTRP (WHO), and Cochrane Library databases. The following search strategy was implemented, and these key words (in the title/abstract) were used: "Memantine" AND "Cognitive Dysfunction" AND "Brain metastasis" AND "Radiotherapy" OR "Whole Brain Radiotherapy." The search strategy was used to obtain the titles, abstracts, and, if necessary, the full text of articles of the relevant studies in English, and they were independently screened to determine the suitability. The reference lists of the studies were also reviewed to ensure literature saturation.

The inclusion criteria were as follows: (1) primary research studies including adult patients with brain metastases; (2) studies evaluating radiation therapy, including whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) either alone or in combination, as initial or postoperative treatment, with or without systemic therapy (immunotherapy and chemotherapy); (3) studies comparing eligible interventions to other eligible interventions or other management approaches; (4) studies reporting on the following outcomes: overall survival, progression-free survival recurrence/cancer control, symptom burden, and health status or health-related quality of life; (5) studies including national and international settings; and (6) all randomized controlled trials (RCTs), prospective experimental and observational studies. The exclusion criteria were as follows: (1) study samples comprising patients with primary brain tumors and done on pediatric samples; (2) studies without WBRT treatment arms; (3) unavailability of results, different study population, and different intervention; (4) partial result information and duplicate studies; (5) reviews, commentaries, viewpoints, or opinions; and (6) animal studies.

Initial search strategies were done by MOT and MCF. Disagreement was decided by a third reviewer, who was either JNO, JAC, or JAF.

The following data were extracted from the included studies: author (year), study design, level of evidence, sample size, inclusion criteria, study arms, outcome, and result of outcome. The search strategy is presented in Figure 1. Table 1 presents the summary of the studies included in the article.

TREATMENT FOR BRAIN METASTASES

The treatment for brain metastasis is individualized depending on the primary cancer, the patient's clinical history, and the number of metastases. The blood-brain barrier protects the brain and is only permeable to limited substances, rendering tumors located in this area difficult to treat with conventional medical therapies[5,6]. Surgery has been performed in single lesions[7]; however, radiation therapy remains the most used treatment modality, especially in low- to middle-income countries (LMICs).

Whole-brain radiation therapy remains the primary therapeutic tool for patients with brain metastases[8-10]. About 100,000 patients with brain tumor who received brain irradiation survive for >6 months and 50–90% of these patients exhibit disabling cognitive dysfunction[11]. Attention has been directed toward neurocognitive decline which affects learning, memory, processing speed, attention, and executive function. The mechanisms of radiation-induced cognitive decline are similar to those seen in vascular dementia patients, and this includes radiation-accelerated atherosclerosis, mineralizing microangiopathy, followed by vascular insufficiency and infarction[12].

The exact mechanism by which WBRT induces cognitive dysfunction is still not fully understood, but brain injury

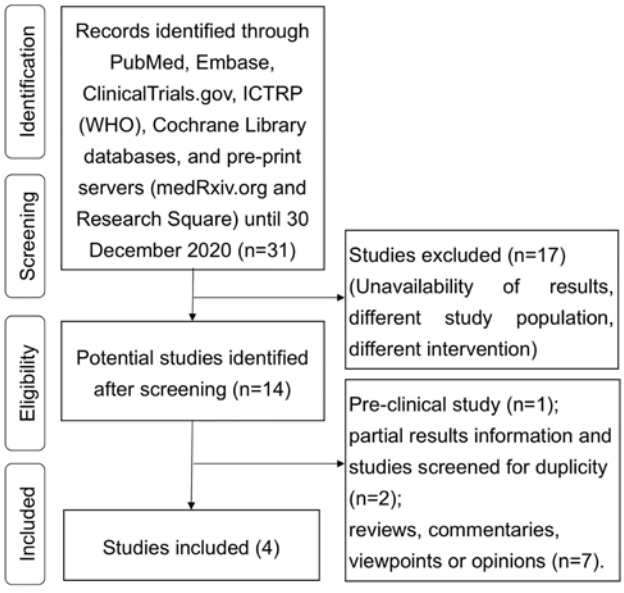

Figure 1. Flowchart depicting the steps of qualitative synthesis of evidence from the literature.

Table 1. Summary of the clinical studies on the effect of memantine for the prevention of cognitive dysfunction in patients with brain metastasis receiving whole-brain radiation therapy.

Author (year)	Study design	Level of evidence	n[1]	Inclusion criteria	Study arms	Outcome	Result of outcome
Brown et al. (2013)[26]	Randomized double-blind, placebo-controlled trial	1	554	Adult patients with brain metastases receiving WBRT[2]	WBRT+memantine WBRT+placebo	HVLT-R for Delayed Recall at 24 weeks	No significant difference in delayed recall (primary outcome) between the two arms p=0.059)
Brown et al. (2020)[28]	Randomized parallel, open-label controlled trial	1	518	Adult patients with brain metastases outside a 5-mm margin around either hippocampus receiving WBRT	WBRT+memantine HA-WBRT[4]+memantine	Time to cognitive function failure	Significant reduction in cognitive failure in patients under HA-WBRT plus memantine (adjusted hazard ratio, 0.74; 95%CI 0.58–0.95; p=0.02).
Wong et al. (2016)[27]	Randomized parallel, open-label placebo–controlled trial	1	14	Adult patients with brain metastases receiving WBRT (12 from RTOG 0614)	WBRT+placebo WBRT+Memantine*	DCE-MRI measures of tumor tissue and normal-appearing white matter (NAWM) vascular permeability	significantly (p=0.01) reduced normal-appearing vascular permeability changes following radiotherapy
Laack et al. (2018)[25]	Randomized parallel, open-label controlled trial	1	442	Adult patients with brain metastases receiving WBRT (from RTOG 0614)	WBRT+memantine WBRT+placebo	Association of health-related quality of life and cognitive function	Baseline cognitive function correlated significantly with Medical Outcomes Scale-Cognitive Functioning Scale (MOS-C).

*One patient did not receive any drug; WBRT: whole-brain radiation therapy.

may be due to injuries in different cell types. Currently, there are several hypotheses by which WBRT may cause cognitive dysfunction. One hypothesis is the significant reduction of neurogenesis in the hippocampus[12]. An experimental study done on rats showed >95% reduction in new neuron production following a single dose of WBRT. The authors further added that there two important ways by which neurogenesis is reduced. First, radiation-induced damage to nasopharyngeal cancers (NPCs) impairs growth potential of the progenitor pool following long-term treatment as exemplified above. Second, radiation may induce changes in the brain microenvironment, leading to prominent inflammatory response. This would lead to activation of microglia, thus impairing neurogenesis[13].

Radiation may also alter the brain's microvasculature that maintains hippocampal neurogenesis. The exact mechanism is still being debated, but studies have shown that disruption caused by the radiation may lead to decreased size in the perivascular clusters of precursor cells. This change may last for several years and may be responsible for the reduction in neurogenesis after completion of cranial radiation therapy[12,13].

Another hypothesis regarding radiation-induced cognitive dysfunction is the vascular hypothesis. It states that the vascular changes seen in post-radiation patients are similar to those seen in cases of vascular dementia. Mechanism includes death of endothelial cells and increased platelet adhesion, leading to thrombus formation. This would eventually result in occlusion of small vessels. In addition, there may also be increased atherosclerosis, ultimately leading to vascular ischemia and/or infarction. Ischemia or infarction may increase the levels of glutamate, the principal excitatory neurotransmitter in the brain[12]. In normal physiological conditions, glutamate activates the NMDA receptors to enhance learning and store memory. However, in diseased conditions, the excessive increase in glutamate could lead to increased neurotoxicity[14]. This mechanism may serve as a target for therapy in radiation-induced cognitive toxicity. These mechanisms are summarized in Figure 2.

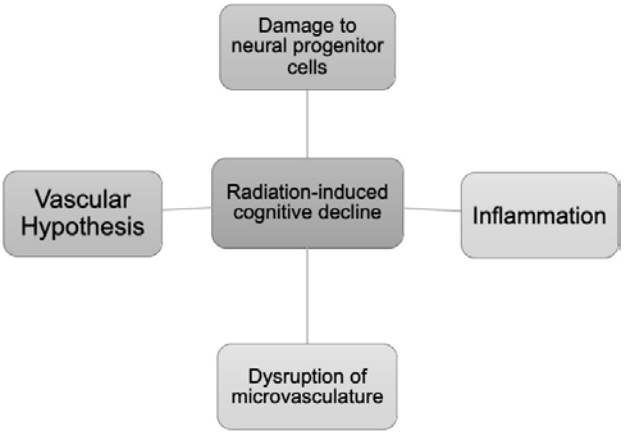

Figure 2. Potential mechanisms in radiation-induced cognitive decline and the role of memantine.

Despite the importance and clear concern about radiation-induced cognitive decline, the pathophysiology driving the progression of this syndrome remains poorly understood.

The pathophysiology of radiation-induced cognitive decline is still not fully understood. For this reason, there is great interest in studying treatments to prevent or reduce radiation-induced cognitive injury.

CURRENT OPTIONS FOR THE PREVENTION OF COGNITIVE DECLINE

Stereotactic radiosurgery

Several treatment options are in current practice for preventing radiation-induced cognitive decline. One such option is SRS. SRS is a procedure that safely delivers high doses of radiation to a defined target and this modality has been studied in a number of clinical trial. An RCT showed the efficacy of SRS alone in lowering the risk of significant decline in learning and memory function when compared to the combined SRS+WBRT[15]. Among patients with one to three lesions, SRS alone again showed significantly less cognitive decline at 3 months when compared to combined SRS+WBRT (-28.2% difference, $p<0.001$) despite no difference in overall survival[16]. Among postoperative patients, the NCCTG N107C/CEC·3[17] trial revealed that there are more frequent cognitive decline in patients receiving WBRT compared to SRS, with no difference in overall survival. A total of 194 patients were randomly assigned to both arms with a median follow-up time of 11.1 months. Primary outcome is cognitive-deterioration-free survival. This was longer in the SRS group compared to patients with WBRT (HR=0.47, $p<0.001$.

Hippocampal avoidance

The hippocampus has been identified as a key player in the process of learning and memory[18]. Several strategies were formulated to primarily avoid this part of the brain during radiation therapy. The RTOG 0933[19] is a single-arm phase II multicenter trial that investigated the concept of avoiding the hippocampus during WBRT. It revealed that there is significantly lower decline in Hopkins Verbal Learning Test-Revised for Delayed Recall (HVLT-R DR) in comparison with a historical control group at 4 months from baseline (mean decline of 7.0 vs. 30% in the control group, $p<0.001$).

Pharmacological options

Pharmacological options were also explored. Donepezil is an acetylcholinesterase inhibitor currently used in the treatment of Alzheimer's disease. A randomized placebo-controlled trial[20] revealed that a single daily dose of donepezil (5 mg for 6 weeks and 10 mg for 18 weeks) did not significantly improve verbal learning, memory, and other composite scores. The authors further added that increasing the dose in future trials may be of greater benefit for patients. Another option is armodafinil, a drug primarily used in the treatment of narcolepsy. A study[21] showed that the drug was well tolerated but had no significant effect on fatigue and cognitive function when given during radiation therapy. Methylphenidate is another option. It is a stimulant used for the treatment of attention-deficit hyperactivity disorder (ADHD). A randomized trial showed that the drug did not significantly improve the quality of life and cognitive outcome measures in patients on radiation therapy.

Memantine

Memantine hydrochloride (MEM) is an indicated treatment for moderate-to-severe dementia of the Alzheimer's type. It has neuroprotective properties and is used as off-label to treat Parkinson's disease, chronic brain syndrome, and spasticity[22]. MEM is a low-affinity uncompetitive antagonist of NMDA and thus displaced rapidly, thereby avoiding its negative consequences on memory. MEM only interacts with the receptor in pathological conditions, such as in radiation-induced cognitive dysfunction and Alzheimer's disease[23]. Microglial NMDA receptors are present and may cause inflammatory responses during overactivation. This inflammatory response is mediated by factors such as interleukins, TNF, ROS, and nitric oxide. This mechanism may be another way by which MEM may help in protecting against cognitive dysfunction[23,24]. Memantine was safe and well tolerated and reduced the risk of cognitive decline, as measured by several standard screening tests[25].

EFFECT OF MEMANTINE ON RADIATION-INDUCED COGNITIVE FUNCTION

A landmark trial by Brown et al.[26] in 2013 evaluated the protective effects of memantine in radiation-induced cognitive dysfunction. This is a randomized, double-blind, placebo-controlled trial that included 508 individuals with confirmed brain metastases by contrast-enhanced magnetic resonance imaging (MRI). Other inclusion criteria include Karnofsky performance status of ≥70, stable disease within 3 months prior to the study, normal serum levels of creatinine, total bilirubin, and blood urea nitrogen (BUN). Participants are also required to have a Mini-Mental State

Examination (MMSE)>18 with no allergy on memantine. Patients with prior treatment such as radiosurgery and surgical resection was included, given the therapy >14 days prior to the start of the study. The primary outcome is cognitive function after 24 weeks as measured by the HVLT-R DR.

The participants were allocated via the Zelen treatment allocation scheme and received either placebo or memantine for 24 weeks within 3 days of the start of radiation therapy. Each subject received escalating doses of memantine starting at 5 mg daily dose to a target daily dose 20 mg at week 4 and maintained until 24 weeks. For the WBRT, each subject received a total dose of 37.5 Gy composed of 15 fractions of 2.5 Gy. Assessment was done at baseline, 8, 16, 24, and 52 weeks after the commencement of the study. This included clinical history, neurological and physical examination, specimen collection, and neuropsychological battery of tests.

Participants were majority female, with 55.1 and 57.5% in the treatment and control groups, respectively. The median age is 60 years for the memantine group and 59 years in the placebo group. Notably, 70% of the subjects have lung cancer as its primary disease site. In terms of neurological functional status, 44.9 and 38.9% are having minor symptoms but fully active in the memantine and control groups, respectively. The primary cognitive outcome for this study was not significant despite having less decline in HVLT-R DR in the memantine arm compared with the placebo arm at 24 weeks (median decline of 0 vs. -0.9). The authors noted that the high attrition rate and low number of subjects analyzed contributed to the non-significant result, having a low 35% statistical power. Other cognitive tests showed statistical significance, including the raw score of the MMSE (median decline 0 vs. -1, p=0.009). Time to cognitive failure was found to have significantly favored the memantine group, with a 21% relative risk reduction. The effect of steroids during treatment was also evaluated and showed that patients treated with steroids had more decline at 8 weeks of treatment. Overall survival and progression had no statistically significant difference between the two arms.

The authors concluded that memantine is well tolerated and safe among these patients. They added that it showed significance in terms of reducing the rate of cognitive decline and the time to cognitive failure despite not having a significant result in their primary outcome. This study is limited by the poor compliance of its participants due to factors such as tumor progression and death. The study also did not include participants with a low Karnofsky score; hence, the benefit of memantine on these patients is still unknown.

Another study done by Wong et al.[27] in 2016 evaluated the ability of dynamic contrast-enhanced MRI (DCE-MRI) in detecting vascular changes in patients receiving WBRT and memantine. There were 14 patients included in this trial, 12 of whom are from RTOG 0614. The primary outcome measure is the normal-appearing white matter area under the curve (NAWM AUC) measured at different time points (8, 16, and 24 weeks) after WBRT. Cognitive and quality-of-life assessment was also done. Each arm had the same number of subjects. In this study, the most common primary site is the lung, followed by the breast.

The patients on memantine therapy had significantly lower AUC at 6 months post-WBRT compared to placebo (p=0.01). The treatment group had better cognitive functions than those on placebo (p=0.03). However, there was no significant difference in the overall survival rates between groups. The study concluded that the results suggest the value of memantine in reducing vascular changes seen in WBRT patients.

RECENT AND FUTURE TRIALS

Recent studies used memantine as their standard of care. One study by Brown et al.[28] in 2020 evaluated the impact of hippocampal avoidance WBRT in preserving cognitive function. The risk for cognitive failure was significantly lower in HA-WBRT plus memantine versus WBRT plus memantine alone as (adjusted HR=0.74; p=0.02). Despite not evaluating the effectiveness of memantine alone in preventing cognitive dysfunction, the trial established this combination as the new standard of care in the setting of WBRT. This would become a reference for future studies.

Unfortunately, studies on memantine are almost exclusively on patients with brain metastases receiving WBRT and it has not been evaluated in pediatric patients and other brain tumors. The SPiRiT (ClinicalTrials.gov Identifier: NCT04567251)[29] trial is a randomized, placebo-controlled, double-blind study evaluating the role of memantine in improving cognitive function in adult cancer survivors who received prior brain irradiation regardless of tumor type. Two studies (i.e., ClinicalTrials.gov Identifier: NCT03194906 and ClinicalTrials.gov Identifier: NCT04217694)[30,31] are currently evaluating the impact of memantine on pediatric patients.

SUMMARY

Although memantine is not used as a standard of care in the clinical setting across all patients receiving WBRT treatment for brain metastases, recent literature supports that memantine use is safe, well-tolerated,

and may have benefit in reducing the rate of cognitive decline. This may be more beneficial among patients who survived longer. The effect may be due decreasing vascular changes post-WBRT treatment. Furthermore, ongoing clinical trials are now using memantine as a standard of care and evaluating its effect in other tumors and in the pediatric population. Future studies could focus on the economic viability of memantine, especially on LMICs.

Authors' contributions. JAC, JNO, JAF: conceptualization, methodology, supervision and Writing – review & editing; MOT, MCF, SLC: data curation, Writing – original draft and Writing – review & editing

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Original Article

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Cognitive assessment of Brazilian patients with multiple sclerosis:

weighing the impact of disability and depressive symptoms

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ABSTRACT. Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. Cognition is not routinely assessed in patients with MS though they frequently have cognitive complaints or dysfunction. **Objective:** The aim of this study was to compare the cognitive status of patients with MS with age, sex, and schooling matched controls and to evaluate the potential influence of clinical parameters on cognition. **Methods:** A total of 35 patients with MS (mean±SD age 37.9 years±11.44, M/F: 12/23) and 33 healthy controls (mean±SD age 38.8 years±12.6, M/F: 12/21) were enrolled in this study. All subjects underwent a structured clinical assessment and the cognitive tools are as follows: Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test (RAVLT), Digit Span, and Verbal Fluency Tests (letters F, A, and S and animal category). Psychopathology was assessed with the Mini International Neuropsychiatric Interview and the Beck Depression Inventory (BDI). The Expanded Disability Status Scale (EDSS) was used for patients. **Results:** Patients performed worse than controls in almost all tests, with approximately 70% of patients presenting cognitive impairment. The most affected cognitive domain was episodic memory (45.7%), followed by verbal fluency (42.8%) and information processing speed (22.8%). SDMT was inversely correlated with disease severity, as assessed by the EDSS. Depression did not influence cognitive performance in this cohort. **Conclusions:** Cognitive dysfunction is common among patients with MS. While motor impairment was associated with information processing speed, depression did not influence cognitive performance.

Keywords: Multiple Sclerosis; Neuropsychological Tests; Cognition; Depression; Memory.

AVALIAÇÃO COGNITIVA DE PACIENTES BRASILEIROS COM ESCLEROSE MÚLTIPLA: ANÁLISE DO IMPACTO DA INCAPACIDADE E DOS SINTOMAS DEPRESSIVOS

RESUMO. A esclerose múltipla (EM) é a doença desmielinizante mais comum do sistema nervoso central. A cognição não é rotineiramente avaliada nos pacientes apesar da ocorrência frequente de queixas ou disfunção cognitivas. **Objetivo:** Comparar o perfil de pacientes com EM com controles pareados por idade, sexo e escolaridade e investigar a potencial influência de parâmetros clínicos na cognição. **Métodos:** Trinta e cinco pacientes com EM (idade média±desvio padrão [DP] 37,9 anos±11,44, H/M: 12/23) e 33 controles saudáveis (idade média±DP 38,8 anos±12,6, H/M: 12/21) foram incluídos neste estudo. Todos os participantes passaram por avaliação clínica estruturada e por testagem cognitiva com os seguintes instrumentos: Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test (RAVLT), Digit Span e testes de fluências verbais (letras F, A e S e categoria-animais). A psicopatologia foi investigada com a Mini International Neuropsychiatric Interview e com o Beck Depression Inventory (BDI). A Expanded Disability Status Scale (EDSS) foi aplicada nos pacientes. **Resultados:** Pacientes tiveram desempenho pior que os controles na maioria dos testes — 70% deles tiveram déficit cognitivo. A função cognitiva mais frequentemente afetada foi memória episódica (45,7%), seguida por fluência verbal (42,8%) e velocidade de processamento (22,8%). A pontuação no SDMT correlacionou-se inversamente com a gravidade da doença, medida pela EDSS. A depressão não influenciou o desempenho cognitivo nesta série de pacientes. **Conclusões:** Declínio cognitivo é comum em pacientes com EM. Enquanto o déficit motor se associou com a velocidade de processamento, a depressão não influenciou o desempenho cognitivo.

Palavras-chave: Esclerose Múltipla; Testes Neuropsicológicos; Cognição; Depressão; Memória.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system caused by a complex interaction among genetic and environmental factors. Several pathophysiological mechanisms, including neuroinflammation, demyelination, and axonal degeneration, are implicated[1-3]. MS affects approximately 2.5 million people worldwide[2,3]. It is the most common cause of nontraumatic neurological disability in young adults[1,4].

Cognitive impairment affects a range of 40–70% of patients[2,5-7]. It can be identified in all stages of the disease, including very early in its course, i.e., clinically isolated syndrome[6,8,9]. Typical cognitive impairment involves attention, memory, and executive functions, notably information processing speed (IPS)[5,6,10-12]. Cognitive impairment has a major effect on patients with MS, affecting their daily living and socio-occupational functioning[6,9,12]. Besides contributing to patients' poor perception of their quality of life, cognitive impairment also reduces adherence to treatment and rehabilitation[10,13,14]. Despite those facts, cognitive function is not routinely assessed in patients with MS. Accordingly, cognitive impairment is frequently overlooked and underdiagnosed in patients with MS[6,10,13,15,16].

There is an emerging interest on the study of cognitive dysfunction in Brazilian patients with MS[17-20]. For instance, Schmidt et al. showed that patients with less than 3 years of MS diagnosis and low disability have preserved cognitive performance in neuropsychological tests (Rey Auditory Learning Test, Controlled Oral Word Association Test, Hooper Visual Organization Test, and Symbol Digit Modalities Test (SDMT)), except for the number of errors in the SDMT[21]. Conversely, Damasceno et al. showed that patients with relapsing-remitting MS evolved with cognitive decline even if they had minimal or no evidence of disease activity[22,23].

Understanding the profile of MS cognitive dysfunction in Brazilian patients is important given the particularities of this population, including its unique genetic background and limited formal literacy. Therefore, the aims of this study were twofold: (i) to compare the cognitive status of MS patients with age, sex, and schooling matched controls and (ii) to evaluate the potential influence of sociodemographic and clinical parameters (focus on depression) on the cognitive performance of these patients.

METHODS

Subjects

We enrolled 35 patients with relapsing-remitting MS diagnosis according to revised 2010 McDonald criteria[24]. These patients were followed at the Neuroimmunology Outpatient Clinic, Pedro Ernesto University Hospital (HUPE), UERJ, Rio de Janeiro, Brazil. For comparison, 33 healthy subjects who matched by sex, age, and educational level were also invited to participate in the study.

All individuals aged 18–65 years and had at least 5 years of formal education. We did not include subjects who had any preexisting condition (e.g., intellectual disability and dementia) that could potentially interfere with neuropsychological assessment. The exclusion criteria were the Expanded Disability Status Scale (EDSS) value of >7.5 or any relapse or steroid therapy within 2 months before the clinical assessment. Volunteers were not included if they had a clinical diagnosis of major depression, as assessed by the Mini International Neuropsychiatric Interview[25], or had a score ≥25 in the Memory Complaint Questionnaire[26] or failed on the Mini-Mental State Examination[27] or on the component A7 of Rey Auditory Verbal Learning Test (RALVT)[28,29].

This study was approved by the HUPE Ethics Committee, and all participants gave written informed consent.

Clinical and cognitive evaluation

We collected sociodemographic and clinical data from all subjects. Neuropsychological tests were selected based on the most impaired cognitive domains in patients with MS[5,6,10]. Paced Auditory Serial Addition Test (PASAT), 3 seconds version[30], was chosen to assess sustained attention, working memory, and IPS; Symbol Digit Modalities Test (SDMT)[31] to assess sustained attention and IPS; Rey Auditory Verbal Learning Test (RAVLT)[28,29] to evaluate learning and verbal episodic memory; Digit Span Test[32] to assess attention and working memory; and F-A-S and animal category[33,34] to assess verbal fluency.

Test scores below 1.5 SD of the Brazilian population normative data mean were considered altered. Cognitive impairment was defined as a failure in at least one of the following tests: Component A7 of RAVLT, PASAT, and SDMT[35,36].

Data analysis

Database and statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software, version 19.0. The level of significance adopted was 5%. Group comparisons on clinical and cognitive tests were performed with Mann-Whitney and χ^2 tests. Correlation between variables was analyzed by the Spearman test.

RESULTS

A total of 52 patients were originally invited to participate in the study, but only 35 met inclusion/exclusion criteria. Table 1 shows the sample's sociodemographic and clinical profile. MS group was predominantly composed of young women who developed the first symptoms around 30 years old. They had less than 10 years of disease and mild neurological impairment. The most frequent treatment for MS was interferon-beta. Approximately 30% had major depression, characterized mainly by mild symptoms.

Patients had worse cognitive performance in almost all neuropsychological tests when compared with healthy controls, except for the Digit Span Test, both versions, and variables A1 and B1 of RALVT (Table 2). The most significant results were related to the following tests: PASAT, SDMT,

Table 1. Sociodemographic and clinical profile of controls and patients.

		Controls (n=33)	Patients (n=35)	p-value
Age (years)	Mean±SD	38.82±12.6	37.91±11.44	0.94*
	(min–max)	(21–63)	(18–61)	
	Median [IQR]	36 [27.5–50.5]	33 [28–49]	
Education (years)	Mean±SD	12.7±2.7	11.6±2.4	0.06*
	(min–max)	(5–15)	(5–15)	
	Median [IQR]	14 [11–15]	11 [11–12]	
Sex (%)	Female	63.6%	65.7	0.85**
EDSS	Mean±SD	NA	2.7±1.9	NA
	(min–max)		(0–6.5)	
	Median [IQR]		2.5 [1–4.5]	
MS first symptoms (years)	Mean±SD	NA	29.7±10.3	NA
	(min–max)		(13–60)	
	Median [IQR]		27 [24–37]	
Disease duration (years)	Mean±SD	NA	8.2±5.3	NA
	(min–max)		(1–22)	
	Median [IQR]		8 [3–12]	
Medication (%)	Interferon-β	NA	57.1	NA
	Glatiramer		22.9	
	Fingolimode		2.9	
	Natalizumab		2.9	
	Azathioprine		2.9	
	No medication		11.4	
Depression (MINI) (%)	Depression	0	28.6	**0.001****
BDI	Mean±SD	8±5.6	11.8±9.2	0.10*
	(min–max)	(0–28)	(0–39)	
	Median [IQR]	7 [6–11]	10 [6–16]	

SD: standard deviation; IQR: interquartile range; *Mann-Whitney; **χ^2; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; MINI: Mini International Neuropsychiatric Interview; min: minimum value; max: maximum value; n: sample size; NA: not applicable; p: level of confidence. Significant values ($p<0.05$) in bold.

Table 2. Results of the neuropsychological tests between groups.

Test		Controls (n=33)	Patients (n=35)	p-value
PASAT	Mean±SD	39.6±13.3	31.4±12.1	**0.008**
	(min–max)	(11–60)	(6–54)	
	Median [IQR]	41 [29.5–49.5]	30 [21–41]	
SDMT	Mean±SD	56.3±13.5	45±16	0.003
	(min–max)	(17–80)	(17–73)	
	Median [IQR]	55 [46–67]	43 [33–57]	
Direct SPAN	Mean±SD	8.1±2.7	8.2±2.3	0.69
	(min–max)	(4–14)	(4–14)	
	Median [IQR]	7 [6–10]	8 [6–10]	
Inverse SPAN	Mean±SD	5.4±2.9	5.1±2.1	**0.30**
	(min–max)	(3–11)	(0–9)	
	Median [IQR]	4 [4–5]	5 [4–6]	
Fluency (F)	Mean±SD	14.9±4.2	11.9±5	**0.007**
	(min–max)	(5–26)	(4–24)	
	Median [IQR]	15 [12.5–18]	11 [7–16]	
Fluency (A)	Mean±SD	13.1±4.2	10.7±4.5	**0.015**
	(min–max)	(3–22)	(3–21)	
	Median [IQR]	14 [10.5–16]	10 [8–14]	
Fluency (S)	Mean±SD	12.8±4.2	10.6±4.1	**0.03**
	(min–max)	(3–19)	(3–19)	
	Median [IQR]	13 [10–16]	11 [7–14]	
Total FAS	Mean±SD	40.8±11.1	33.2±11.6	**0.008**
	(min–max)	(13–63)	(15–61)	
	Median [IQR]	41 [35.5–48]	33 [24–42]	
Animals fluency	Mean±SD	21.9±5.9	17±4.3	**0.001**
	(min–max)	(12–35)	(9–28)	
	Median [IQR]	21 [17.5–26.5]	17 [14–20]	
RALVT – A1	Mean±SD	6.2±1.9	5.4±1.5	0.72
	(min–max)	(1–10)	(2–8)	
	Median [IQR]	6 [5–7.5]	6 [4–7]	
RALVT – A2	Mean±SD	9.7±2	7.9±1.9	**0.001**
	(min–max)	(5–13)	(4–12)	
	Median [IQR]	10 [8–11]	8 [7–9]	
RALVT – A3	Mean±SD	11.2±1.9	9.4±2.2	**0.003**
	(min–max)	(8–14)	(4–13)	
	Median [IQR]	11 [10–13]	10 [8–11]	

Continue...

Table 2. Continuation.

Test		Controls (n=33)	Patients (n=35)	p-value
RALVT – A4	Mean±SD	12.2±1.6	10.1±2.3	**0.000**
	(min–max)	(9–15)	(6–15)	
	Median [IQR]	12 [11–13.5]	10 [9–12]	
RALVT – A5	Mean±SD	12.7±1.8	11±2.5	**0.004**
	(min–max)	(10–15)	(6–15)	
	Median [IQR]	13 [11–14.5]	11 [9–13]	
Total A1–A5	Mean±SD	52.2±7.4	44±9.1	**0.000**
	(min–max)	(40–65)	(25–62)	
	Median [IQR]	53 [45–59]	43 [39–49]	
RALVT – B1 (interference)	Mean±SD	5.9±2.2	5.1±1.6	0.20
	(min–max)	(3–12)	(1–8)	
	Median [IQR]	6 [4–7]	5 [4–6]	
RALVT – A6	Mean±SD	10.6±2.5	8.4±3.4	**0.007**
	(min–max)	(6–15)	(1–15)	
	Median [IQR]	10 [8–12.5]	8 [7–11]	
RALVT – A7 (late recall)	Mean±SD	10.8±2.7	7.6±3.4	**0.000**
	(min–max)	(6–15)	(1–14)	
	Median [IQR]	11 [9–13]	8 [5–10]	
RALVT (recognition)	Mean±SD	28.7±1.5	28.3±4	**0.018**
	(min–max)	(24–30)	(7–30)	
	Median [IQR]	29 [28.5–30]	28 [27–30]	

SD: standard deviation; IQR: interquartile range; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; RALVT: Rey Auditory Verbal Learning Test; min: minimum value; max: maximum value; n: sample size; p: level of confidence; Significant values ($p<0.05$) in bold.

Verbal Fluency Test (letter F, FAS total, and animal category), and RALVT (A2–A6, total A1–A5 and late recall).

Cognitive impairment was detected in 68.6% of patients. Episodic memory (late recall) was affected in 45.7% of patients, information processing speed in 22.8% of patients, and verbal fluency in 42.8% of patients. Patients with or without cognitive impairment did not differ in sociodemographic and clinical parameters (Table 3).

In an exploratory analysis, neuropsychological performance was correlated with clinical parameters. The only significant association that emerged was the inverse correlation between EDSS and SDMT (rho=-0.58; p=0.003).

DISCUSSION

Cognitive dysfunction has been recognized as a central problem in patients with MS[2,5,6,12] By affecting daily living activities, work capacity, and social relationships, it h.as a significant effect on the patients' quality of life[9,12,14]. Its early recognition and management may have a relevant meaning for patients with MS[9,37].

In the current study, patients with MS performed worse compared to controls in almost all neuropsychological tests. The most significant differences were in the PASAT, SDMT, Verbal Fluency Test (total FAS and animal category), and RALVT (learning and late recall), corroborating the concept that IPS and episodic memory/learning are the most affected cognitive domains in patients with MS[5,6,10-12]. While 45.7% of the patients with

Table 3. Comparisons between patients with and without cognitive impairment.

		Preserved cognition (n=11, 31.4%)	Impaired cognition (n=24, 68.6%)	p-value
Age (years)	Mean±SD	36±11	38.7±11.7	0.70*
	Median [IQR]	33 [28–47]	34.5 [28–49.7]	
Education (years)	Mean±SD	11.4±1.2	11.6±2.8	0.40*
	Median [IQR]	11 [11–12]	11.5 [11–15]	
EDSS	Mean±SD	2.9±2	2.7±1.9	0.84*
	Median [IQR]	2.5 [1–5]	2.2 [1–3.8]	
Disease duration (years)	Mean±SD	7.,1±4.9	8.6±5.4	0.50*
	Median [IQR]	6 [2–13]	8.5 [3.2–11.7]	
Depression (MINI) (%)	n – %	2 – 18%	8 – 33%	0.35**
BDI	Mean±SD	12.2±8.8	11.6±9.8	0.64*
	Median [IQR]	10 [6–15]	9 [4–16.7]	
Sex (%)	Female	8–35%	15–65%	0.55**
	Male	3–25%	9–75%	
Medication (%)	Interferon-β	46%	63%	0.51**
	Glatiramer	27%	21%	
	Fingolimode	9%	0%	
	Natalizumab	0%	4%	
	Azathioprine	0%	4%	
	No medication	18%	8%	

SD: standard deviation; IQR: interquartile range; *Mann-Whitney; **χ^2; EDSS: Expanded Disability Status Scale; MINI: Mini International Neuropsychiatric Interview; BDI: Beck Depression Inventory; n: sample size; p: level of confidence.

MS had deficits in episodic memory, IPS was impaired in 22.8% of patients who performed below the normative data for the PASAT (17.1%) and/or SDMT (11.4%). Similar results have been described in other Brazilian and Latin American studies: 22.5% in SDMT according to the study by Negreiros et al. [38]; 12 and 21.8%, respectively, in PASAT and SDMT, according to the study by Caceres et al.[39] When analyzing verbal fluency, 42.8% of impairment was observed. Negreiros et al.[38] found a similar rate of 40.7%. In contrast, other studies reported lower indexes of around 16–19%[36,39,40].

The performance in the Digit Span was similar between patients and controls. A similar finding was reported by Balsimelli et al. [41], while Negreiros et al.[38] reported differences in both direct and inverse component scores of the Digit Span. In international studies on patients with MS, the direct component is usually not impaired, whereas deficits have been reported in the indirect component[5,32,42]. Differences in sample characteristics (e.g., disease severity and comorbidities) might explain these discrepant results.

Cognitive impairment was identified in approximately 70% of patients. Although this frequency is high, it is in accordance with data from international[5,6] and national studies[38,43]. It is worth emphasizing that interpretation and comparison of the studies on cognitive impairment in MS are challenging as there is no consensus about its definition. Some authors define cognitive dysfunction as the impairment in one of the three tests, regardless of the cognitive domain, in a series of tests applied[12,44]. Neuropsychological tests also vary significantly among studies. Another issue is the definition of neuropsychological test alteration. In general, an altered result is determined by the performance below a threshold chosen by authors (SD below the normative population or control data mean). This choice has varied

among Brazilian studies: from 1 SD[45,46], to 1.5 SD[40,43], up to 2 SD[36,47] below the mean.

Approximately 30% of patients had a clinical diagnosis of depression, a figure similar to previous studies[39,45,47]. We did not observe an influence of depression on the cognitive performance of patients with MS. In addition, there was no significant correlation between BDI and neuropsychological scores, consistent with some studies[45]. In contrast, some authors have shown a significant, but weak, association between depression and cognitive performance in patients with MS[40,48].

In the current sample, as cognitive dysfunction in patients with MS does not seem to be influenced by mood symptoms, we hypothesized that it is primarily a consequence of MS-induced changes in the brain structure and/or functioning. Corroborating in part this assumption, we found an inverse correlation between SDMT and EDSS, an index of disease-related disability. The degree of physical disability can inform about the extension and/or severity of brain damage and, as a consequence, cognitive functioning. Physical disabilities have been associated with cognitive performance in several Brazilian and international studies[35,40,43,45], but not in all studies[36,38,47].

Disease duration did not influence cognitive performance in our sample, in contrast to some of the Brazilian studies[36,45]. Actually, some studies[35,40] have reported an inverse correlation between disease duration and cognitive scores, especially SDMT. The exclusion of patients with EDSS>7.5, who usually have a longer disease duration, might explain this contradicting result.

While our study has strengths, such as well-established inclusion and exclusion criteria ruling out clinically defined depression and cognitive impairment, it also has clear limitations. First, our study involved a relatively small (n=35) sample of patients lacking neuroimaging results coupled with clinical assessment. Moreover, it was not possible to control for different immunomodulatory treatments. Most patients were treated using interferon and glatiramer (Table 1), which increases the chance of subtle MS activity detected only through sensitive neuroimaging techniques that can negatively affect cognitive performance[49]. While our sample size is comparable to former Brazilian studies[35,43,46,47], it is more homogeneous, highlighting the presence of cognitive impairment even in patients with higher formal education and without clinically defined depression, a condition that influences cognitive performance. Another limitation concerns the cognitive domains tested. We assessed only domains that are classically implicated in patients with MS, such as attention, episodic memory, IPS, and executive function, using well-studied tools in this context. The expansion of neuropsychological testing to other functions, such as visuospatial skills and social cognition, and the use of new tools would provide a more comprehensive understanding of MS-related cognitive profile.

In conclusion, our results support previous findings, showing that cognitive impairment is common among patients with MS without clinically defined depression, suggesting an important role played by MS pathology in cognition.

Authors' contributions. PSA: collected cognitive/clinical data, performed statistical analyses, and drafted the first version of the manuscript. ACRC, ACC, FRS, JMGB: collected cognitive/clinical data and critically reviewed the manuscript for intellectual content. ALT, LCS: designed the study and critically reviewed the manuscript for intellectual content. All authors read and approved the final manuscript.

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Health status of persons with dementia and caregivers' burden during the second wave of COVID-19 pandemic: an Indian study

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ABSTRACT. Due to the disruption of normal flow of treatment during the restrictions related to the coronavirus disease 2019 (COVID-19) pandemic, the health status of persons with dementia (PwD) and their caregivers' burden might worsen. **Objective:** The article aims to find out the health status of PwD and caregivers' burden during the peak of second wave of COVID-19 and make a comparison with the preceding trough phase. **Methods:** The study was conducted with 53 PwD and their caregivers in two phases. On their visit to the hospital during the unlock phase (phase 1), data were collected for CDR from PwD, and NPI-Q and ZBI from their caregivers. During the peak of second wave (phase 2), data were collected for NPI-Q, ZBI, and DASS-21 through telephonic communication, and statistical analyses were performed on the collected data. **Results:** Significantly higher caregiver burden (p=0.001) and neuropsychiatric symptoms (NPSs) [both in severity (p=0.019) and distress (p=0.013)] were observed among the respondents during the peak of second wave of the pandemic as compared to the preceding trough phase. Positive correlations were observed between the caregiver burden and depression, anxiety, and stress of the caregivers (p<0.001) and between the severity of dementia in PwD and caregiver burden (p<0.001) for both the first and second phases. Positive correlation was also observed between the severity of dementia in PwD and depression (p=0.042) and stress (p=0.023) of caregivers. **Conclusions:** Significant increase in the burden and distress was observed among caregivers due to increased NPSs of PwD during the second wave of COVID-19 pandemic.

Keywords: Caregiver Burden; COVID-19; Health Evaluation; Dementia.

ESTADO DE SAÚDE DE PESSOAS COM DEMÊNCIA E SOBRECARGA DOS CUIDADORES DURANTE A 2ª ONDA DA PANDEMIA DE COVID-19: UM ESTUDO INDIANO

RESUMO. Devido à interrupção do fluxo normal de tratamento durante as restrições relacionadas à pandemia de COVID-19, o estado de saúde das pessoas com demência (PcD) e a sobrecarga de seus cuidadores podem piorar. **Objetivo:** O artigo teve como objetivo conhecer o estado de saúde da PcD e a sobrecarga dos cuidadores durante o pico da 2ª onda de COVID-19 e fazer uma comparação com a fase anterior. **Métodos:** O estudo foi realizado com 53 PcD e seus cuidadores em duas fases. Em sua visita ao hospital durante a fase de desbloqueio (Fase 1), CDR, NPI-Q e ZBI foram administrados às PcD e seus cuidadores. Durante o pico da segunda onda (Fase 2), NPI-Q, ZBI e DASS-21 foram administrados por telefone e foram realizadas análises estatísticas dos dados coletados. **Resultados:** Foram observados sobrecarga do cuidador significativamente maior (p=0,001) e sintomas neuropsiquiátricos [tanto em gravidade (p=0,019) quanto angústia (p=0,013)] entre os entrevistados durante o pico da 2ª onda da pandemia em comparação com a fase anterior de passagem. Foram observadas correlações positivas entre sobrecarga do cuidador e depressão, ansiedade e estresse dos cuidadores (p<0,001) e entre gravidade da demência em PcD e sobrecarga do cuidador (p<0,001) tanto para a 1ª quanto para a 2ª fase. Também foi observada correlação positiva entre a gravidade da demência em PcD e depressão (p=0,042) e estresse (p=0,023) dos cuidadores. **Conclusões:** Foi observado um aumento significativo na sobrecarga e angústia entre os cuidadores devido ao aumento dos sintomas neuropsiquiátricos de PcD durante a 2ª onda da pandemia de COVID-19.

Palavras-chave: Fardo do Cuidador; COVID-19; Avaliação em Saúde; Demência.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has caused severe threats to public health both physically and mentally[1]. Across the world, the geriatric population being the most vulnerable group during the pandemic has faced its adverse effects[2]. The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive case in India was reported in the state of Kerala on January 30, 2020[3]. Thereafter, the number of cases started rising rapidly throughout the country, which was designated as the "first wave" of the pandemic. The peak of COVID-19 cases in the first wave in India was seen in September 2020[4]. To impose social distancing, a nationwide lockdown was initiated on March 25, 2020, and the same was extended in a phase-wise manner till May 31, 2020[5]. Subsequently, with reduction in number of cases in the country, the government announced resumption of services in phased manner termed as "unlock" period, which started on June 8, 2020[6], and extended up to November 2020. COVID-19 cases once again started rising from March 2021, signaling the arrival of the second wave in India[7].

During the spread of the pandemic, the number of lockdowns and unlock-downs were seen in India. Before the second wave entered the country, the trough phase of the disease was seen between December 2020 and February 2021 when there was a reduction in number of cases with easing of restriction called "unlock phase" with easier accessibility of resources. This allowed patients to avail consultations at hospitals and other health care facilities. Due to the second wave of COVID-19 in the country, partial lockdown was announced in different states.

In West Bengal, the peak of the second wave was seen between May and June 2021. Partial lockdown/self-imposed restrictions were announced in the state[8]. This included halting of rail and public transport services, limited hours for opening the markets, and night curfew, among others. Visiting health care facilities became difficult due to the lack of public transportation and fear of infection. The pandemic had its effects on daily living that were caused by shutting down of public venues, implementation of social distancing, economic downfall, and high levels of mortality across the population[9-11].

Previous research on this global pandemic showed increase in mental distress[12,13], especially in the vulnerable population like older adults[14] and those in poverty[15]. One of the common diseases among older adults is dementia, which is associated with a greater risk of death[16]. The worsening of the disease is not solely due to vulnerability to infection[17], but may also relate to the cognitive, behavioral, and psychological effects of rapid environmental changes brought by the pandemic. The vulnerability to the virus in patients with dementia is specifically related to their poor clinical status and their limited understanding of respiratory hygiene, such as hand sanitizing and the use of masks[18]. Deterioration of cognitive impairment in elderly persons with dementia (PwD) has also been reported following the pandemic[19-21]. Studies have also shown that community measures implemented to slow the spread of the virus have forced to social distancing and cancelation of cognitive stimulation programs, contributing to generate loneliness, behavioral symptoms, and worsening of cognition in patients with dementia[22]. Therefore, caregiver burnout is an expected consequence of increased demand for health care of PwD. Hence, the care provided by the caregivers may be troubled by their overwhelming load of work and homecare[23].

Studies have described an abrupt worsening of neuropsychiatric symptoms (NPSs) of PwD, including depression, anxiety, aggression, agitation, and insomnia[24], leading to an increase in distress among the caregivers[25]. Worsening of NPS leads to contamination[19] and risk of self-injury, hospitalization, and death. Managing NPS in elderly PwD has been particularly challenging during the COVID-19 pandemic[19]. However, the effects of decline in the NPS and its burden over the caregivers are still unclear.

Informal caregivers of PwD experienced different difficulties during the pandemic that did not relate to their caregiving role[26]. Initially, hospital visits for regular follow-ups were difficult as well as the lack of certain necessary supply of goods and facilities followed by an overall drop in the economy[27]. In India, informal caregivers of PwD already face immense burden and stress due to the care they provide[28]. The lockdown followed by the first wave of pandemic caused incredible difficulties and challenges to PwD caregivers, increasing their caregiver burden[26,29] and anxiety[30]. Despite a large number of PwD residing in low- and middle-income countries (LMICs) like India, studies on their health condition and caregiver's distress during this pandemic are few.

Therefore, this study aimed to explore the change from the preceding unlock/trough phase during the pandemic in India, if any, in the burden of PwD caregivers and the patients' health condition during the second wave of COVID-19.

METHODS

The study was conducted with PwD and their caregivers. This is a part of an ongoing research of the department and permission was obtained for it from the Institutional Ethics Committee.

Operational definitions

- *First phase of the study*: Unlock/trough phase between the months of December 2020 and February 2021 that had a decline in COVID-19 cases and relaxation of restrictions imposed by the government.
- *Second phase of the study*: Peak phase of COVID-19, i.e., second wave, in West Bengal, India, between May and June 2021.

Sample

All PwD who visited our clinic during unlock/trough phase between the months of December 2020 and February 2021 were included in the study. PwD without a reliable caregiver was excluded.

Procedure

Data were collected in two phases. In the first phase, data were collected for Clinical Dementia Rating Scale (CDR) from 54 PwD and CDR, Neuropsychiatric Inventory – Questionnaire (NPI-Q), and Zarit Burden Interview (ZBI) from their caregivers while they visited the clinic between December 2020 and February 2021, before the second wave hit India. In the second phase, i.e., during the partial lockdown when patients and caregivers were unable to visit the cognitive clinic of the hospital, data were collected for NPI-Q, ZBI, and Depression, Anxiety Stress Scale – 21 items (DASS-21) on the same caregivers of PwD through telephonic communication between May and June 2021. A psychologist (RM) collected the data in both phases. The caregivers were called and asked about their convenience of time and availability for the telephonic conversation. The purpose of the survey was explained to them, and the interview was conducted after their verbal approval. As one patient died due to COVID-19, the final sample consisted of 53 respondents.

Tools

The following tools were used for the study:

- *Information Schedule* – A semi-structured questionnaire was constructed by experts, which included sociodemographic details along with the current COVID-19 and vaccination status of the patients and the caregivers. The patients' health status was also included. Information were obtained from caregivers during the second phase of the study.
- *Zarit Burden Interview* (ZBI)[31] – ZBI measures the subjective burden among caregivers of PwD and consists of 22 items rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always). The sum of the score ranges between 0 and 88. Higher scores indicate greater burden.
- *Neuropsychiatric Inventory – Questionnaire*[32] – This questionnaire provides a brief assessment of neuropsychiatric symptomatology of the patients and their caregivers' distress related to it. It consists of 12 domains reflecting on the cardinal symptoms of the patient with responses "Yes" (present) or "No" (absent). In case of "Yes," the informant is asked to rate the severity of the symptom on a 3-point scale and their own distress related to it on a 5-point scale. Total sum of the score in both 3- and 5-point scale reflects the severity and the distress related to it.
- *Depression, Anxiety Stress Scale – 21 Items* (DASS-21)[33] – It is a scale that measures the emotional states like depression, anxiety, and stress. Each subscale contains 7 items and is rated on a 3-point scale ranging from 0 (not applicable) to 3 (very much). Summation of the score for each subscale reflects the severity of the emotional state from normal to severe. This scale was applied to caregivers of PwD.
- *Clinical Dementia Rating Scale* (CDR)[34] – CDR is used to measure the severity of dementia. The global score is used for grouping patients on the severity of dementia in the categories of 0 (no impairment), 0.5 (questionable/very mild), 1 (mild), 2 (moderate), and 3 (severe). The sum of boxes is also used for grouping patients on the severity of dementia ranging from 0 to 18.00. In this study, the global scoring of the scale was calculated and used. While some responses of CDR were elicited from PwD, others were obtained from their caregivers.

Statistical analysis

Statistics was carried out by using Statistical Package for the Social Sciences (SPSS version 21). Frequency (percentage) of categorical variables and mean (standard deviation) of the continuous variables were calculated. Pearson's product moment correlation coefficient was used to analyze the significant relationship between ZBI and NPI-Q (both severity and distress) [first and second phases]; ZBI and DASS-21 (each subscale) [second phase]; CDR [first phase] and ZBI [first and second phases]; and DASS-21 (each subscale) [second phase]. Paired t-test was used to compare between first and second phase of ZBI and NPI-Q (both severity and distress). The p-value at the level of <0.05 was considered significant.

RESULTS

Demographic details

A total of 61 patients visited our clinic during the first phase of our study; of them, 54 were eligible

for recruitment. As one of them succumbed due to COVID-19, a total 53 PwD were available for analysis. There were 32.1% female patients and 79.2% female caregivers in the sample. In all, 66.04 and 22.6% of patients and caregivers were of 60 years of age and above, respectively. The patients and the caregivers who had education till standard 10 and above were 58.5 and 69.8%, respectively. 3.8% patients and 24.5% caregivers were working. All were family caregivers providing informal care to PwD. Among them, 64.2% of caregivers were the spouse of the PwD and 32.08% were sole primary caregivers. 58.5% patients were suffering from the Alzheimer's disease (Table 1).

As diagnosed by CDR, 9.43% of the patients were suffering from very mild dementia, 28.3% each from mild and severe dementia, and 33.96% from moderate dementia. As reported by the participants, respectively, 28.3 and 32.1% of patients and carers were partially

Table 1. Characteristics of patients and primary caregivers.

Characteristics		Patient, n (%)	Primary caregiver, n (%)
Gender	Male	36 (67.9)	11 (20.8)
	Female	17 (32.1)	42 (79.2)
Age (years)	Below 60	18 (33.96)	41 (77.4)
	60 and above	35 (66.04)	12 (22.6)
Years of education	<10	22 (41.5)	16 (30.2)
	10 and more	31 (58.5)	37 (69.8)
Occupation	Working	2 (3.8)	13 (24.5)
	Non-working	51 (96.2)	40 (75.5)
Relation	Spousal	–	34 (64.2)
	Non-spousal (children)	–	19 (35.8)
Number of caregivers	Sole	–	17 (32.08)
	Multiple	–	36 (67.92)
Diagnosis	AD	31 (58.5)	–
	VAD	8 (15.1)	–
	FTD	7 (13.2)	–
	PDD	4 (7.5)	–
	Mixed	2 (3.8)	–
	DLB	1 (1.9)	–
Severity of dementia	Very mild	5 (9.43)	–
	Mild	15 (28.3)	–
	Moderate	18 (33.96)	–
	Severe	15 (28.3)	–
Vaccination status	Vaccinated	15 (28.3)	17 (32.1)
	Non- vaccinated	38 (71.7)	36 (67.9)
COVID-19 cases	Positive	4 (7.55)	4 (7.55)
DASS-21 (mild to extremely severe)	Depression	–	11 (20.8)
	Anxiety	–	11 (20.8)
	Stress	–	15 (28.3)

AD: Alzheimer's disease; DASS-2: Depression Anxiety Stress Scale – 21 Items; DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; Mixed: mixed dementia; PDD: Parkinson's disease dementia; VaD: vascular dementia.

(single dose) vaccinated, and 7.55% COVID-19-positive cases each in patients and carers group who were found to have recovered (Table 1). Decline in patients' memory was also reported by 47.16% of the caregivers.

Caregiver distress

As calculated from DASS-21, 28.3% caregivers were found to suffer from stress and 20.8% each from depression and anxiety. Significant difference was found in caregiver burden (ZBI) and NPSs, both in severity and distress (NPI-Q) between the first and second phase of the data collection (Table 2). In ZBI, 26.42% caregivers reported financial difficulties in taking care of the PwD; 13.22% reported lack of socialization; 11.32% caregivers reported an increased feeling of stress between caring for the patient and trying to meet other responsibilities along with the fear of future regarding the patient; 9.43% reported anger, strain, and health deterioration due to the care they provide; and an equal number of caregivers also reported complete dependency of the patients on them.

As reported in ZBI, in the first phase, 18 participants had less or no caregiver burden, and in the second phase, there were 15 of them. Twenty-five participants reported mild-to-moderate caregiver burden in both the first phase and the second phase. Nine participants reported moderate-to-severe caregiver burden in the first phase and 11 reported the same in the second phase. One participant reported extremely severe burden in the first phase and two reported the same in the second phase.

Correlates of caregiver distress

In between the first and second phase, a positive correlation was found between caregiver burden (ZBI) and NPSs, with both severity and distress (NPI-Q). Positive correlation was also found between second phase caregiver burden (ZBI) and depression, anxiety, and stress (DASS-21). A significant correlation ($p<0.001$) was also found between the severity of dementia (CDR) and both first and second phases caregiver burden (ZBI) along with depression and stress (Table 3).

As reported by the caregivers in NPI-Q, delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, disinhibition, irritability, motor disturbances, and problems related to eating were present in the first phase, which increased in the second phase (Figure 1).

Table 3. Correlates of caregiver burden.

Variables		Correlation (r)	p-value
NPI-Q and ZBI	Severity	0.912	<0.001*
	Distress	0.953	<0.001*
DASS-21 and ZBI	Depression	0.655	<0.001*
	Anxiety	0.491	<0.001*
	Stress	0.663	<0.001*
CDR and ZBI	First phase	0.333	0.015*
	Second phase	0.313	0.023*
CDR and DASS-21	Depression	0.281	0.042*
	Anxiety	0.197	0.157
	Stress	0.312	0.023*

CDR: clinical dementia rating scale; DASS-21: Depression Anxiety Stress Scale – 21 Items; NPI-Q: The Neuropsychiatric Inventory; ZBI: The Zarit Burden Interview; *p<0.05 is considered significant.

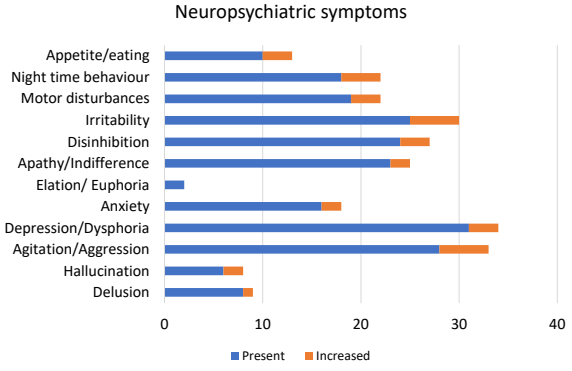

Figure 1. Frequencies of neuropsychiatric symptoms during the second wave of COVID-19.

Table 2. Difference in caregiver burden and neuropsychiatric symptoms between the first and second phases of the study.

	ZBI		NPI-Q			
			Severity		Distress	
Study phase	1st Phase	2nd Phase	1st Phase	2nd Phase	1st Phase	2nd Phase
Mean±SD	27.87±14.89	30.04±15.54	7.43±5	8.11±5	5.16±5.15	5.8±6
t-value	-3.58		-2.41		-3	
p-value	0.001*		0.019*		0.013*	

NPI-Q: The Neuropsychiatric Inventory; ZBI: The Zarit Burden Interview; *p<0.05 is considered significant.

DISCUSSION

COVID-19 pandemic has affected the care of older adults with dementia severely[35]. The present study shows that there has been an increase in caregiver burden among informal carers of PwD during the second wave of pandemic. In this study, all were family caregivers and majority of them were spouse (64.2%) of the PwD. The depression, anxiety, and stress as well as burden of these caregivers should be viewed in relation with the bond and the time these caregivers spent with their near-and-dear one. The longing of these caregivers to keep their loved one safe and healthy with the limited resources during the pandemic increased the burden. Although this study did not attempt to compare the distress between family caregivers with professional one, literature say distress is much higher in the former[36]. Carers mostly reported difficulties regarding their financial condition and daily expenditure. This was probably due to the national economic and industrial downfall. They also reported lack of socialization due to stay-at-home order, fear of future uncertainty about themselves and the patients regarding the infection, and the fatality related to it. Difficulty in meeting family and work responsibilities along with caregiving, deterioration of their own health condition, and other psychological distress were also reported.

In an LMICs like India, which is among top five in COVID-19 cases till now, various concealed aspects of the pandemic have in one way, or another added to the difficulties of caregiving. Health care infrastructure, domestic issues, mental and physical health, and education system are challenged due to the lifestyle change. This is because of distant education, disrupted human resource management, effects on the labor class, monetary issues, lack of public transportation, unavailability for informal caregivers, etc., along with other difficulties faced by both the administration and the public during this pandemic[35]. Social distancing, stay-at-home order, and restrictions on gatherings, along with the unbalanced impact of COVID-19 itself on mortality and morbidity among older adults, have created challenges and changes to the type and intensity of caregiving, as well as to caregivers' burden[29].

The caregivers in this study mostly reported amplified NPSs like agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, disinhibition, irritability, motor disturbances, and nighttime behavioral difficulties of PwD during the second phase. During COVID-19 second wave, NPS appeared to worsen after protracted isolation and lack of socialization due to environmental restrictions, which may have also cultivated behavioral disturbances.

Prolonged lack of proper medical follow-ups due to the pandemic may also lead to deterioration of health condition among PwD. This can lead to acute medical conditions, which might manifest increased NPSs like anxiety, agitation, and apathy[37]. However, as pointed out by Gilmore et al., emotional distress might also generate some NPS[38]. Social isolation and psychological symptoms may also increase cognitive (memory) decline in PwD during the pandemic[39].

This study shows an increase in caregiver's burden with increase in NPS and distress caused by it along with severity of PwD. This may be again due to the increased personal involvement of carers in terms of extensive amount of time for caregiving. Increase in NPS and severity of dementia can be attributed to the irregular medical follow-ups due to different restrictions during the pandemic leading to rapid deterioration of their health. Caregivers' burden has been found to vary with the type of dementia due to varying pattern and severity of NPS in dementia subtypes[40]. However, in this study, we did not look into this.

This study also demonstrated that burden of caregiving increased with increasing severity of disease. The burden of caregiving inevitably increases with the progression of the disease[41]. Older adults with cognitive impairment are often taken care by informal caregivers, and the amount of this informal care is extensive and increases sharply as cognitive impairment worsens as pointed out by Langa et al.[42]. Prolonged period of the pandemic might also attribute to the negative apprehension of the carers regarding the patients' health conditions. This increased burden may sometimes lead to psychological distress like stress and depression among the caregivers as seen in this study.

The limitation of the study was that the mode of data collection differed in the two phases: in phase 1, it was face to face; in phase 2, it was telephonic as the participants were not available for face-to-face interaction. Another limitation was the lack of previous data on depression, anxiety, and stress of caregivers to compare with that during the second wave of COVID-19. The strength of the study, however, is the availability of baseline data for CDR, NPI-Q, and ZBI obtained face to face during the unlock/trough phase preceding the second wave, which could be compared with the changes during the second wave.

In conclusion, this study shows significant increase in caregivers' burden and distress among caregivers due to amplified NPSs of PwD in the second wave of COVID-19 pandemic. A positive correlation was also

seen between caregiver burden and NPSs, regarding both severity and distress. Caregiver burden in the second phase was associated with depression, anxiety, and stress. Severity of dementia was also seen to be associated with caregiver burden, along with stress and depression among carers. Although our study clearly established increase caregivers' burden in the second wave of COVID-19 and we could demonstrate its relationship with certain factors, some other factors not considered may also be related to caregiver stress.

Authors' contributions. RM: data curation, writing – original draft. BB: methodology, writing – original draft. AM: conceptualization, project administration. GD, SD: supervision, writing – review & editing. AB: conceptualization, writing – review & editing.

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Original Article

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Differences in the predictors of the resilience between carers of people with young- and late-onset dementia:
a comparative study

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ABSTRACT. Resilience is a subjective process related to both protective and risk factors, external and internal to the individual. Considering the psychosocial differences between young-onset dementia (YOD) and late-onset dementia (LOD) groups, carers' resilience may not be understood in the same way in both groups. **Objective:** The aim of this study was to compare the resilience of carers in YOD and LOD and to examine which factors might be associated with resilience in both groups of carers. **Methods:** The study was conducted with 120 people with dementia (49 YOD) and their primary carers. The carers had their resilience, quality of life, depressive symptoms, and burden assessed and answered the sociodemographic questionnaire. We assessed care recipients' global cognition, dementia severity, social cognition, facial expression recognition, awareness of disease, the ability to perform activities of daily living, depressive symptoms, and neuropsychiatric symptoms. For data analysis, unpaired two-tailed Student's *t*-test and linear regressions were conducted. **Results:** Resilience did not differ between groups (p=0.865). Resilience was inversely related to carers' depressive symptoms in both YOD (p=0.028) and LOD (p=0.005) groups. The carers' schooling (p=0.005), duration of disease (p=0.019), and depressive symptoms of care recipient (p<0.001) were related to carers' resilience only in LOD group. **Conclusions:** The context of care, clinical status of the care recipient, and mental health resources affected the carers' resilience in the LOD group. Conversely, resilience seems to be affected only by carers' mental health in the YOD group. The understanding of these differences is crucial for the developing of intervention strategies.

Keywords: Caregivers; Resilience, Psychological; Dementia.

DIFERENÇAS NOS PREDITORES DA RESILIÊNCIA ENTRE CUIDADORES DE PESSOAS COM DEMÊNCIA DE INÍCIO PRECOCE E TARDIO: UM ESTUDO COMPARATIVO

RESUMO. A resiliência é um processo subjetivo relacionado a fatores de proteção e risco, externos e internos ao indivíduo. Considerando as diferenças psicossociais entre demência de início precoce (DIP) e demência de início tardio (DIT), a resiliência dos cuidadores pode não ser entendida da mesma maneira em ambos os grupos. **Objetivo:** O objetivo deste estudo é comparar a resiliência de cuidadores de DIP e DIT e examinar quais fatores poderiam estar associados à resiliência em ambos os grupos de cuidadores. **Métodos:** O estudo foi realizado com 120 pacientes com demência (49 DIP) e seus cuidadores primários. Os cuidadores tiveram sua resiliência, qualidade de vida, sintomas depressivos e sobrecarga avaliados e responderam ao questionário sociodemográfico. Avaliou-se a cognição global, a severidade da demência, a cognição social, o reconhecimento da expressão facial, a consciência da doença, a funcionalidade em atividades de vida diária, e os sintomas depressivos e neuropsiquiátricos dos pacientes. Para a análise dos dados, foram realizados teste *t* de Student bicaudal não pareado e regressões lineares. **Resultados:** Não houve diferença na resiliência entre os grupos (p=0,865). A resiliência foi inversamente relacionada com sintomas depressivos dos cuidadores em DIP (p=0,028) e DIT (p=0,005). A escolaridade do cuidador (p=0,005), tempo de doença (p=0,019) e sintomas depressivos dos pacientes (p<0,001) foram relacionados à resiliência apenas no grupo DIT. **Conclusões:** O contexto do cuidado, o estado clínico do paciente e os recursos de saúde mental afetaram a resiliência do cuidador no grupo DIT. Em contrapartida, a resiliência parece ser afetada apenas pela saúde mental do cuidador em DIP. O entendimento dessas diferenças é crucial para o desenvolvimento de estratégias de intervenção.

Palavras-chave: Cuidadores; Resiliência Psicológica; Demência.

This study was conducted by the Center for Alzheimer's Disease, Institute of Psychiatry, Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil.

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INTRODUCTION

Across the world, care for people with dementia is frequently given by family members[1]. Carers of people with dementia are often understood as the invisible second patients[2]. The negative physical and mental health consequences of caring for a person with dementia have been well documented[2-4].

Carers of people with dementia are a group that requires attention due to high levels of stress, distress, and burden[5,6]. In addition, some studies indicate that these carers contemplate suicide at more than four times the rate of the general population (with some even contemplating homicide suicide)[7-9] and that they have an increased risk of mortality[10].

Nonetheless, there are differences within the carers' group. The most of cases of dementia occur among older adults, although people under 65 years may also develop the dementia[11]. Previous studies reported that carers of people with young-onset dementia (YOD) present more severe depressive symptoms and burden than carers of people with late-onset dementia (LOD)[12-16]. Usually, carers of people with YOD are unready for the carer's tasks and experience increased burden when compared to carers of people with LOD[12-16].

Despite this, some carers, even suffering great caregiving demands, seem to cope fairly well and present fewer negative outcomes of caregiving than others[17]. Positive aspects of caregiving are reported in some studies, including an improved rapport between carer and people with dementia and the carer's feeling of accomplishment[18]. This aspect may potentially be understood as an indicator of resilience.

Resilience is described as the process of well adjustment in cases of trauma, adversity, threats, tragedy, or even a considerable cause of stress[19]. Some studies consider the experience of caregiving as adversity[20,21], while other studies consider the negative consequences of caregiving reported by carers of people with dementia as the adversity that carers must adjust to or overcome[21,22].

The resilience may be considered a dynamic process[23] involving both protective and risk factors, external and internal to the individual[24]. Resilience involves the interaction of protective factors such as confidence in caregiving, problem-solving skills, a strong sense of religion or spirituality, and social support[25,26]. The predominance of protective factors may make the carer more resilient. More resilient carers generally cope better with the changes in people with dementia behavior because they seem to be better prepared for the inexorable changes arisen from the dementia process.

Existing research suggests that resilience is inversely associated with burden, anxiety, and depression and is viewed as an essential factor in suicide prevention[5,22,27-30]. Resilience has been found to be positively related to factors that promote positive outcomes, including self-efficacy, self-esteem, problem-focused coping, mastery, flexibility, and adaptation[5,22,27]. In addition, resilience provides an optimal psychological adaptation and improves other coping strategies in feedback to the demands of dementia care[31].

In the current literature, there is not a study that compares the resilience of carers of people with YOD with the resilience of carers of people with LOD. Taking that resilience is a subjective process and the psychosocial diversity among both groups of carers, this study hypothesizes that resilience is poorer in the YOD group than in the LOD group. Therefore, the aim of this study was to compare the resilience of carers in YOD and LOD and to examine which factors might be associated with resilience in both groups of carers.

METHODS

This observational cross-sectional descriptive study was performed between February 2016 and December 2019 in the Center for Alzheimer's Disease outpatient clinic of Institute of Psychiatry of Federal University of Rio de Janeiro, Brazil.

Participants

The sample consisted of 120 dyads of home-dwelling outpatients with dementia and their primary carers, with 49 in the YOD group and 71 in the LOD group.

Dementia was diagnosed by a psychiatrist according to the criteria established by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[32]. In this study, 114 people were diagnosed with Alzheimer's disease and 6 people were diagnosed with vascular dementia.

People with mild-to-severe dementia according to Clinical Dementia Rating (CDR)[33] and those who score below 26 in Mini-Mental State Examination (MMSE) were included in this study[34]. The exclusion criteria were people with severe communication problems, traumatic events, and alcohol or substance dependency or abuse.

The primary carer was the principal person for the care of people with dementia, and they should be able to give elaborate information about the care recipients and be an informal carer. Carers with a reported history of cognitive or psychiatric disorders prior to the dementia diagnosis were not included in this study.

This study was authorized by the ethics committee of the Institute of Psychiatry of the Federal University of Rio de Janeiro. At the outpatient clinic, all people

with dementia and their carers signed informed consent forms before the assessment, according to the Declaration of Helsinki.

Procedure

Each person with dementia completed assessments of global cognition, social cognition, facial expression recognition, and awareness of disease. Additional data, including the ability to perform activities of daily living, depressive symptoms, neuropsychiatric symptoms, dementia severity, and sociodemographic data, were obtained through questionnaires and instruments answered by the carer. The carers also had their resilience, quality of life (QoL), depressive symptoms, and burden evaluated and answered the sociodemographic questionnaire.

Measures

Cognition

Mini-Mental State Examination (MMSE): This instrument is composed of 30 items that measures orientation, comprehension, learning, short-term memory, language, and basic motor skills. The total score ranges from 0 to 30, with lower scores signaling more impaired cognition[34].

Severity of dementia

Clinical Dementia Rating (CDR): This test assesses the severity of dementia. The stage ranges from 0 (no dementia) to 3 (severe dementia) according to the degree of cognitive, activities of daily livings, and behavioral impairment[33].

Functionality

The Pfeffer Functional Activities Questionnaire (PFAQ): This inventory evaluates the activities of daily living. The score for each item ranges from normal (0) to dependent (3), with a total of 30 points. Higher score suggests greater functional impairment[35].

Depressive symptoms

The Cornell Scale for Depression in Dementia (CSDD): This scale assesses circadian functions, physical signs, mood, and behavioral symptoms related to depressive symptoms between people with dementia. The total rating ranges from 0 to 38. Score>13 suggests the presence of depressive symptoms[36].

Neuropsychiatric symptoms

Neuropsychiatric Inventory (NPI): This inventory assesses delusions, hallucinations, agitation, apathy, anxiety, depression, euphoria, irritability, disinhibition, aberrant motor behavior, change in appetite, and nighttime behavior disturbances. Each item is assessed in relation to their frequency (1=absent to 4=frequently) and intensity (1=mild to 3=severe). The total rating ranges from 0 to 144. Higher score suggests greater levels of neuropsychiatric symptoms. We used 12 items[37].

Awareness of disease

Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (ASPIDD): The ASPIDD is a 30-question scale centered on people with dementia and carer reports. This scale was designed to assess awareness of disease based on the scoring of discrepant responses through four domains, namely, cognitive functioning, health condition, emotional state, social functioning/relationships, and instrumental and basic activities of daily living. The carer responds the same questions as the people with dementia, with one point being scored for each discrepant response. The ratings of awareness range from preserved (0–4), mildly impaired (5–11), moderately impaired (12–17), to absent (<18)[38].

Social and emotional functioning

Social and Emotional Questionnaire: This instrument is composed of 30 items based on 5 factors: recognition of emotion, empathy, social conformity, antisocial behavior, and sociability. The ratings for each item range from strongly disagree (1) to strongly agree (5). We used the carer's version about people with dementia emotional and social current functioning. The score is measured on five-point Likert scale, ranging from "strongly disagree" (1) to "strongly agree" (5). Lower score indicates more impaired social and emotional functioning[39].

Facial expression recognition ability

Facial Expression Recognition Ability Scale (FACES): We used an adaptation of an experimental task developed by Shimokawa et al. Task 1 investigates the visuoperceptual ability to identify faces. Task 2 evaluates the ability to comprehend facial emotions. Task 3 examines whether subjects can recognize the expression of emotion conceptually. Task 4 assesses the people with dementia's ability to comprehend the nature of a situation and the appropriate emotional state that one would experience in that situation. For each correct response, the subject receives 1 score. FACES is composed of 16 tasks, and the highest possible score is 16. Lower score suggests impaired recognition[40].

Carer measures

Resilience

Resilience Scale by Wagnild and Young: This original resilience measure, considered the "gold standard" for resilience evaluation, has 25 items that assess psychosocial adaptation to adversity. The score ranges from 25 to 175 and was classified as follows: 25–124: low; 125–145: moderate; and 146–175: high resilience[41].

Quality of life

Quality of Life in Alzheimer's Disease (QoL-AD): The QoL-AD includes 13 domains (i.e., physical health, energy, mood, living situation, memory, family, marriage, friends, you as a whole, ability to do chores, ability to do things for fun, money, and life as a whole) that are rated as poor (1), fair (2), good (3), or excellent (4). We used the carer's QoL version (C-QoL). The total score ranges from 13 to 52. Higher score indicates better QoL[42].

Burden

Zarit Burden Interview (ZBI): This assessment consists of 22 items that evaluate the impact of caring for people with dementia on the carer's life by appointing how often the carer experiences a particular feeling: never (0), rarely (1), sometimes (2), quite frequently (3), or nearly always (4). The total score ranges from 0 to 88. Higher score indicates a higher level of burden[43].

Depressive symptoms

Beck Depression Inventory (BDI): This is self-report scale, composed of 21 items based on symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The total score ranges from 0 to 63 and categorized as follows: 0–11: mild symptoms, 12–19: mild to moderate, 20–35: moderate to severe, and 36–63: severe symptoms[44].

Statistical analysis

All statistical analyses were performed with SPSS software for Windows version 23.0. The variables were inspected for normality before analysis. Initially, the descriptive analyses of all the variables were carried out by observing the means, standard deviation, and frequency (percentage) according to the type of variable studied. All analyses were performed by thematic blocks, namely, sociodemographic data of the people with dementia and carer and clinical data of people with dementia and carer. Depending on the variable of interest, we utilized t-tests for independent samples (with homoscedasticity test) and the χ^2 test, the Fischer's exact test, or the Mann-Whitney U test to test for significant group differences.

Multivariate linear regressions with the stepwise method were elaborated using resilience as dependent variable. All demographic and clinical variables were included as independent variables. Regression models were performed separately for YOD and LOD groups and the best models were selected according to highest explained variance of the R^2 and the variance inflation factor (VIF) close to 1, for the collinearity in each independent variable. For all analyses, the α level was set at $p \leq 0.05$.

RESULTS

Sociodemographic characteristics

The mean age of YOD people was 63.69±6.2 years. The majority of people with dementia were men (51%, n=25) and married (67.3%, n=33). While most of carers were women (83.7%, n=41). The majority of carers were wives or husbands (55.1%, n=27), with a mean age of 52.06±14.2 years.

The mean age of LOD people was 79.65±5.7 years. Most of the people with dementia were women (67.6%, n=48). The majority were widowers (42.3%, n=30). Also, most of the carers in this group were women (73.2%, n=52). Regarding the kinship, the majority were daughters or sons (54.9%, n=39), with a mean age of 57.89±14.3 years.

Table 1 lists the sociodemographic characteristics of people with dementia and carers.

Clinical characteristics of dyads

Comparison between groups showed that people with YOD were more cognitively impaired according to the MMSE ($p<0.001$) and also had more deficits in functionality as rated on the PFAQ ($p=0.046$).

We did not observe a significant difference in carers' resilience ($p=0.865$) and in the other clinical characteristics between both carers' groups. Carers of both groups reported moderate to high levels of resilience. However, the YOD group of carers presented a slight level of burden and depressive symptoms than the LOD one.

The clinical characteristics of people with dementia and carers are synthesized in Table 2.

Multivariate analyses

The linear regression model showed that lower levels of resilience of carers of people with YOD were related to higher levels of carers' depressive symptoms ($p=0.028$).

Table 1. Sociodemographic characteristics of people with dementia and carers according to age of onset.

			YOD (n=49)	LOD (n=71)	p-value
PwD	Female, n (%)		24 (49.0)	48 (67.6)	
	Age, mean (SD)		63.69 (6.2)	79.65 (5.7)	<0.001*
	Age of onset, mean (SD)		57.73 (4.9)	75.03 (6.0)	<0.001*
	Duration of disease, mean (SD)		5.76 (3.1)	4.62 (3.3)	0.062
	Schooling, mean (SD)		10.00 (4.1)	7.15 (4.0)	<0.001*
	CDR, n (%)	Mild	20 (40.8)	47 (66.2)	
		Moderate	20 (40.8)	21 (29.6)	
		Severe	9 (18.4)	3 (4.2)	
	Marital status, n (%)	Singles	2 (4.1)	6 (8.5)	
		Married	33 (67.3)	27 (38.0)	
		Widowers	6 (12.2)	30 (42.3)	
		Divorced	8 (16.3)	8 (11.3)	
Carers	Female, n (%)		41 (83.7)	52 (73.2)	
	Age, mean (SD)		52.06 (14.2)	57.89 (14.3)	0.030*
	Schooling, mean (SD)		11.41 (3.9)	12.08 (3.2)	0.328
	Kinship, n (%)	Wives/ husbands	27 (55.1)	22 (31.0)	
		Daughters/sons	15 (30.6)	39 (54.9)	
		Others	7 (14.3)	10 (14.1)	

PwD: people with dementia; YOD: young-onset dementia; LOD: late-onset dementia; SD: Standard deviation; CDR: Clinical Dementia Rating; *significant result.

Table 2. Clinical characteristics of people with dementia and carers according to age of onset.

		YOD (n=49)	LOD (n=71)	p-value
PwD	MMSE (SD)	15.57 (5.8)	19.18 (5.0)	<0.001*
	ASPIDD (SD)	9.25 (5.6)	9.82 (5.4)	0.584
	SEQ C-PwD (SD)	100.90 (17.3)	105.38 (15.1)	0.146
	FACES (SD)	9.63 (4.0)	10.82 (3.0)	0.069
	CSDD (SD)	8.51 (6.0)	7.28 (5.4)	0.247
	PFAQ (SD)	20.12 (7.9)	16.96 (8.7)	0.046*
	NPI Total (SD)	21.69 (19.1)	18.85 (19.9)	0.436
Carers	QoL-AD (SD)	35.00 (5.8)	35.79 (6.7)	0.507
	ZBI (SD)	33.45 (17.4)	31.14 (16.2)	0.459
	BDI (SD)	8.43 (7.2)	7.86 (7.2)	0.674
	RS (SD)	140.67 (14.0)	140.13 (19.1)	0.865

PwD: people with dementia; YOD: young-onset dementia; LOD: late-onset dementia; SD: Standard deviation; MMSE: Mini-Mental State Examination; ASPIDD: Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia; SEQ C-PwD: carers' reports on social and emotional functioning of people with dementia; FACES: recognize facial expressions; CSDD: Cornell Scale for Depression in Dementia; PFAQ: Pfeffer Functional Activities Questionnaire; NPI: neuropsychiatric inventory; QoL-AD: Quality of life in Alzheimer's disease scale (carers' reports on their own quality of life); ZBI: Zarit Burden Interview; BDI: Beck Depression Inventory; RS: Resilience Scale; *significant result.

The analysis of the LOD group showed that resilience was inversely related to carers' depressive symptoms (p=0.005) and their schooling (p=0.005) and duration of disease (p=0.019). Moreover, resilience was associated with depressive symptoms of people with dementia (p<0.001). Carers reported high levels of resilience when people with dementia exhibited more depressive symptoms.

The adjusted R^2 values and the standardized regression weights are presented in Table 3.

DISCUSSION

In this study, we investigated the resilience of carers of people with YOD compared to carers of people with LOD. Carers of both groups presented moderate to high levels of resilience, a fact that may clarify the lack of significant difference in the carers' resilience between groups. We may suppose the occurrence of a positive adjustment of the carers to the conditions of care. In addition, there were no significant differences in the clinical characteristics of both carers' groups. It is worth highlighting that they were part of a treatment center for people with dementia that provides support for their carers. The presence of an external resource seems to assist the carers in coping with the demands involved in providing care to people with dementia and to keep their levels of health.

The hypothesis of our study was not confirmed. However, our results indicate that the factors that affected resilience differ according to the age of onset of dementia.

The carers' depressive symptoms were the only predictor of the resilience of carers of people with YOD. Also, a previous study conducted by our group found the same relationship between resilience and depressive symptoms[45]. Other studies have already shown that higher levels of resilience were related to lower levels of depressive symptoms of carers[28,46]. Therefore, in the YOD group, carers' resilience seems not to be associated with the cognitive and clinical symptoms of the people with dementia[22]. Our findings showed that carers' depressive symptoms were also a predictor of the resilience of carers of people with LOD. Despite the low levels of depressive symptoms of carers of both groups, the results propose that resilience may impact carers' mental health.

Resilience may be influenced by context of care, status of the care recipient, and individual, family, and community resources[22]. Thus, our findings demonstrated the interaction between these constellation of aspects in carers' resilience. We observed that a lower level of carers' schooling was associated with higher resilience in the LOD group. Our study was realized in a Latin American country, which may justify this outcome. People with a lower level of schooling can be amenable to the role of carer since society demands higher levels of schooling for the formal labor market. Gaugler et al.[22] also found a negative relationship between education and carer resilience. People with less education may be dedicated to caring tasks of their dependent family members and have more possibility to develop resilience[22].

In the LOD group, carers' resilience was inversely associated with the duration of disease. With the progression of the disease, the carer may develop a burden due to the increase in dependency of people with dementia. In the literature, there is a negatively strong correlation between burden and resilience[5,21,22,47,48]. Resilient carers who detected their proper ability to cope with adversity reported less burden[5]. We may hypothesize that the negative relation between resilience and duration of

Table 3. Regression model of factors related to resilience.

	R	R^2	Adj. R^2	B	Beta	t	p-value
YOD	0.318	0.101	0.081				
BDI				-0.608	-0.318	-2.272	0.028
LOD	0.533	0.284	0.241				
BDI				-0.820	-0.312	-2.931	0.005
Carer's schooling				-1.837	-0.312	-2.910	0.005
Duration of disease				-1.462	-0.256	-2.395	0.019
CSDD				0.770	0.219	2.090	0.041

B: linear coefficient; BETA: standardized beta coefficient; T: YOD: young-onset dementia; LOD: late-onset dementia; BDI: Beck Depression Inventory; SEQ PwD: Social and Emotional Questionnaire (self-reported PwD ratings); CSDD: Cornell Scale for Depression in Dementia.

disease was influenced by the level of carer's burden. Further studies should employ a path analysis approach to better understand the interface between resilience, duration of disease, and burden.

Another substantial result of our study was the effect of the depressive symptoms of people with dementia on the resilience of carers of the LOD group. Resilience enables carers to manage and respond positively to stressing caregiving conditions[22,28]. Being resilient does not mean a lack of difficulties when confronted with adversity, but that the person faces difficulties effectively[28]. Therefore, despite the presence of depressive symptoms of people with dementia, many carers may keep resilient.

The literature supports the idea that there are specific experiences and needs of carers based on the age at onset of disease of care recipient[12-16]. Our data supply insights that could enable a more significant appreciation of the resilience of carers of people with YOD and LOD and your predictors. Few studies recognize the heterogeneity of existing characteristics among carers, considering this group as a single block. The study by Ducharme et al.[49] showed that, besides taking care of a person with dementia, carers of people with YOD are younger, which causes double stigmatization. The carers' resilience must be understood as having particular characteristics that may vary according to YOD or LOD groups.

Limitations

We studied a relatively small and convenience sample and this was a cross-sectional study. The inclusion of people with other dementias besides dementia due to Alzheimer's disease was another limitation of our study. Moreover, we did not evaluate the carers' personality traits. These factors could impact the resilience of carers in both YOD and LOD groups.

This article is the first to study about the factors related to the resilience of carers of people with YOD compared to carers of people with LOD. The context of care, the status of the care recipient, and individual resources influenced the carers' resilience in the LOD group. Conversely, in the YOD group, carers' resilience seems to be influenced only by individual resources.

Understanding these aspects is crucial for developing intervention strategies more appropriately designed to suit the demands of each of these groups. Furthermore, increasing the levels of carers' resilience may mitigate the negative outcomes of caregiving, allowing caregivers to remain in the role for longer, improving the quality of care they provide, and reducing the early institutionalization of people with dementia.

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Original Article

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Validation of the Brazilian version of the Hinting Task and Facial Emotion Recognition Test (FERT-100) in patients with schizophrenia

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ABSTRACT. Social cognition is an especially relevant domain in schizophrenia due to its association with functional impairment. However, we still do not have studies that have validated instruments with internationally established psychometric qualities for the Brazilian population. **Objectives:** This study aimed to present psychometric qualities and contribute to the validation of the Brazilian version of the Hinting Task and Facial Emotion Recognition Test (FERT-100). **Methods:** A total of 104 stabilized patients living in the community diagnosed with schizophrenia and 89 controls were evaluated. We assess the psychometric properties of Hinting Task and FERT-100 for discriminant construct validity, divergent construct validity, convergent construct validity, concurrent criterion validity, and reliability. **Results:** There is a statistically significant difference between patients and controls regarding social cognition (Hinting Task: Z=6.85, p<0.001; FERT-100: t=4.88, p<0.001). The main predictors of variation in social cognition were the neurocognitive domains. The associations between social cognition tests and other studied variables are similar to what is found in the literature. Social cognition maintains correlation with functional capacity even when neurocognition is taken into account. **Conclusions:** The validity of the Brazilian version of Hinting Task and FERT-100 can be determined, since the relationship of these tests with other clinical variables is similar to that observed in the literature.

Keywords: Schizophrenia; Social Cognition; Validation Study; Theory of Mind.

VALIDAÇÃO DA VERSÃO BRASILEIRA DO *HINTING TASK* E DO TESTE DE RECONHECIMENTO DE EMOÇÕES FACIAIS (FERT-100) EM PACIENTES COM ESQUIZOFRENIA

RESUMO. A cognição social é um domínio especialmente relevante na esquizofrenia devido à sua associação com o comprometimento funcional. No entanto, ainda não temos estudos que validaram instrumentos com qualidades psicométricas internacionalmente estabelecidas para a população brasileira. **Objetivos:** Apresentar as qualidades psicométricas e contribuir para a validação da versão brasileira do *Hinting Task* e do Teste de Reconhecimento de Emoções Faciais (FERT-100). **Métodos:** Foram avaliados 104 pacientes estabilizados residentes na comunidade com diagnóstico de esquizofrenia e 89 controles. Avaliou-se as propriedades psicométricas do *Hinting Task* e FERT-100 para validade de construto discriminante, validade de construto divergente, validade de construto convergente, validade de critério concorrente e confiabilidade. **Resultados:** Houve uma diferença estatisticamente significativa entre pacientes e controles quanto à cognição social (*Hinting Task*: Z=6,85; p<0,001. FERT-100: t=4,88; p<0,001). Os principais preditores da variação na cognição social foram os domínios neurocognitivos. As associações entre os testes de cognição social e outras variáveis estudadas são semelhantes às encontradas na literatura. A cognição social mantém correlação com a capacidade funcional mesmo quando a neurocognição é levada em consideração. **Conclusões:** A validade da versão brasileira do *Hinting Task* e do FERT-100 pode ser determinada, pois a relação desses testes com outras variáveis clínicas é semelhante à observada na literatura.

Palavras-chave: Esquizofrenia; Cognição Social; Estudo de Validação; Teoria da Mente.

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INTRODUCTION

Social cognition is defined as the mental operations behind social interactions, which include the human capacity to perceive intentions and dispositions of others. In short, this means how people think and form impressions of people[1-3]. Although the processing of socially relevant information also depends on neurocognition (e.g., attention or memory), it has been shown that neurocognition and social cognition are dissociable domains[3].

The domains most studied in this broad construct are theory of mind (ToM) and emotion processing (EP)[4-6]. Emotion processing refers to perception and use of emotions and usually involves tests that evaluate recognition of emotional expressions on faces[7]. Human face is one of the richest sources to accurately infer other people's mental and emotional state. This information is relevant to the observer on how to behave in the social environment[8]. ToM is conceptualized as a system of references that enables comparisons between the internal, subjective world, and the external world, of others[9,10]. According to the study by Premack and Woodruff[11], an individual has a ToM if he imputes mental states to himself and to others. Additionally, a system of inferences of this nature is properly seen as a "theory" because such states are not directly observables and the system can be used to make predictions (theorizations) about the behavior of others. The ToM tests generally rely on short verbal reports and/or interactions between characters who have a false belief or use irony or indirect speech.

Several studies and meta-analysis[12] suggest that deficits in EP and ToM are present in patients with schizophrenia and their first-degree relatives. These deficits are stable over time and do not respond to antipsychotic treatment. Thus, social cognition can be considered an endophenotype of schizophrenia[7,13].

A meta-analysis by Savla et al.[1] demonstrated that patients with schizophrenia have impaired social cognition compared to controls, with an effect size (g) of 0.96 for ToM and 0.89 for EP. And although deficits in social cognition are moderately correlated with neurocognition, negative, and disorganized symptoms, these deficits remain relevant even when considering such factors, with social cognition impaired in schizophrenia even in stabilized patients[1].

Importantly, social cognition is strongly and independently related to functional performance[2,4-6].

The Social Cognition Psychometric Evaluation (SCOPE) initiative[14] evaluated several social cognition tests available based on (1) test-retest reliability, (2) utility as a repeated measure, (3) relationship with functional performance, and (4) practicality and tolerability. This initiative found that only one ToM test, one Hinting Task, and two facial emotion recognition tasks had the best psychometric properties and were recommended for use in clinical trials. Unfortunately, we do not yet have instruments that assess ToM and EP in patients with schizophrenia validated for the Brazilian population.

The objective of this study was to adapt to Brazilian Portuguese and analyze some of the psychometric properties of the Hinting Task and the Facial Emotion Recognition Task (FERT-100) in patients with schizophrenia.

METHODS

Participants

A total of 104 stabilized schizophrenia outpatients, aged between 18 and 65 years, participated in this study. Patients diagnosed with schizophrenia undergoing outpatient treatment at the Raul Soares Institute (Belo Horizonte – MG) and at the psychiatry outpatient clinic of the city of Nova Lima (MG) were invited to participate in the study. A structured interview using the MINI-plus was used to confirm the diagnosis[15,16]. Patients with alcohol or any drug dependence (except nicotine), history of neurological disease, mental retardation, or brain trauma were excluded. Stabilization was defined by scoring 19 or less in the Positive and Negative Syndrome Scale (PANSS) positive subscale (see below) and 4 or less in any item of this subscale[17].

Schizophrenia patients were matched for gender and age to 89 controls. Students from the youth and adult education program from two municipal schools in Belo Horizonte (MG) were selected through written and/or oral invitation to participate as controls. Criteria for inclusion and exclusion of controls were as follows: age over 18 years and under 65 years, having no history of neurological disease, mental retardation or brain trauma, and not having any pathology of axis one of the *Diagnostic and Statistics Manual of the American Psychiatric Association* (*DSM-IV*), confirmed by MINI-plus[15,16].

All invited participants were instructed on the study design and its objectives. Those who agreed to participate signed an informed consent form, according to the local ethics committee.

Evaluation scales

Clinics/psychopathology

The PANSS[18,19] and the Calgary Depression Scale for Schizophrenia (CDSS)[20,21] were used to assess positive/negative symptoms and depressive symptoms,

respectively. The Positive and Negative Syndrome Scale is composed of seven items in each subscale (positive and negative symptoms). A score of "1" is given in the absence of symptoms, and a score of "7" is given to the most severe symptomatology. Thus, both subscales have a minimum score of 7 and a maximum score of 49[18,19]. The CDSS is composed of nine items. The score is given so that "zero" corresponds to the absence of the evaluated symptom and "3" to its presence in maximum severity. The score 21 is the maximum score possible.

Neurocognition

The Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess neurocognition[17,22,23]. This instrument is an easy and fast to administer neuropsychological battery developed to assess the main cognitive domains impaired in schizophrenia: verbal memory (measure: number of words remembered in any order-score: 0–75), working memory (digit span test — measure: number of correct answers; score: 0–28), motor speed (token motor task — measure: number of tokens correctly placed in the container during 1 min; score: 0–100), verbal fluency (semantic and phonetic — measures: number of words generated), processing speed (symbol coding — measure: number of correct answers; score: 0–110), and reasoning/problem solving (Tower of London — measure: number of correct answers; score: 0–22)[17]. To compare the mean scores presented by participants with schizophrenia in relation to controls, we calculated the Z-score. Its calculation consists of subtracting the mean score obtained from participants with schizophrenia in relation to controls and dividing the result by the standard deviation of controls.

Social cognition

Hinting Task (Brazilian version)

This task was conceived to assess subjects' ability to infer implicit intentions. It comprises 10 small stories, each one with a very obvious hint about what one of the character implicitly meant. If the participant gives a correct answer about the character intention, it scores two points. Otherwise, an even more obvious hint is given. In this phase, a correct and a wrong answer score one and zero point, respectively. The final score ranges from zero to 20. All stories are read aloud with the appropriate prosody[10]. The instrument was translated to Brazilian Portuguese and back-translated to English with the supervision of the original author (R. Corcoran). A pilot study with 20 people with 9 years of schooling was carried out in order to assess the understanding of the stories and instructions. After minor modifications, the final version was applied to the study participants (see Supplementary Material I for task full final version).

Facial Emotion Recognition Task

In this task, participants are asked to recognize emotions in 100 black and white pictures of Caucasians' faces from Ekman catalogue of facial emotion[24]. Each picture was presented in a 15-inch computer screen for 0.5 s. Participants had 2 s to guess, by pressing a computer key, which emotion best describe the one they saw in the picture. The emotions are fear, anger, disgust, sadness, surprise, and happiness. A total of 96 pictures of these emotions were randomly distributed in the same amount, in four different intensities (30, 50, 70, and 100% of intensity), to be present to each patient. There were also four pictures with faces without any emotion, to which patients should guess NEUTRAL. The task was run in a Matlab program, version R2007a.

Functional capacity assessment

The UCSD Performance-based Skills Assessment (UPSA) assesses the ability to perform tasks typical of everyday life in community. It comprises five domains: comprehension and planning (score range: 0–27), finance (score range: 0–10), communication (score range: 0–9), mobility (score range: 0–6), and home care (score range: 0–4). Each domain is scored as follows: the number of points obtained is divided by the total possible points and this result is multiplied by 20. Score range is 0–100. The Brazilian-Portuguese version has shown good psychometric properties to assess functional capacity[25,26].

Validation of social cognition tests

We assess the psychometric properties of Hinting Task and FERT-100 as follows:

- For discriminant construct validity, we compared the results obtained between patients and controls.
- For divergent construct validity, we looked at associations of social cognition tests with each other, sociodemographic data, symptomatology, and neurocognition.
- For convergent construct validity, we looked at associations between tests of social cognition and functional capacity.
- For reliability, we use internal consistency (Cronbach's alpha).
- For concurrent criterion validity, we compared our results with the original test (Hinting task) and with the literature (Hinting Task and FERT-100), in "DISCUSSION" section.

Design

Each participant was tested in one session of about one and a half hour. The instruments were applied as follows: sociodemographic questionnaire, MINI-plus, PANSS, BACS, Hinting Task, FERT-100, and UPSA.

Statistical analysis

The SPSS software (IBM), version 20, was used for the statistical analysis of the data. Parametric distribution of all variables was verified using the Kolmogorov-Smirnov test. Pearson's (for parametric data) and Spearman's (for nonparametric data) correlations were made between the variables of interest. For comparisons between patients and controls, Student's *t*-test or Mann-Whitney U test was used, depending on the normality of data. For comparison between gender of patients and controls, χ^2 test was used. Hinting Task and FERT-100 internal consistency was calculated using Cronbach's alpha. ANOVA test was also used to compare the number of correct answers to different intensity of emotions, assessed by the FERT-100. Multiple linear regression analysis was performed to assess predictors of social cognition tests. The score obtained in Hinting Task was normalized using reflected logarithm. This transformation allows normalization of data with a negative asymmetric distribution, using the following formula: Transformed data = log10 (highest value obtained in the test + 1 – original data)[27]. It is a trend in literature that just carrying out tests of significance of the null hypothesis is not enough to compare difference in means of two or more variables. Estimation techniques such as effect size and confidence intervals are increasingly being used to observe the magnitude of difference between two variables and thus establish the real importance of an intervention[28]. Thus, Hedge's g effect size was calculated.

RESULTS

Sample

Sociodemographic and clinical data are shown in Table 1. There was no statistically significant difference between mean age, gender, and education between patients and controls. Patients have low scores on the subscale of positive symptoms of PANSS and depressive symptoms on Calgary and low-to-moderate scores on the subscale of negative symptoms.

Discriminant construct validity

Comparison between patients and controls

Hinting Task

As distribution of the Hinting Task result does not follow a normal distribution, the Mann-Whitney U test was performed to compare the score of patients and controls. As can be seen in Table 2, there is a statistically significant difference between patients and controls on this task.

Calculating effect size (Hedge's g) for difference between the mean of correct answers in tests, it is observed that Hinting Task obtained a value of g = 1.2. This means that there is an overlap between the scores of patients and controls of 37%. With normalization of the results obtained in Hinting Task by calculating the reflected logarithm of the scores obtained in this

Table 1. Sociodemographic and clinical data for patients and controls.

		Patients (n=104)	Controls (n=89)	Statistical test	p-value
Mean age (SD)		41.99 (12.07)	40.23 (11.58)	T=-1.07	0.286
Gender, male (%)		59 (56.6)	49 (55.1)	X^2=0.53	0.818
Education years (SD)		7.12 (4.19)	7.77 (2.46)	Z=1.72	0.085
Antipsychotic dose à chlorpromazine equivalent/mg (SD)		316.05 (216.93)			
PANSS (SD)	Positive	9.94 (2.86)			
	Negative	18.57 (6.86)			
	General	26.05 (6.46)			
	Total	54.35 (12.78)			
Calgary		1.98 (2.27)			

T: Student's *t*-test; Z: Mann-Whitney U test; SD: standard deviation; PANSS: Positive and Negative Syndrome Scale.

test[27,29], the effect size remains practically unchanged (g=1.16). Thus, despite caution when analyzing the effect size for Hinting Task, data normalization revealed very similar values.

FERT-100

In FERT-100, Student's *t*-test was used to compare the score of patients and controls as these data obey a normal distribution. In this case, there was a statistically significant difference between mean total correct answers between patients and controls (Table 2).

FERT-100 presented a Hedge's g value=0.8. This means that there is an overlap between the scores of patients and controls of 53%.

Analysis of scale items

Hinting Task

A comparison between the 10 stories of Hinting Task was also performed using the Mann-Whitney U test (Supplementary Material II Table 1). It is observed that the scores of patients and controls differ in all histories, with the exception of story 02, whose p-value is 0.065 (Table 3). Removing story 02, Cronbach's alpha goes to 0.66, so it was decided to keep the original 10 test stories in other analyzes of this work.

Hinting Task and Facial Emotion Recognition Test

An assessment of concordant correct answers between patients and controls, in each of the types and intensities of emotions, was performed in FERT-100 (Supplementary Material II Table 2). Happiness was the emotion with the highest mean of concordant correct answers between patients and controls, and fear was the least. A higher level of intensity of emotions was accompanied by greater accuracy, both in patients and controls, as observed when performing an ANOVA of repeated measures (patients: F=230.142; controls: F=259.307; p<0.001).

A comparison was also made between the mean scores of patients and controls regarding the type and intensity of emotions observed during the performance of the FERT-100, using Student's t-test (Supplementary Material II Table 2). The mean of correct answers differs between patients and controls among all levels of intensity of emotions. As for the type of emotions, all means of correct answers differed between patients and controls, except fear and sadness. When considering the 95% confidence interval between the averages, in addition to fear and sadness, the intensity of 30% of the emotions also shows an intersection between the confidence intervals of patients and controls (Supplementary Material II Table 2).

Divergent construct validity

Associations with sociodemographic data, symptomatology, and neurocognition

As can be seen in Table 3, social cognition tests do not correlate with age and antipsychotic dose in patients. FERT-100 test correlated with education years (r=0.380; p<0.01) in this sample.

There was no correlation between sociodemographic data and social cognition in the controls.

Hinting Task correlated with negative PANSS (rho=-0.241, p<0.05) and Calgary (rho=-0.248; p<0.05). FERT-100 was not related to symptoms.

Table 2. Difference between controls and patients: social cognition.

Social cognition tasks	Patients (n=104) Mean (SD)/median	Controls (n=89) Mean (SD)/median	Statistical test	p-value	Cronbach's alpha
Hinting Task	13.89 (3.41)/ 15	17.11 (1.98)/17	Z=-6.85	<0.001	0.68
FERT-100	34.59 (13.00)	44.17 (10.92)	T=4.88	<0.001	0.87

SD: standard deviation; FERT-100: Hinting Task and Facial Emotion Recognition Test.

Table 3. Social cognition correlations.

	Age	Years (education)	PANSS		Calgary	FERT-100	UPSA
			Positive	Negative			
Hinting Task	-0.08	0.211	-0.67	-0.241*	-0.248*	0.288**	0.518**
FERT-100	-0.13	0.38**	0.09	-0.134	0.15		0.548**

PANSS: Positive and Negative Syndrome Scale; FERT-100: Hinting Task and Facial Emotion Recognition Test; *p<0.05; **p<0.01.

The Hinting Task correlates weakly with FERT-100 (rho=0.288, p<0.01), which would be expected, as both assess social cognition, but different domains (ToM and perception of emotions, respectively). The Hinting Task and FERT-100 also correlate weakly or moderately across all domains of general cognition, with the exception of motor speed (Token motor task), as shown in Table 4. The mean BACS Z-score for patients was -1.08, replicating result of meta-analysis[30].

Multiple linear regressions were also performed to analyze predictors of social cognition scores tests. All variables that showed statistically significant correlations with social cognition tests were evaluated. Regarding Hinting Task, only verbal fluency and working memory (digit span task) remained in the model, together explaining 26% of the variation (22% for verbal fluency and 4% for working memory) (Supplementary Material II Table 3). Using BACS Z-score instead of cognitive domains in isolation, the model had a lower prediction. Normalization of data through reflected logarithm did not bring significant changes to the model. Despite this, these data should be analyzed with caution, since Hinting Task score does not have a normal distribution.

Linear multiple regression for FERT-100 found that the BACS Z-score explains 37% of test variation (Supplementary Material II Table 4). In this case, the model with BACS Z-score brought a greater prediction to the FERT-100 than use of cognitive domains separately. Other variables that showed significant simple correlations with the test did not maintain significant statistical value (p<0.05) in multiple regression.

Convergent construct validity

Social cognition tests also correlate moderately/strongly with functional capacity, assessed by UPSA-BR (Hinting Task: rho=0.52; p<0.001; FERT-100: r=0.55; p<0.001). Social cognition tests and UPSA correlation remains significant even when result is controlled taking neurocognition into account (r=0.42; p=0.002 for Hinting Task and r=0.27; p=0.05 for FERT-100). And when social cognition tests' scores are considered, the correlation between neurocognition and UPSA-BR loses strength, going from r=0.65 to 0.52 (p<0.001) when controlling the result considering Hinting Task and to 0.39 (p=0.003) when controlling the result considering FERT-100.

Reliability

As for internal consistency, Cronbach's alpha was 0.68 for the Hinting Task, which approaches the appropriate value of 0.8 for use as a research tool[14] and is also a value very similar to that found by Gil et al.[31] (0.69), who validated the Hinting Task for Spanish and identical to the value found by Pinkham et al.[14]. The Cronbach's alpha for FERT-100 was 0.87.

DISCUSSION

The concurrent criterion validity of a test may be assessed by comparing the results obtained with those seen in literature[32]. The means and standard deviations of Hinting Task found in our study were very similar to the study by Pinkham et al.[33] (patients: 13.89±3.41 vs. 13.59±3.87; controls: 17.11±1.98 vs. 16.82±2.05). Another similarity was between the correlation Pinkham et al.[33] also found an association of Hinting Task with UPSA (r=0.462) very similar to the one found in the present study (r=0.518), both with p<0.001.

The effect sizes for difference between patients and controls regarding ToM and EP found in this study (1.2 and 0.8, respectively) are similar to that found in meta-analysis by Savla et al. (0.96 for ToM and 0.89 for EP)[1]. They are also very similar to the effect size observed by Pinkham et al.[33], who observed an effect size for Hinting Task d=1.06. These same group also demonstrated that Hinting Task and emotion recognition tests show the best psychometric qualities among several evaluated social cognition tests and recommend them for use in clinical trials[14]. The emotion recognition tests evaluated by these authors were Penn Emotion Recognition Task (ER-40) and Bell Lysaker Emotion Recognition Task (BLERT). The ER-40 uses 40 static pictures and just 4 emotions. This instrument was only recommended for use after modifications that allowed it to increase its ability to predict functional performance. BLERT uses the same seven emotions as the FERT-100. Through 21 videos, a male actor provides

Table 4. Social cognition and neurocognition correlations.

	Verbal memory	Digit span	Token	Verbal fluency	Symbol	T. London	Z-score
Hinting Task	0.397**	0.323**	0.125	0.386**	0.383**	0.314**	0.451**
FERT-100	0.366**	0.355**	0.135	0.411**	0.443**	0.540**	0.502**

FERT-100: Hinting Task and Facial Emotion Recognition Test; **p<0.01.

information about his emotions through facial mimicry, tone of voice, and body movements. This instrument has been indicated for use in clinical trials without modifications. It is observed that the emotion recognition test of the present study (FERT-100) presents characteristics of both tests analyzed above, being more comprehensive than the ER-40 and simpler than the BLERT, eliminating the need for video. These characteristics proved to be valid, since the FERT-100 was able to correlate with measurement of functional capacity.

Another aspect that reflects the psychometric qualities of the Hinting Task is its discriminative validity with the emotion recognition test. The correlation between them is weak ($r=0.29$; $p<0.01$), which is expected, since they assess different subdomains of social cognition (ToM and EP, respectively)[34]. This finding is supported by Lysaker et al.[35] and Hagiya et al.[36], who found a correlation between the Hinting Task and a facial expression recognition test similar to that found in our study ($r=0.33$ and $r=0.34$, respectively).

Mehta et al.[37] found that neurocognition predicts about 19% of the variation in ToM and 39% of the variation in emotion recognition in remitted patients with schizophrenia. These results are similar to this study, whose multiple regression demonstrated that neurocognition explains 26% of the variation in Hinting Task and 37% in FERT100 (Supplementary Material II Tables 3 and 4). The meta-analysis by Ventura et al.[38] also confirms that correlations between social cognition and neurocognition are mostly moderate and consistent.

This study corroborates the study by Brown et al.[39], in the findings that Hinting Task is associated with negative symptoms, but not with positive symptoms, and that there are no associations between symptomatology and facial emotion recognition tests. Brown's study did not assess depressive symptoms, which correlate weakly with Hinting Task in this study. It is worth remembering, however, that both negative and depressive symptoms did not enter Hinting Task's multiple linear regression model.

This study showed that fear and sadness were the emotions in which there were no significant differences between patients and controls in the FERT-100. It was also found that happiness is the emotion with the highest number of correct answers and fear the least, in both patients and controls. In addition, the increase in intensity in the expression of emotions increases the number of correct answers. These results are similar to those found by Hargreaves et al.[40], who also demonstrated that happiness and fear are the emotions with the highest and lowest average scores, respectively, as well as that accuracy increases with the intensity of emotions. However, in this study, the emotion that did not differ in correct answers between patients and controls was surprise. The finding of this study that fear is an emotion with less identification in controls and patients is also supported in the literature[41,42].

A very relevant finding of this work is that tests of social cognition correlate with measurement of functional capacity (UPSA), even when neurocognition is considered, which is also demonstrated in works of Pinkham et al.[14,33]. This finding reinforces the importance of social cognition tests, as this cognitive domain is an essential factor to understand, propose, and evaluate interventions aimed at the full functional recovery of patients with schizophrenia.

We are not aware of any study that comprehensively validated specific social cognition tests for patients with schizophrenia in the Brazilian population. The work by Fonseca et al.[43] assessed the psychometric assessment of MATRICS consensus cognitive battery (MCCB) for the Brazilian population. This cognitive battery contains an instrument for assessing social cognition, the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT-ME): Managing Emotions. This is not a test that specifically and comprehensively assesses domains of ToM and EP. The work by Negrão et al.[44] adapted and validated the "Faux Pas Recognition Test"[45], considered a test that assesses ToM, initially used to assess this domain in patients with frontal lobe lesions. This test has not been evaluated in the work by Pinkham et al., and thus, we cannot infer its employability as a measure that relates to functional performance in schizophrenia, for example.

The main limitation of the study was the inability to compare the results obtained with the application of the Hinting Task and FERT-100 to social cognition scales already validated for schizophrenia in the Brazilian population.

In summary, this study confirms data from literature that patients have deficits in social cognition compared to controls, that social cognition is related to neurocognition and functional performance, providing an additional explanation for neuropsychological tests in relation to functional impairment. In addition, Hinting Task weakly correlates with negative symptoms and facial emotion recognition. Thus, this evidence suggests that the instruments used are valid tools to assess social cognition in schizophrenia.

Impairments in social cognition are fundamental characteristics of schizophrenia and are closely linked to impaired functional performance that occurs in this mental disorder[5]. There are few duly validated tests that

assess social cognition for the Brazilian population that suffers from this disorder, limiting the assessment of this important construct in this population. In this study, social cognition tests (Hinting Task and FERT-100) showed psychometric qualities that give validity to their use in Brazilian population with schizophrenia.

Authors' contributions. BFC, JVS: conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing – original draft and writing – review & editing. RC, CMDB: supervision, validation and writing – review & editing AMO: data curation, investigation and writing – review & edition.

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Original Article

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The ability of patients with Parkinson's disease to recognize masked faces during the COVID-19 pandemic

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ABSTRACT. Patients with Parkinson's disease (PwP) have face recognition difficulties. **Objective:** This study aimed to evaluate the difficulties of PwP in recognizing masked faces during the COVID-19 pandemic. **Methods:** A total of 64 PwP, 58 age-matched older healthy controls (OHCs), and 61 younger healthy controls (YHCs) were included in the study. The Benton Face Recognition Test – short form (BFRT-sf) and the 13-item questionnaire on face recognition difficulties due to masks during the pandemic developed by the authors were applied to all three study groups. **Results:** Both the PwP and OHC groups scored worse in BFRT-sf when compared with the YHC group ($p<0.001$ and $p<0.001$, respectively). The number of those who had difficulty in recognizing people seen every day and the number of those who asked people to remove their masks because they did not recognize them were higher in the PWP group ($p=0.026$ and $p=0.002$, respectively). The number of individuals who looked at the posture and gait of people when they did not recognize their masked faces and those who stated that this difficulty affected their daily lives were higher in the OHC group ($p=0.002$ and $p=0.009$, respectively). The number of participants whose difficulty in recognizing masked faces decreased over time was higher in the YHC group ($p=0.003$). **Conclusions:** The PwP group demonstrated similar performance to their peers but differed from the YHC group in recognizing masked faces. Knowing difficulties experienced by elderly people in recognizing people who are masked can increase awareness on this issue and enhance their social interaction in pandemic conditions through measures to be taken.

Keywords: Parkinson Disease; COVID-19; Facial Recognition.

A CAPACIDADE DOS PACIENTES COM DOENÇA DE PARKINSON DE RECONHECER ROSTOS MASCARADOS DURANTE A PANDEMIA DE COVID-19

RESUMO. Pacientes com doença de Parkinson (PcP) têm dificuldades de reconhecimento facial. **Objetivo:** Avaliamos as dificuldades de PcP em reconhecer rostos mascarados durante a pandemia de COVID-19. **Métodos:** Incluímos 64 PcP, 58 controles saudáveis mais velhos (CSVs) pareados por idade, 61 controles saudáveis mais jovens (CSJs) no estudo. O *Benton Face Recognition Test-short form* (BFRT-sf) e o questionário de 13 itens sobre dificuldades de reconhecimento facial devido a máscaras durante a pandemia desenvolvido pelos autores foram aplicados a todos os três grupos de estudo. **Resultados:** Ambos os grupos PcP e CSV tiveram pior pontuação no BFRT-sf quando comparados com o grupo CSJ ($p<0,001$ e $p<0,001$, respectivamente). O número daqueles que tiveram dificuldade em reconhecer as pessoas atendidas todos os dias e o número daqueles que pediram para as pessoas retirarem suas máscaras por não as reconhecer foram maiores no grupo PcP ($p=0,026$ e $p=0,002$, respectivamente). O número de indivíduos que olharam para a postura e marcha das pessoas quando não reconheceram seus rostos mascarados e aqueles que afirmaram que essa dificuldade afetou seu cotidiano foi maior no grupo CSV ($p=0,002$ e $p=0,009$, respectivamente). O número de participantes cuja dificuldade em reconhecer rostos mascarados diminuiu ao longo do tempo foi maior no grupo CSJ ($p=0,003$). **Conclusões:** O grupo PcP demonstrou desempenho semelhante aos seus pares, mas diferiu do grupo CSJ no reconhecimento de rostos mascarados. Conhecer as dificuldades vivenciadas pelos idosos em reconhecer as pessoas mascaradas pode aumentar a conscientização sobre essa questão e potencializar sua interação social em condições de pandemia por meio de medidas a serem tomadas.

Palavras-chave: Doença de Parkinson; COVID-19; Reconhecimento Facial.

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INTRODUCTION

Efforts to decrease the transmission of the novel coronavirus (COVID-19) have resulted in the widespread use of masks, which has significantly affected our facial recognition abilities and thus our social interaction. When the lower portion of the face is obscured by a mask, holistic processing strategies, which constitute the hallmark of face perception[1], are expected to be ineffective and replaced by feature-based processing[2]. Holistic processing is defined as an upper-level strategy that is sensitive to the configuration and distances between all of the sub-features of the face (i.e., eyes, eyebrows, nose, chin, and lips) and predominant in recognizing familiar faces, whereas feature-based processing is a more primitive strategy that is useful on detecting unfamiliar or partially visible faces[3].

Patients with Parkinson's disease (PwP) generally have multiple visual dysfunctions attributed to the dopaminergic deficit in the retina and frontostriatal circuit[4,5]. To comprehend the scope of visual processing disorders in PwP, face recognition ability is frequently evaluated[6-9]. While some studies have revealed a general impairment in facial recognition and perception according to the Benton Facial Recognition Test (BFRT) in PwP compared to their peers with no PD, other studies report impairment in more specific, specialized tasks such as detecting similarities between morphed faces and evaluating facial expression from photographs[9,10]. Studies have reported that elderly individuals experience difficulties using holistic processing strategies in face perception[11,12]. A similar situation may also be valid for PwP and they may experience more difficulties than their peers in tasks that prioritize holistic processing, such as facial expression recognition[7]. Feature-based processing used in face recognition has been found to be intact in PwP under laboratory conditions[7,12]; however, challenges experienced by this population during daily exposure to masked faces remain uncertain.

It is well documented that feature-based processing strategies can be utilized in facial recognition of masked individuals[2]. Obligation to use masks provides a valuable opportunity to evaluate the ecological validity of previous studies.

In this study, we aimed to evaluate difficulties experienced by PwP in recognizing masked faces that are now considered as the new norm of current daily life.

METHODS

Study participants

Ethical approval was obtained from the Local Ethics Committee (dated December 28, 2020, no. 2020/017). The scope of the study was explained to each participant and all individuals provided written informed consent for participation. A total of 64 PwP over 50 years of age participated in the study. All these patients met the clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank[13]. Each patient's disease severity was assessed with the Hoehn and Yahr scale[14]. All the patients were undergoing dopamine replacement therapy and were tested in their "on" state. Patients who met PD dementia criteria[15] and those who scored below 24 points in the Mini-Mental State Examination (MMSE)[16] were excluded.

A total of 58 older healthy controls (OHCs) were recruited from the caregivers of patients without PD or members of the hospital staff. They were matched with the PwP group in terms of age, sex, and education level ($p=0.235$, $p=0.743$, and $p=0.881$, respectively).

As previous studies reported that individuals aged 30–35 years were the most successful group in face recognition[17], 61 younger healthy controls (YHC) of this age range were also recruited from the hospital staff or caregivers of patients without PD. None of the individuals in the OHC and YHC groups had any psychiatric or neurological disorder (including dementia) or a family history of PD.

The best-corrected visual acuity measurements of all the study participants were normal. In addition, it was ensured that none of the participants had any diagnosis of eye disease (e.g., cataracts, diabetic retinopathy, glaucoma, optic neuritis, and macular degeneration) to reduce the possibility that peripheral visual impairments could interfere with face perception.

Study design and procedures

Global cognitive efficiency was evaluated using MMSE in participants who were older than 50 years of age. All the participants were administered the Benton Face Recognition Test – short form (BFRT-sf)[18], in which the subject has to match different photographs of the same unfamiliar face by choosing among six photographs. Some trials include views of the face taken from different angles, different facial expressions, or under different lighting conditions (minimum score: 0, maximum score: 27; a higher score indicates better face recognition). In addition, all the participants were asked to respond to a questionnaire prepared by the authors of this study, Face Recognition Difficulties due to Mask Use during the Pandemic, which consisted of 13 items to evaluate difficulties in recognizing masked faces (Table 1). We aimed to evaluate the participants' face recognition difficulties, compensation methods used to overcome this difficulty, and the impact of difficulty in recognizing masked faces on their daily lives.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22 for Windows 11.5 (SPSS Inc., Chicago, IL, USA). For descriptive data, quantitative variables were expressed as mean±standard deviation and median (min–max) values, while categorical (qualitative) variables were expressed as percentages (frequency). Mean values were compared using Student's t-test if the normal distribution assumptions were met, and the Mann-Whitney U test was used otherwise. The relationship between two categorical variables was compared with the chi-square

Table 1. Face recognition difficulties due to mask use during the pandemic questionnaire and analysis of responses.

	Patients with Parkinson's disease % (yes, agree/total)	Older healthy controls % (yes, agree/total)	Younger healthy controls % (yes, agree/total)	p-value
Q1. Difficulty recognizing masked faces Have you ever been unable to recognize people, even momentarily, because they were wearing a mask during the pandemic? YES NO	87.5 (56/64)	91.4 (53/58)	96.7 (59/61)	0.167*
For those who responded yes to the question above				
Q2. Difficulty recognizing people seen almost every day Have you ever been unable to recognize the face of someone you normally see almost every day while he/she was wearing a mask? (Family members, colleagues, housemates, etc.) YES NO	10.7 (6/56)	5.7 (3/53)	0.0 (0/59)	0.026*
Q3. Difficulty recognizing people seen two to three times a week Have you ever been unable to recognize someone you would normally see at least two to three times a week while he/she was wearing a mask? (Neighbors, neighborhood residents, shopkeepers, relatives, etc.) YES NO	28.6 (16/56)	26.4 (14/53)	20.3 (12/59)	0.571**
Q4. Difficulty recognizing people seen every two to three weeks Have you ever been unable to recognize someone you would normally see every two to three weeks while he/she was wearing a mask? (Family doctor, rarely seen friends, and relatives, etc.) YES NO	51.8 (29/56)	47.2 (25/53)	42.4 (25/59)	0.600**
Q5. Difficulty recognizing people seen less than once a month Have you ever been unable to recognize someone you would normally see less than once a month while he/she was wearing a mask? (Distant relatives, acquaintances living in another city, etc.) YES NO	85.7 (48/56)	84.9 (45/53)	89.8 (53/59)	0.705**
Utilization of alternative cues used in the presence of difficulty in recognizing masked faces				
Q6. Looks carefully at the eye region When I am unable to recognize a person wearing a mask, paying attention to their eyes allows me to recognize them. AGREE NOT AGREE	78.6 (44/56)	83 (44/53)	83.1 (49/59)	0.781**
Q7. Looks carefully at the head region When I am unable to recognize a person wearing a mask, I need to look at their hairstyle or head accessories (hat, headscarf, necklace, earrings, glasses, etc.) more carefully in order to recognize them. AGREE NOT AGREE	55.4 (31/56)	35.8 (19/53)	37.3 (22/59)	0.068**

Continue...

Table 1. Continuation.

	Patients with Parkinson's disease % (yes, agree/total)	Older healthy controls % (yes, agree/total)	Younger healthy controls % (yes, agree/total)	p-value
Q8. Needs to hear the person's voice When I am unable to recognize a person wearing a mask, I need to hear their voice in order to recognize them. AGREE NOT AGREE	58.9 (33/56)	54.7 (29/53)	39.0 (23/59)	0.078**
Q9. Looks carefully at the clothes When I am unable to recognize a person wearing a mask, I need to look at their clothes more carefully in order to recognize them. AGREE NOT AGREE	30.4 (17/56)	37.7 (20/53)	28.8 (17/59)	0.565**
Q10. Looks carefully at posture and gait When I am unable to recognize a person wearing a mask, I need to look at their gait, posture, and body shape in order to recognize them. AGREE NOT AGREE	53.6 (30/56)	60.4 (32/53)	30.5 (18/59)	0.004**
Q11. Needs the person to remove his/her mask I have asked a person to remove their mask because I was unable to recognize them at least once. AGREE NOT AGREE	37.5 (21/56)	22.6 (12/53)	10.2 (6/59)	0.002**
Impact of difficulty in recognizing masked faces in daily life and changes in face recognition ability over time				
Q12. Increased success in recognizing masked faces Do you think you have improved at recognizing people wearing masks since the beginning of the pandemic? YES NO	43.8 (28/64)	55.2 (32/58)	73.8 (45/61)	0.003**
Q13. Daily life affected due to difficulty in recognizing faces Does difficulty recognizing masked people negatively affect your daily life? YES NO	12.5 (8/64)	29.3 (17/58)	9.8 (6/61)	0.009**

Q: question. p<0.05 is considered significant; *One-way analysis of variance; **Kruskal-Wallis H test.

test or Fisher's exact test. The relationship between three categorical variables was compared with one-way analysis of variance or the Kruskal-Wallis H test. The Bonferroni-corrected Mann-Whitney U test was used for the paired comparisons of statistically significant results in the comparisons between the three groups, and the significance level was set at p<0.05.

RESULTS

Clinical characteristics

The clinical characteristics of the study groups are presented in Table 2.

Analysis of neuropsychological test data

The mean MMSE score was 28.2±1.4 (24.0–30.0) in the PwP group and 28.4±1.2 (24.0–30.0) in the OHC group (p=0.056). The mean BFRT-sf score was 18.3±2.4 (13.0–34.0) in the PwP group, 18.4±2.8 (min–max 8.0–24.0) in the OHC group, and 21.0±2.2 (min–max 16.0–27.0) in the YHC group (p<0.001). When the three groups were compared in terms of the BFRT-sf scores, there was no statistically significant difference between the PwP and OHC groups (p=1.000), but a statistically significant difference was observed between the PwP and YHC groups and between the OHC and YHC groups (p<0.001 and p<0.001, respectively).

Table 2. Clinical characteristics of the participants.

Variable		PwP group (n=64)	OHC group (n=58)	YHC group (n=61)
Sex (F/M)		29/35	28/30	36/25
Age (years)	Mean±SD Median (min–max)	61.5±6.5 61.0 (50.0–80.0)	59.9±8.0 60.5 (50.0–74.0)	32.7±1.7 33.0 (30.0–35.0)
Education (years)	Mean±SD Median (min–max)	8.4±4.5 8.0 (0.0–16.0)	8.8±5.1 7.0 (0.0–21.0)	14.6±3.4 15.0 (8.0–21.0)
Disease duration (years)	Mean±SD Median (min–max)	6.1±3.5 5.0 (2.0–17.0)	N/A	N/A
UPDRS III	Mean±SD Median (min–max)	30.8±13.3 31.0 (3.0–68.0)	N/A	N/A
Hoehn and Yahr staging	Mean±SD Median (min–max)	2.2±0.7 2.5 (1.0–4.0)	N/A	N/A
MMSE	Mean±SD Median (min–max)	28.3±1.9 28.0 (24.0–30.0)	28.5±1.8 29.0 (24.0–30.0)	N/A
BFRT-sf	Mean±SD Median (min–max)	18.3±2.4 18.5 (13.0–24.0)	18.4±2.8 19.0 (8.0–24.0)	21.0±2.2 21.0 (16.0–27.0)

Values are presented as mean±SD and median (min–max). PwP: patients with Parkinson's disease; OHC: older healthy control; YHC: younger healthy control; F: female, M: male; SD: standard deviation; UPDRS III: Unified Parkinson's Disease Rating Scale Part III motor score; MMSE: Mini-Mental State Examination; BFRT-sf: Benton Face Recognition Test – short form.

Analysis of questionnaire results

When the responses to the first question were evaluated, it was observed that 87.5% of the PwP, 91.4% of the OHCs, and 96.7% of the YHCs had experienced difficulty recognizing masked faces at least once during the pandemic (p=0.167). Only the individuals who had experienced difficulty recognizing masked faces (responded yes to question 1) were asked to answer questions 2 to 11 to assess helpful strategies they used to recognize masked individuals.

When the participants were evaluated in terms of difficulty recognizing masked people that they saw at different intervals, the PwP and OHC groups and the OHC and YHC groups were determined to have similar rates of difficulty recognizing people they saw every day (p=1.000 and p=0.309, respectively). However, the PwP group had a higher rate of individuals with this difficulty compared to the YHC group (p=0.036).

The rates of participants that observed posture and walking to help identify masked people when they could not recognize them were similar between the PwP and OHC groups (Bonferroni-corrected; p=1.000), while it was significantly higher in the YHC group compared to the remaining two groups (p=0.003 and p=0.036, respectively). The rate of individuals asking an unrecognized person to remove their mask to recognize them were similar between the PwP and OHC groups and between the YHC and OHC groups (p=0.273 and p=0.219, respectively) but significantly higher in the PwP group than in the YHC group (p=0.003).

The number of participants indicating that they became more successful at recognizing masked faces compared to the beginning of the pandemic was similar between the PwP and OHC groups and between the YHC and OHC groups (p=0.624 and p=0.102, respectively), but it was significantly higher in the YHC group compared to the PwP group (p=0.003).

The number of participants indicating that difficulty recognizing faces affected their daily lives was similar between the PwP and OHC groups and between the PwP and YHC groups (p=0.066 and p=1.000, respectively), but it was significantly higher in the OHC group compared to the YHC group (p=0.021). Table 1 presents the analysis of the participants' responses to the questionnaire items.

DISCUSSION

We approached the face recognition ability of PwP from a different perspective than the published data by evaluating the ability to recognize masked faces in daily life rather than performing an office-based assessment. With this approach, we aimed to understand difficulties experienced by PwP in this new challenge of being exposed to masked faces on a daily basis.

According to an online study conducted with younger healthy people, recognizing faces with a mask requires feature-based processing rather than holistic processing[2]. In studies related to face recognition abilities in PwP and in people older than 50 years, deterioration was shown from early stages in tasks involving the use of holistic processing strategies, such as the detection of facial expression. Feature-based processing, however, is generally intact in PwP[7,12,19,20]. Therefore, it may be considered that none of our groups was at a disadvantage in terms of their ability to recognize masked faces. However, the data of our questionnaire produced slightly different results than expected.

A previous study that used eye-tracking devices showed that directing attention more frequently toward the eye region increased the accuracy of recognizing members of the Caucasian people. Considering the large population of the Caucasian people in our society and the data indicating that looking at the eye area to identify people improves recognition accuracy in this group[21], it can be deduced that directing attention toward the eye region will minimize difficulty identifying a familiar masked face. According to the results of our questionnaire, the need to direct attention to visual clues other than the eye area was more common in the >50 years group. This may indicate that people over the age of 50 years have more difficulty than younger people in recognizing masked faces and are, therefore, at a disadvantage compared to the later in such a task requiring feature-based processing. Although previous studies have stated that feature-based processing is intact in PwP and OHCs[7,12], our findings indicate that this may differ in daily life.

Derya et al. reported that the PwP performed similar to their peers in detecting facial expression shown on a video whereas they were at a disadvantage when asked to recognize facial expressions from photographs in a laboratory task[22]. When this finding is evaluated together with the results of previous studies reporting a disconnection of the pathways extending from the prefrontal region to the ventral and dorsal pathways of visual processing in PwP[23], the PwP performing similar to their peers in recognizing facial expressions in a more dynamic circumstance of a video may indicate that the dorsal pathway associated with dynamic processes is less affected in PD. In this regard, the parallel responses of our PwP and OHC groups to most items of the questionnaire may be related to our evaluation of face recognition in a dynamic process, similar to a video. Likewise, the parallel responses to the questionnaire and BFRT-sf scores among the individuals aged over 50 years in the OHC and PwP groups, which separates them from the YHC group, may also be associated with age-related degeneration.

In this study, the BFRT-sf scores of the PwP and OHC groups without dementia were similar, while the performance of both groups was worse compared to the younger group, which is consistent with data in the literature demonstrating that this test score decreases with age[18].

In brief, when we examined the results of BFRT-sf and the 13-item questionnaire prepared for this study, the PwP and OHC groups displayed similar performance in the domain of recognizing masked faces during the pandemic and performed significantly worse than the YHC group. The rates of individuals with difficulty recognizing people they saw every day and asking an unrecognized person to remove their mask to recognize them were higher in the PwP group than in the YHC group, but there was no statistically significant difference between the OHC and YHC groups. These findings are consistent with the results of another study that compared PwP, OHC, and YHC groups in terms of recognizing facial expressions on a video[22]. However, in contrast to that study evaluating tasks using holistic processing, we assessed a challenging aspect of daily life that emphasizes feature-based processing, which is reportedly intact in individuals over the age of 50 years. In this regard, our study is valuable in terms of revealing how tests performed in the laboratory and daily life experiences can differ. In this way, it is important to acknowledge difficulties experienced by elderly people with or without PD in masked face recognition and improve conditions that facilitate their social life in prolonged pandemic conditions.

A limitation of this study is that we did not evaluate the presence of depression and anxiety disorders among the participants, which could affect their facial recognition performance. Since there is no validated scale or visual test evaluating masked face recognition, our data based on subjective opinion of the participants collecting by a questionnaire, which is a pitfall of the study. However, the reason for these was to shorten their duration of hospital stay to prevent the possible transmission of COVID-19 disease among the researchers and subjects.

In conclusion, the widespread use of facemasks due to the pandemic poses a new challenge in face recognition. According to the results of BFRT-sf and the participants' responses to the Face Recognition Difficulties due to Mask Use during the Pandemic Questionnaire, the PwP group demonstrated similar performance to their peers but differed from the younger people in recognizing masked faces requiring feature-based processing.

Various strategies may be useful to prevent elderly people from decreasing their social interaction due to

the use of facemasks. For example, web-based masked face recognition tests can be designed for training as social cognitive rehabilitation. In addition, the use of transparent masks can be an alternative method to improve interpersonal communication.

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Original Article

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Clinical utility of Phototest via teleneuropsychology in Chilean rural older adults

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ABSTRACT. The COVID-19 pandemic has shown the need for neuropsychological care for older adults with memory complaints in different contexts, including rural areas or areas with difficult access. **Objective:** This study aimed to analyze the clinical utility of the Phototest, through telemedicine, to identify mild cognitive impairment in rural older adults with memory complaints, during the COVID-19 pandemic. **Methods:** We performed a cross-sectional, case-control, and clinical utility comparison of brief cognitive tests (BCTs). The sample included 111 rural elderly people with mild cognitive impairment (MCI) and 130 healthy controls from the Los Lagos region, Chile. The instruments adopted were modified Mini-Mental State Examination (MMSEm) and adapted version of the Phototest (PT) for Chile. **Results:** To identify mild cognitive impairment, using a cutoff score of 27–28 points, the Phototest showed a sensitivity of 96.6% and a specificity of 81.8%; indicators superior to those of the MMSEm. **Conclusions:** The Phototest is more accurate than the MMSEm in identifying cognitive alterations in rural older adults with cognitive memory complaints through telemedicine. Therefore, its use in primary care is recommended in order to perform early detection of preclinical cognitive alterations in mild cognitive impairment or neurodegenerative diseases.

Keywords: Neuropsychological Tests; Telemedicine; Cognitive Dysfunction; Rural Population; COVID-19.

UTILIDADE CLÍNICA DO PHOTOTEST VIA TELENEUROPSICOLOGIA EM IDOSOS RURAIS CHILENOS

RESUMO. A pandemia de COVID-19 mostrou a necessidade de cuidados neuropsicológicos para adultos idosos com queixas de memória em diferentes contextos, incluindo áreas rurais ou áreas de difícil acesso. **Objetivo:** Analisar a utilidade clínica do Phototest, por meio da telemedicina, para identificar uma leve deficiência cognitiva em adultos idosos rurais com queixas de memória, durante a pandemia de COVID-19. **Métodos:** Realizamos uma comparação transversal, caso-controle e utilidade clínica dos testes cognitivos breves. Amostra: Cento e onze idosos rurais com deficiência cognitiva leve (DCL) e 130 controles saudáveis da região de Los Lagos, Chile. Instrumentos: Minimental modificado (MMSEm) e versão do teste fotográfico (PT) adaptada para o Chile. **Resultados:** Para identificar a DCL, usando pontuação de corte de 27-28 pontos, o Phototest mostrou sensibilidade de 96,6% e especificidade de 81,8%; indicadores superiores aos do MMSEm. **Conclusões:** O Phototest é mais preciso que o MMSEm para identificar, por meio da telemedicina, alterações cognitivas em adultos idosos rurais com queixas de memória cognitiva. Sendo assim, seu uso na atenção primária é recomendado para realizar a detecção precoce de alterações cognitivas pré-clínicas em DCL ou doenças neurodegenerativas.

Palavras-chave: Testes Neuropsicológicos; Telemedicina; Disfunção Cognitiva; População Rural; COVID-19.

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INTRODUCTION

Due to the Coronavirus pandemic, several medical and hospital care services focused on the elderly were suspended to control the viral spread and reduce mortality[1]. One of these services was routine clinical and neuropsychological assessments related to cognitive impairment (CD), given their nature in terms of the interpersonal contact involved[2]. Unfortunately, during quarantine, there was evidence that medical conditions such as diabetes and hypertension[3], considered risk factors for CD[4], worsened and that neuropsychiatric symptoms and the risk of CD increased among the elderly[5]. Therefore, the field of neuropsychology had to quickly evolve and adapt, by incorporating telehealth or teleneuropsychology (TNP) assessments to continue providing cognitive assessment and monitoring services to the elderly[6,7].

There is a growing literature that supports TNP as a feasible and reliable way to conduct neuropsychological tests and assess the cognitive status of elderly, given the barriers that this technology allows to overcome[8]. During the global COVID-19 pandemic, TNP has proven to be useful in detecting and monitoring CD in the elderly[9,10]. The available literature shows that TNP can provide reliable and valid assessments[11,12], reaching geographically distant populations to identify CD[13,14], thus becoming a tool of major clinical value to address the current situation of confinement and social distancing, especially in primary health care[15,16].

However, the development of TNP in Latin America (LA) is still in its incipient, and the assessment of CD with the brief instruments through telehealth formats in rural seniors has not been conducted in the region[17]. Few studies have analyzed the reliability and validity of neuropsychological tests in the telehealth context among Latin or Hispanic people[18]; mainly in preclinical phases of dementia, such as mild cognitive impairment (MCI).

Likewise, several of the brief cognitive tests (BCTs) available in the region have experienced problems of general clinical utility, low sensitivity, and specificity, especially in early stages of CD such as in MCI[19,20]. The difficulties of diagnostic utility have been described in a population with low schooling[21,22]; in addition, most of the research that has validated BCTs has been carried out in an urban population[19].

In contrast, the Phototest (PT)[23] has demonstrated its usefulness in primary health care centers, since it does not use pencil or paper, which facilitates its performance and evaluation, especially in people with lower educational levels or in those who are illiterate[24,25]. It has a higher sensitivity and specificity than traditional tests with respect to dementia and MCI[26,27] and has shown to be more effective and cheaper than the Mini-Mental State Examination (MMSE) in multiple studies[27-29]. Finally, given its structural and managing characteristics, it is believed to be easily adapted to virtual assessment formats.

Therefore, considering that the percentage of rural seniors in LA is higher than their urban counterparty[29], they have fewer years of schooling, higher disease burden, restricted access to specialized medical controls, and a lower probability of having contracted health insurance, it is necessary to have MCI-sensitive instruments that can be applied in rural settings through TNP. Therefore, our objective was to analyze the clinical utility of the PT to detect MCI in older adults in rural areas of Chile during the SARS-CoV-19 pandemic, using TNP.

METHODS

Design

This is a cross-sectional, case-control study of clinical utility analysis of BCTs, using TNP, in a non-probability sample of 111 rural elderly with MCI and 130 controls. It was carried out during the second half of 2020, i.e., during national quarantine, due to the global pandemic of the COVID-19.

Participants and procedure

The initial sample was composed of 354 rural seniors, aged 65 years or older, who attended the annual checkup part of the Preventive Medicine Program for the Older Adult (EMPAM for its acronym in Spanish). This is a national program of the Chilean Ministry of Health that is carried out in all primary care centers in the country[30]; it is implemented by an interdisciplinary team (e.g., medicine, nursing, kinesiology, and psychology). It consists of a comprehensive, periodic, and follow-up clinical evaluation to detect factors that may affect the health, autonomy, and independence of this population. In this annual medical control, the Functional Examination of the Elderly (EFAM) is applied, which is used to predict the loss of functionality of the elderly. This instrument allows classifying the subjects according to the degree of functionality: self-valent or autonomous, self-valent with risk, and those at risk of dependence. The EFAM includes a clinical and sociodemographic record, anthropometric measurements (e.g., blood pressure, pulse, weight, height, and body mass index, waist circumference, and physical activity), together with a functional assessment [Barthel test[31], Pfeffer and risk of falls using the unipodal station test[32,33], and the Timed Up and Go (TUG)[34]], cognitive assessment [abbreviated Mini-Mental or MMSE-EFAM (MMSE-EFAM)[35,36]], and mood evaluation [Yesavage depression

scale[37]]. The EFAM[30] consists of two parts. In part A, the functional aspects are evaluated, and in part B, the cognitive and emotional dimensions are examined; in addition, the aspects that affect the mental health and functionality of the elderly person are also examined. The results allow the identification of loss of functionality, health problems, suspicion of depression, and CD. This information guides the professional in assessing the cognitive and functional status of the elderly person.

In the context of this annual evaluation, 354 older adults were assessed at a family health center (CESFAM) in a rural sector of the Los Lagos region (southern Chile). Of these, 181 reported having memory problems and 173 did not report such problems. All patients were evaluated with the EFAM, together with a CDR clinical interview and medical assessment. The assessment was performed through the Zoom platform, except for the anthropometric measurements, the TUG, and the unipodal station test, which was performed in person at the rural doctor's office, during the patient's first visit.

In the first group, with memory complaints, 111 participants were identified with MCI, but autonomous or functional, whereas, in the second group, without memory complaints, 130 participants were confirmed as autonomous or functional elderly, without cognitive problems. In both the groups, clinical and psychometric criteria were applied to confirm the MCI group and the healthy control (HC) group. To identify the subjects as MCI and HC, first, the results of the EFAM functional tests (i.e., Barthel Test, Pfeffer, TUG, and unipodal station test) were considered. In the case of the MCI group, the result of the functional assessment should classify the patient as a self-sufficient or autonomous older adult, according to the first part of the EFAM. Although individuals with very mild functional failure in instrumental activities of daily living were included. Then, in the second part of the EFAM, the patient had to obtain CD scores on the abbreviated MMSE or MMSE-EFAM (≤13 points). In addition, the score on the CDR had to be 0.5. In contrast, HC had to be classified as self-valent or autonomous on the EFAM, obtaining high scores on the abbreviated MMSE (≥14 points) and classified by the CDR as 0.0.

After being evaluated with the EFAM, 113 subjects were excluded from the study for presenting functional problems, suspected dementia, depression, or voluntarily withdrew from the study. But they were redirected to the psychosocial care program. Finally, the presumptive diagnosis made by primary care professionals was reviewed and validated by a neuropsychologist and an expert neurologist. Subsequently, two groups were established, one consisting of older adults with MCI (MCI=111) and healthy controls (HC=130). Then, all patients underwent a TNP assessment, where the modified MMSE (MMSEm)[38] and the PT[39] were administered.

Instruments and digital platform

The PT [23] is a short cognitive test that can be used for free under a Creative Commons license and is very suitable for primary care centers. This test does not use pencil and paper and is easy to administer and score, especially for people with low educational levels. The PT comprises three parts (Annex 1 Supplementary Material): (1) a naming task (30–60 seconds), with six color photographs of common objects in prototypical position (i.e., card, car, pear, trumpet, shoes, and spoons); (2) a verbal fluency test (names of people: men and women separately, 30 s each); and (3) a free recall task and recall facilitated by the cues, using the six objects of the naming test (30–60 s). The administration of the test lasts for approximately 3 min.

The team of health center professionals was trained in virtual telehealth programs and TNP procedures; in addition, they were trained by neurologists and neuropsychologists with expertise in cognitive pathology and detection of CD and dementia. They were trained in the use of clinical criteria, clinical interview (CDR), and cognitive instruments, including the MMSEm and PT. For the TNP assessment of subjects with MCI and HC, the modified Mini-Mental[38], the adapted version of the PT for Chile[39], and a demographic card was included. The Zoom platform was used for real-time neuropsychological assessment. The MMSE tasks that required writing and drawing were assessed remotely using pencil and paper. Patients were asked to show their drawings to the camera for the practitioner to examine. The evaluator graded, allowing the family member, companion, or caregiver to assist them with the use of the computer and webcam. The PT was projected on the virtual platform and did not require patients or their companions to manipulate the test. International clinical guidelines and recommendations for TNP assessments in times of pandemic were followed[2,12].

Statistical analysis

A descriptive analysis of the demographic characteristics and the results of cognitive tests was performed on the groups analyzed. A comparison between groups was performed using Student's t-test, and an analysis of the clinical utility of the instruments was performed using ROC curves. Sensitivity (Sn) and specificity (Sp) values were calculated along with the cutoff scores suggested in the Chilean literature for the MMSEm (≤21=CD; ≥22=HC)[38] and the PT (28–29=MCI; ≥30=HC)[23]. SPSS version 25 was used.

Formal aspects

The procedures performed in the present study complied with the ethical standards of the pertinent national committees and institutions on human experimentation and the Declaration of Helsinki 1975, which was revised in 2008. All participants were informed about the nature of the study and signed consent. This study was approved by the Institutional Ethics Committee of Universidad Santo Tomás, in Chile (CEC UST Nº 15), and of Universidad de La Costa, in Colombia (Act No. 092). The research is part of an international and multicenter study.

RESULTS

The flow diagram of the participants is shown in Figure 1. As can be seen in Table 1, no significant differences were found in terms of age and schooling among

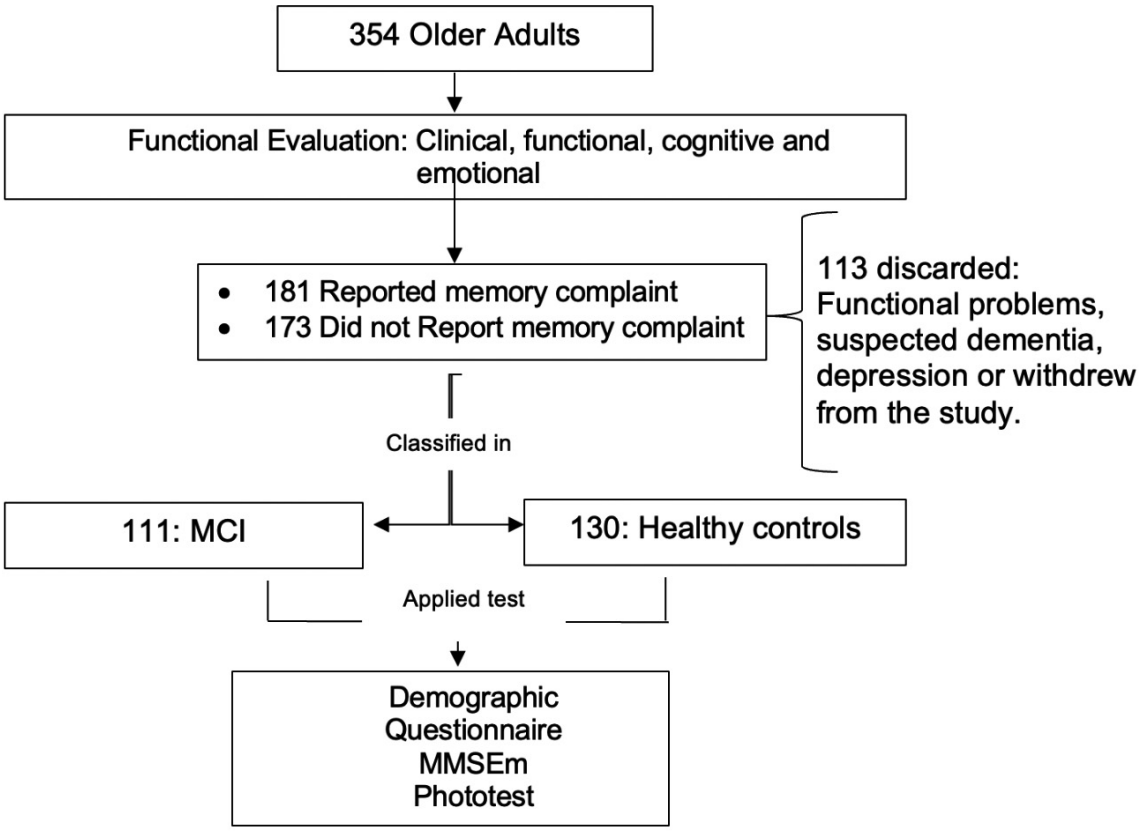

Figure 1. Study flow diagram.

Table 1. Demographic characteristics and results of the cognitive tests of the participants.

Number		MCI		HC		Student's t /χ^2	
		M	SD	M	SD	F	p
		111		130			
Age		70.342±9.51		71.12±7.85		25.40	0.239
Gender	Women	71		81		2.17	0
	Men	40		49			
Years of schooling		6.72±2.45		6.91±3.00		6.18	0.644
MMSE		23.82±2.96		25.83±3.77		147.80	0.00
Phototest		26.82±3.82		36.16±6.28		100.34	0.00

MCI: mild cognitive impairment; HC: healthy control; M: mean; SD: standard deviation; MMSE: Mini-Mental State Examination.

participants. In contrast, gender and average cognitive test performances between the study groups did show significant differences. Subjects without cognitive complaints showed better cognitive performance.

A comparison between the PT and the MMSEm was performed among participants. Table 2 shows the aROC along with the cutoff score, in which Sn and Sp are best balanced for CD. The PT used a cutoff score of 26/27 points and exhibited a higher Se=96.6 and Sp=81.8 than the MMSE (Se=56.9; Sp=72.7). Similarly, ROC curve analysis showed that the PT has a higher area under the curve (AUC=90%) than the MMSEm (AUC=69%) in the MCI group.

DISCUSSION

The MMSE is the gold-standard test for the detection of CD[40,42]. Despite this, difficulties have been reported with this instrument for several years. Test administration is not standardized for TNP formats in all LA countries, where the cultural, educational, and socioeconomic characteristics of the patient may bias scores[42]. This test does not measure executive function as it can detect only moderate or advance dementia[43]; and it is also not sensitive to MCI[44,45], early stages of Alzheimer's-type dementia, and non-Alzheimer's-type dementias[46]. As a pencil and paper task, the MMSE conducted through telehealth means requires the use of complex digital platforms or the user to interact with other systems to complete the assessment[47]. Additionally, the use of the MMSE in primary health care is limited due to its long completion time and educational bias; consequently, it cannot be applied to illiterate people since several of its items require verbal and writing skills.

Moreover, the PT is a very brief test (<3 min) that can be used in primary health care and clinical contexts that have very limited time and large volumes of patients seeking treatment[48]. It can be applied to illiterates and is not affected by the level of education[47]. In addition to memory, the PT assesses executive function, and it is a test that has no ceiling effect[20]. It has proven to be more effective, economical, and efficient than the MMSE in identifying dementia in primary health care and can differentiate MCI from dementia[25,26,49]. In this study, the PT with a cutoff score of 26/27 points exhibited excellent psychometric indicators (Sn=96.6 and Sp=81.8), for identifying MCI; far superior to those of the MMSE (Se=56.9; Sp=72.7) revealing greater clinical utility (PT: AUC=90% vs. MMSE: AUC=69%).

Recent studies have reported the superiority of the PT in identifying CD in general and MCI in various health contexts[29,50], including their identification in illiterate or low-schooling subjects[51,52], showing that PT was one of the most accurate tests to detect suspected CD, especially in patients with lower levels of education or in those coming from different cultural backgrounds. Nevertheless, in a systematic review of BCTs for early detection of dementia in LA elders, Custodio et al.[53] reported difficulties in a broad spectrum of BCTs, including MoCA, ACE-R, and the Ineco Frontal screening. The authors of this study argued that most of the tests required cultural adjustment and different cutoff scores depending on educational level, while others were to be analyzed in populations with low levels of education. This review did not take into account the analysis of the PT. But in the same year, Burke et al.[54] analyzed 10 cognitive tests for dementia in the Spanish-speaking population, using the PT and concluded that this instrument presented the highest statistical indicators to detect dementia and MCI and was the most appropriate to be applied in contexts of low levels of education and literacy. We believe that the origin of these discrepancies may be the lack of studies analyzing the properties of the PT in LA. The fact is that the PT is receiving more and more support, given its diagnostic accuracy and its usefulness in detecting CD in people with a low level of education or illiteracy[25,52].

Another interesting result was related to the characteristics of the digital platform used and the effectiveness of remote neurocognitive assessment, to identify CD in the participants of this study. Since the PT is not a pencil and paper task and does not require the subject to manipulate the test, its inclusion in the digital platform was easy. Also, the PT has several advantages over other available BCTs. The test (face-to-face or remote) starts with a naming task that includes a slide with six images, which is shown to the patient. The developers of this instrument have created several slides

Table 2. Sensitivity and specificity of the Mini-Mental State Examination and the Phototest.

Participants	Test	Cutoff	aROC	Se	Sp
MCI vs. HC	Phototest	27–28	0.90 (0.80–0.99)	96.6 (0.85–0.99)	81.8 (0.71–0.91)
	MMSE	≤ 21	0.69 (0.54–0.83)	56.9 (0.27–0.86)	72.7 (0.61–0.84)

aROC: curve area; Se: sensitivity; Sp: specificity; MCI: mild cognitive impairment; HC: healthy control.

to perform the assessment, thus reducing the learning effect and diagnostic errors of the instrument (http://www.fototest.es/). Additionally, the application of the test is notably fast[55], easy to score and interpret, and did not generate rejection among the participants of this study. On the contrary, MMSEm usage experience through virtual assessment resulted in several participants rejecting the orientation items, arguing they had been disrespected. In other cases, family or technological support was needed to complete the writing and drawing tasks. Therefore, some cases required the training of patients or companions on the answering of the test. In other cases, the application of the MMSEm could not be completed by low-schooling or illiterate subjects, thus producing rejection and several people desist from participating in the study.

Therefore, despite the evidence supporting the assessment of dementia in vulnerable populations through telemedicine[15,56-59], some conditions must be met. The main recommendations considered in our study was training in TNP; for professionals to develop competencies to manipulate telehealth platforms, ethical issues such as informed consent, and biosafety procedures; and ability to address technical problems, connectivity, and social communication strategies and empathy through a screen[2]. In addition, the recommendations of the working group for the practice of TNP in LA[60] were considered. These focused on the actions during the PT and MMSE administration procedure. It was verified that the patients had the necessary materials for the assessment (e.g., pen, pencil, and paper), the presence of a companion or facilitator, when appropriate, and the technological requirements[60].

Therefore, since care should be provided to confined patients in rural areas of Chile, where access to medical care is limited[60], our working group designed a strategy for TNP assessment. First, to use cognitive tests that could be used through virtual platforms and that the cognitive tests available for use using video technologies were fast, efficient, and reliable[12], they should be adapted and implemented in culturally diverse populations, with low educational levels or illiterate[61]. In this order of ideas, the PT would meet the conditions to be administered to detect CD and dementia in elderly people with a low educational level or illiterate through TNP. This would be the first study that supports the use of PT through the TNP in LA, although the computerized version of the RUDAS 65 was recently analyzed in Peru and reported adequate psychometric indicators to discriminate CD and dementia in populations with heterogeneous educational levels, illiterate, and rural[19,62,63].

This is pioneering research in LA, although it has some limitations. The authors of this study believe that follow-up studies are needed to gather evidence in favor of the PT using videoconferencing technologies for remote neuropsychological assessments. However, geographical and confinement limitations, in addition to limited access to professionals with expertise in cognitive pathologies, highlight the relevance of rapid TNP assessments. On the other hand, it would have been interesting to have compared the performance of this sample in urban populations. Unfortunately, this was not possible due to the sanitary measures of confinement. It was also not possible to analyze in depth the impact of quarantine or social isolation on the mental health and cognition of the participants. During the functional assessment (EFAM), subjects who exhibited significant symptoms of mood alterations, or those whose symptoms were reported by their caregivers or relatives, were excluded from this study and referred to the psychosocial care program. Questions about the emotional situation of the elderly during confinement were not included in the TNP assessment.

In addition, it was not possible to incorporate extensive neuropsychological assessments or to have complete cognitive profiles. Similarly, it was not possible to specify the type of MCI, due to logistical problems, bandwidth, and the complexity of applying extensive neuropsychological assessments remotely through these virtual environments. Recent reports stress that such connection-related difficulties can affect processing speed tasks. The low resolution of the screens can affect the discrimination of colors present in the tests. Finally, the quality of the audio can lead to loss of information or interruption[18]. These situations were addressed through the recording of the assessments and subsequent reviews.

Thus, PT proved to be more accurate in identifying MCI in elderly people in rural Chile using TNP compared with the gold-standard measure. Its use is recommended in primary health care contexts to detect preclinical cognitive alterations, such as MCI.

Authors' contributions. NC: conceptualization, writing – original draft, writing – review & editing and investigation. MSA: conceptualization, writing – original draft, writing – review & editing, supervision and project administration. LC, MFP, CRF and MRH: data curation, investigation, writing – original draft, writing – review & editing. JHP: methodology and writing – original draft, writing, SS: data curation and formal analysis. PAG: conceptualization, writing – original draft, Writing – review & editing, supervision and project administration. NL: conceptualization, writing – original draft, writing – review & editing, supervision and project administration.

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Original Article

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The reliability of neurobehavioral tests in a thai adult population

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ABSTRACT. Early detection of decline in neurobehavioral (NB) performance requires reliable methods of testing. Although NB tests have been shown to be consistent and reliable in Western countries, there has been limited research in Asian populations. **Objective:** The purpose of this study was to investigate the test-retest reliability of NB tests in a Thai adult population and examine the impact of demographic data on NB tests. The aspects of the tests chosen were memory, attention, hand-eye coordination, motor speed, and dexterity. **Methods:** The three NB tests used were digit span, Purdue Pegboard, and visual-motor integration. All three were administered to a population of 30 Thai adults. **Results:** The outcomes of all Pearson's correlation coefficient tests (r) were positive and greater than 0.60, and subtest-retest reliability correlation coefficients ranged from 0.63 ($p<0.001$) to 0.81 ($p<0.001$). Interestingly, the outcomes of all of these tests were not affected by demographic data, with the exception of the Purdue Pegboard test, in which performance on the preferred hand and both hands assessment was weakly associated with age ($\beta=-0.09$, $p<0.001$ and $\beta=-0.08$, $p<0.05$, respectively). **Conclusions:** NB tests have adequate reliability and are useful for the evaluation of clinical memory, attention, hand-eye coordination, motor speed, and dexterity in Thai adults. These tests were not affected by demographic data. However, further studies to measure the validity of the digit span, Purdue Pegboard, and visual-motor integration tests are needed.

Keywords: Mental Status and Dementia Tests; Neurobehavioral Manifestations; Reproducibility of Results; Memory, Short-Term.

A CONFIABILIDADE DOS TESTES NEUROCOMPORTAMENTAIS EM UMA POPULAÇÃO ADULTA TAILANDESA

RESUMO. A detecção precoce do declínio no desempenho neurocomportamental (NC) requer métodos confiáveis de teste. Embora os testes NC tenham se mostrado consistentes e confiáveis em países ocidentais, as pesquisas em populações asiáticas ainda são limitadas. **Objetivo:** O objetivo deste estudo foi investigar a confiabilidade de teste-reteste dos testes NC em uma população adulta tailandesa e o impacto dos dados demográficos nos testes NC. Os aspectos dos testes escolhidos foram memória, atenção, coordenação óculo-manual, velocidade motora e destreza. **Métodos:** Os três testes RC utilizados foram o *digit span*, o *Purdue Pegboard* e a integração visomotora. Todos os três foram usados em uma população de 30 adultos tailandeses. **Resultados:** Os resultados de todos os testes de coeficiente de correlação de Pearson (*r*) foram positivos e superiores a 0,60, e os coeficientes de correlação de confiabilidade subteste-reteste variaram de 0,63 ($p<0,001$) a 0,81 ($p<0,001$). Curiosamente, os resultados de todos esses testes não foram afetados pelos dados demográficos, com exceção do teste *Purdue Pegboard*, no qual o desempenho na mão preferida e a avaliação de ambas as mãos foi fracamente associado à idade ($\beta=-0,09$, $p<0,001$ e $\beta=-0,08$, $p<0,05$, respectivamente). **Conclusão:** Os testes NC apresentam confiabilidade adequada e são úteis para avaliação da memória clínica, atenção, coordenação óculo-manual, velocidade motora e destreza em adultos tailandeses. Esses testes não foram afetados por dados demográficos. No entanto, são necessários mais estudos para medir a validade dos testes de *digit span*, *Purdue Pegboard* e IVM.

Palavras-chave: Testes de Estado Mental e Demência; Manifestações Neurocomportamentais; Reprodutibilidade dos Testes; Memória de Curto Prazo.

This study was conducted at the Department of Community Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

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INTRODUCTION

The discipline of neurobehavioral (NB) toxicology has expanded to encompass approaches for the detection of subclinical abnormalities. Research in this field has focused on the use of traditional neuropsychological tests to identify atypical cases. NB test batteries have been commonly used to assess the impact of acute pesticide exposure on the NB in adult occupational populations[1]. One study discovered a relationship between occupational exposure and impairment in psychomotor speed, executive function, visuospatial ability, working memory, and visual memory[2]. Computerized performance evaluations have recently been introduced, and they appear to be applicable for carrying out standardized efficient field investigations. However, earlier studies have shown that due to the demand for alphabetic knowledge, computerized examinations may not be appropriate for the assessment of individuals with lower levels of education[3].

In this study, the Purdue Pegboard, visual-motor integration (VMI), and digit span tests were selected, assigned to specific cognitive domains, and were used with people with lower education levels. The Purdue Pegboard is a low-cost, simple method for assessing fine motor skills, which has been shown to have strong test-retest reliability[4]. The Purdue Pegboard can be used to assess the ability of an applicant to perform an activity that requires hand dexterity and involves sensorimotor motor-related regions as well as the basal ganglia striatum[5]. In clinical and research settings, VMI is a widely used and standardized procedure. The VMI Beery-Buktenica Developmental Test is used to examine VMI, visual perception, and motor coordination impairment, which require cerebellar, brainstem, and frontal lobe function[6,7]. The digit span test is a memory and attention function test that requires the learning of digit sequences involving the right dorsolateral prefrontal cortex and superior frontal gyrus[8,9]. Attention and executive function have been linked to backward digit span. Forward digit span, in contrast, has been linked to short-term rote auditory memory[10].

According to several authors in earlier investigations, NB tests are adequately consistent and reliable[11,12]. In Western nations, traditional NB tests and those administered using computers have been established and standardized; however, there has been little research into their reliability in Asian populations[13]. It is acknowledged that various factors associated specifically with Asian populations, for example, race and culture, could influence NB performance[14]. Furthermore, characteristics such as education, age, ethnicity, and cultural background could all influence the consistency of performance[15]. As a result, the detection methods developed for Western cultures need to be translated and modified to accommodate a new cultural context[12]. The modified digit span, Purdue Pegboard, and VMI were created specifically for Thai children who had been exposed to pesticides, but these tests have only been used with children[16,17]. Very few studies have investigated the potential impact of hazards on the cognitive development of Thai adults. To verify the potential future usefulness of NB tests in this population, this study aimed to investigate the test-retest reliability of NB tests, which included those assessing memory, attention, hand-eye coordination, motor speed, and dexterity. This study also examined the impact of demographic data on the testing.

To the best of our knowledge, this the first study of this type in a Thai community that examines the test-retest reliability for the digit span, Purdue Pegboard, and VMI. We also aimed to develop instructions for the administration of the tests facilitating their broader use in the prevention of cognitive decline in the Thai population.

METHODS

Participants

To determine the test-retest reliability of these NB tests, 30 participants between the ages of 25 and 65 years who were fluent in Thai and had no history of intellectual, mental, physical, or cognitive impairment participated in the tests. To reduce the risk of measurement error caused by transitory swings in anxiety, motivation, attention, and exhaustion, participants were instructed to have adequate sleep, avoid drug and alcohol use, and limit smoking on the days prior to the tests. The study was thoroughly explained to participants who then completed the consent form. The study was approved by the Ethics Committee of Chiang Mai University Faculty of Medicine's Research Ethics in Humans (COM-2563-07707).

NB tests

Three non-computerized NB tests were delivered by an examiner, namely, digit span, Purdue Pegboard, and VMI. These tests, which were originally part of the Behavioral Assessment and Research System (BARS), have been modified and enhanced for use with children aged 5 years and older[18,19]. It has been translated into other languages, including Thai, and was piloted by a research team before being used in previous study. A bilingual co-investigator translated all test

stimuli and standardized instructions into Thai and then back-translated them[17]. All examiners were trained in administration by a psychologist (psychometric testing) and experienced investigators.

Digit span test

The process for the digit span forward and backward tasks was modified in this version, and the number order was pseudo-randomized to avoid repetition. There are two sections to this task. The initial step is to digit span forward, which involves repeating numerals in the same order as they were received. At a rate of roughly one per second, the investigator pronounces a succession of digits. The list is then repeated by the participant in the same sequence. Following that, participants must reverse or backward order digits in the digit backward test.

In the digit span forward, the length of sequences gradually increases. The test begins with a two-number sequence and gradually increases to nine. Different sets of digit span forward tasks were employed in Trial 1 and Trial 2. Trial 1 is completed before Trial 2 to test the cognitive flexibility component. The digit span backward task is approached in the same way as the digit span forward task, with the exception that the longest list has eight items. The span scores are represented by five different values. The sum of the accurate digit span forward and backward responses from Trial 1 and Trial 2 is initially two values. In this study the maximum digit length achieved by each participant, specifically the longest sequence that they could correctly answer in both digit span forward and backward, was determined. Finally, the total subtest score was calculated by summing the results of both the forward and backward digit span tasks.

Purdue Pegboard test

In the Purdue Pegboard (Lafayette Instrument Company, USA) test, the investigator followed the testing procedure as described in the Purdue Pegboard test user instructions for Model 32020A. There are three components to the test, namely, right hand, left hand, and both hands. Two vertical rows of 25 small holes run down the center of the exam board, with 4 cups across the top. Each of the 2 exterior cups has 25 pins. The processes used for administration and scoring the test were as follows: participants must use their dominant hand first, then their non-dominant hand to place as many pins as possible along each row within 30 s. This completes the right-hand and left-hand subtests. In the both hands subset, the test is bimanual and participants use both hands at the same time to place as many pins as possible down both rows in 30 s. The number of pairs of pins placed in 30 s determines the score for this subtest. For each subtest, the individual was instructed to carry out the test twice. The average number of pins placed in the allocated time was used to calculate the score for each of these subtests.

VMI test

The Beery-Buktenica developmental test of visual-motor integration (VMI-6th) was the VMI tool used in this study[20]. In this paper-and-pencil test, participants must copy increasingly complicated designs. The full format test consists of 30 items that use geometric shape drawing to assess VMI. The Beery VMI was typically given in a single session and took 10–15 min to complete[21]. For each test score, a summary of raw scores and standardized scores was calculated, and the findings were presented and analyzed in terms of both raw and standardized scores.

Procedures

The participants were evaluated twice at an interval of 2 weeks. All NB tests were carried out in a quiet setting, with just one adult being evaluated at a time. An investigator gave the participants instructions at each test station. A well-trained investigator monitored the practice tests to ensure that the participants understood the instructions. The investigator also offered encouragement in order to keep the participant's attention on the examination.

To reduce inter-investigator variation in the test administration procedure, and also the impact of participant judgment on scoring, the same instructor evaluated and scored all NB tests. In both trials, participants were given similar fundamental ambient conditions, such as a comfortable room temperature, enough lighting, and a quiet setting.

Statistical analysis

The statistical analysis was carried out using SPSS for Windows. Data pertinent to demographics were analyzed using frequency, mean, standard deviation, and range. All parameters were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The mean values and standard deviation of each variable were calculated. Pearson product-moment correlations were calculated and utilized to investigate test-retest reliability. Recommendations regarding five reliability cutoff values made in a previous study were used as guidelines for this study[22]. These cutoff values were as follows: coefficients

of 0.10 and below represent negligible correlation, coefficients between 0.10 and 0.39 represent a weak correlation, coefficients between 0.40 and 0.69 represent a moderate correlation, coefficients between 0.70 and 0.89 represent a strong correlation, and coefficients of 0.90 and above are considered very strong. Linear regression was used to analyze the effect of demographic data such as age, gender, education, income, and occupation. A p-value <0.05 was accepted as statistically significant.

RESULTS

Descriptive analysis

Table 1 shows the demographic information for all participants. The majority of the participants were female and married, with a mean age of 51.4±13.5 years. The majority of participants were Thai (90%) and had at least finished primary school as their level of education (66.7%). The three most common occupations among the participants were an employee (29.7%), housewife (24.3%), and farmer (18.9%), with monthly income ranging from 4,500 to 10,000 Baht.

Test-retest reliability

Table 2 shows the mean values, standard deviations, and correlation coefficients for the subtests of the test-retest reliability administration. Based on the criteria described by Schober et al.[22], reliability estimates for each subtest ranged from moderate (0.40–0.69) to strong (0.70–0.89). All reliability correlation coefficients were positive and greater than zero. The test-retest reliability correlation coefficients of subtests were 0.66 ($p<0.001$) to 0.81 ($p<0.001$) for the digit span subtests. For the Purdue Pegboard, the test-retest reliability correlation coefficients of subtests were 0.73 ($p=0.005$) to 0.78 ($p<0.001$). Finally, the test-retest reliability correlation coefficients for the VMI raw score were 0.72 ($p<0.001$) and 0.63 ($p<0.001$) for VMI standard score.

Effect of demographic characteristics on NB tests

Age was negatively associated with performance on the preferred hand and both hands only in Purdue Pegboard (β±SE=-0.09±0.03 and -0.08±0.03, respectively). Education, gender, income, and occupation were not associated with the subtests of Purdue Pegboard. Performance on digit span and the VMI was not significantly affected by age, education, gender, income, or occupation. The results of these analyses are presented in Table 3.

Table 1. Demographic data of participants (n=30).

Parameters		n (%)	Mean±SD (min–max)
Gender	Male	6 (20.0)	
	Female	24 (80.0)	
Status	Single	3 (10.0)	
	Married	20 (66.7)	
	Divorced	7 (23.3)	
Race	Thai	27 (90.0)	
	Other	3 (10.0)	
Occupation	Farmer	7 (18.9)	
	Employee	11 (29.7)	
	Housewife	9 (24.3)	
	Merchant	3 (8.1)	
Health	Underlying disease	4 (13.3)	
	No underlying disease	26 (86.7)	
Income (baht)	<4,500	11 (16.7)	
	4,500–10,000	15 (50.0)	
	10,000–15,000	1 (3.3)	
	15,000–20,000	3 (10.0)	
Education	Primary education	20 (66.7)	
	Secondary education	9 (30.0)	
	Higher education	1 (3.3)	
Dominant hand	Right	27 (90.0)	
	Left	3 (10.0)	
Age			51.4±13.5 (25.0–65.0)
Weight (kg)			64.9±15.8 (44.0–104.0)
Height (m)			1.6±0.1 (1.5–1.7)
Body mass index			26.1±0.9 (18.7–35.6)
Systolic blood pressure (mmHg)			126.3±9.8 (107.0–140.0)
Diastolic blood pressure (mmHg)			75.8±8.6 (63.0–96.0)
Heart rate (bpm)			85.7±11.5 (66.0–108.0)

SD: standard deviation.

Table 2. Test-retest reliability of digit span, Purdue Pegboard, and visual motor integration tests (n=30).

Studied tests	Subtest	1st	2nd	Correlation	
		Mean±SD	Mean±SD	r	p-value
Digit span	Correct score digits forward	10.00±2.46	10.20±2.16	0.81*	≤0.001
	Maximum digits forward	6.50±1.28	6.87±1.11	0.68*	≤0.001
	Correct score digits backward	3.63±1.29	3.60±1.47	0.66*	≤0.001
	Maximum digits backward	3.10±0.84	3.07±0.83	0.68*	≤0.001
	Total correct score	13.63±3.18	13.80±3.03	0.75*	≤0.001
Purdue Pegboard	Preferred hand	14.12±1.96	14.82±1.69	0.78*	≤0.001
	Non-preferred hand	13.68±1.61	13.82±1.79	0.76*	≤0.001
	Both hands	11.65±1.62	11.57±1.87	0.73*	0.005
Visual motor integration	Raw score	22.00±2.70	22.20±2.85	0.72*	≤0.001
	Standard score	74.90±14.65	74.87±14.96	0.63*	≤0.001

SD: standard deviation. *p<0.001.

Table 3. Effect of demographic data on digit span, Purdue Pegboard, and visual motor integration tests (n=30).

Studied tests	Subtest	β±SE (95%CI)				
		Age	Education	Gender	Income	Occupation
Digit span	Correct score digits forward	-0.01±0.04	0.88±1.08	1.48±1.12	0.09±0.54	0.55±0.46
		(-0.10, 0.08)	(-1.34, 3.10)	(-0.84, 3.79)	(-1.02, 1.19)	(-0.40, 1.51)
	Maximum digits forward	-0.01±0.02	0.29±0.55	0.68±0.57	0.09±0.27	0.31±0.24
		(-0.05, 0.04)	(-0.84, 1.42)	(-0.50, 1.86)	(-0.48, 0.65)	(-0.15, 0.83)
	Correct score digits backward	-0.40±0.03	-0.34±072	0.35±0.75	0.09±0.36	0.63±0.31
		(-0.10, 0.02)	(-1.82, 1.13)	(-1.19, 1.88)	(-0.64, 0.83)	(-0.01, 1.26)
	Maximum digits backward	-0.02±0.02	-0.08±0.40	0.28±0.42	0.13±0.20	0.33±0.17
		(-0.05, 0.02)	(-0.91, 0.75)	(-0.59, 1.14)	(-0.28, 0.54)	(-0.02, 0.69)
	Total correct score	-0.05±0.56	0.54±1.44	1.82±1.50	0.18±0.72	1.18±0.62
		(-0.17, 0.07)	(-2.43, 3.50)	(-1.26, 4.91)	(-1.30, 1.66)	(-0.09, 2.45)
Purdue Pegboard	Preferred hand	-0.09±0.03	-0.15±0.68	0.87±0.71	0.17±0.34	0.35±0.29
		(-0.14, -0.03)*	(-1.56, 1.25)	(-0.59, 2.34)	(-0.53, 0.87)	(-0.25, 0.96)
	Non-preferred hand	-0.09±0.03	-0.43±0.78	0.12±0.82	-0.13±0.39	0.34±0.34
		(-0.16, -0.03)	(-2.04, 1.19)	(-1.56, 1.81)	(-0.94, 0.67)	(-0.32, 1.04)
	Both hands	-0.08±0.03	-0.14±0.83	1.11±0.87	-0.05±0.41	0.52±0.36
		(-0.15, -0.01)+	(-1.85, 1.58)	(-0.68, 2.89)	(-0.91, 0.80)	(-0.22, 1.26)
Visual motor integration	Raw score	-0.09±0.05	0.21±1.28	-1.07±1.42	0.02±0.67	0.63±0.58
		(-1.19, 0.01)	(-2.85, 2.44)	(-3.99, 1.86)	(-1.37, 1.41)	(-0.58, 1.83)
	Standard score	-0.14±0.28	-0.06±7.61	-3.42±8.43	-0.02±3.99	2.77±3.47
		(-0.73, 0.44)	(-15.76, 15.64)	(-20.82, 13.99)	(-8.26, 6.28)	(-4.39, 9.23)

Values are presented as unstandardized β and standard error (SE), confidence interval (95%). *p<0.001; +p<0.05.

DISCUSSION

This study aimed to investigate the test-retest reliability of NB tests in a population of Thai adults. The aspects of the tests focused on were memory, attention, hand-eye coordination, motor speed, and dexterity. This study also examined the impact of demographic characteristics on the tests. Our results showed a significant positive correlation in the test-retest of digit span, Purdue Pegboard, and VMI. There were moderate to strong correlation coefficients (r=0.63–0.81) in the digit span and VMI, while in the Purdue Pegboard, correlation coefficients were strong (r=0.73–0.78). Straub et al.[23] suggested that acceptable reliability levels for a pilot study should be 0.60 or above.

The results of digit span tests were consistent with the study by Waters and Caplan[24], who found that the reliability for backward digit span test is moderate (r=0.65). In addition, the reliability of the digit span was statistically significantly in the medium to high range for most of the Pearson's correlation coefficients[24]. However, all of the correlations from these findings were higher than those of previous available studies. Rohitrattana et al.[17] found that the reliability coefficients for maximum digits forward and backward in Thai children were 0.41 and 0.48, respectively. It is possible that children aged 6–8 years have lower levels of attention control than adults due to their susceptibility to auditory distraction[25,26]. Farahat et al.[27] found that the reliability coefficients for forward and backward digit span in healthy population were 0.35 and 0.62, respectively. The low reliability coefficients might be due to the differences in measurement between the verbal and computerized digit span tests. Lower reliability in computerized digit span tests might be a result of a decline in visuospatial processes[28].

With regard to the impact of demographic characteristics on the digit span, our findings suggested that demographic characteristics had no effects on the data. However, the results contradicted other previous studies[29-32]. Zimmermann et al.[29] and Ostrosky-Solis and Lozano[30] suggested that education and cultural context affected both forward and backward digit span tests. Farahat[31] claims that participants with a higher degree of education had much higher digit span ability in both forward and backward spans. To add weight to this finding, Peña-Casanova et al.[33] reported that age, education level, and language had an effect on the digit span. The probable reason that the demographic characteristics had no effects on the digit span in this population of Thai adults is that most participants in this study had finished primary school; therefore, there were more likely to have the same level of performance in the digit span test[34]. Another possibility is that the study population were culturally and linguistically homogeneous. Therefore, this study suggested that the digit span may be used to test memory and attention in the Thai adult population without impacts of demographic characteristics.

When considering the reliability for the VMI test, our findings found that the reliability was 0.63 for the standard scores and 0.72 for the raw scores. The standard score reliability of this study was higher than a prior study that found a test-retest reliability intraclass correlation coefficient (ICC) value of 0.58[35]. However, this result was similar to the correlation coefficients for totally correct VMI previously reported[17]. The raw scores from the VMI test in our study were shown to be reliable (r=0.72). Brown et al.[36] reported a strong correlation (r=0.77) for the test-retest reliability for the Development Test of the VMI (DTVMI) and Bahk et al.[37] found 0.79 correlation coefficients for VMI-6th. In our results, the correlation coefficients for both the VMI standard score and the raw score were lower than those found in previous studies. It is possible that the length of interval testing had an effect on pattern memory. Beery and Beery[38] showed a test-retest reliability of 0.88 for 1-week interval testing, while our study investigated 2-week interval testing. This indicates that practice effects with shorter interval duration may enhance sensorimotor integration[39].

Another possibility is that racial, cultural, or ethnic variance might affect the reliability correlation[38,40]. In Thailand, the Beery VMI test was utilized in a prior study to assess hand-eye coordination in children, but this study employed it in adults. Before using this test in a new country, it should be pilot tested to guarantee that it is reliable and valid for that culture[19]. Our results suggested that demographic characteristics had no effects on the Beery VMI test. Beery and Beery[38] stated that the standardized scores were the cumulative frequency distributions of the raw scores created for each age group. Leading test experts and professional organizations, however, stated that it should be used with caution.

With regard to the Purdue Pegboard test, our results were consistent with the study by Rohitrattana et al.[17], who found that the Pearson's correlation reliability coefficients for assessing Thai children showed a strong correlation (r=0.71–0.72). However, all of these correlations from our finding were higher than those of previous studies. It is possible that the number of trials per subtest had an effect on the reliability. Buddenberg and Davis[41] found that the correlation coefficients ranged from 0.37 to 0.82 for one-trial administrations

over intervals of 1–2 weeks. Doyen and Carlier[42] tested for three-trial administrations and found that the reliability ranged from 0.81 to 0.89. Our results, therefore, suggested that the reliability of subtests by two-trial administrations was greater and still acceptable when compared to previous studies.

Our results found that age had an effect on the Purdue Pegboard in the preferred hand and in both hands. These results agreed with the study by Rohitrattana et al.[17], who found that higher scores of Purdue Pegboard correlated with higher age. These results were also consistent with a study by Brito and Santos-Morales[43] who found that age had an effect on motor speed and dexterity performance, even in samples of children. Gur et al.[44] also found that motor speed and dexterity were negatively associated with age. The decline in performance was related to frontotemporal function with age. Decline in dexterity was caused by slow movement and kinematic changes[45].

These tests are applicable to a broader population because demographic characteristics have no effect on the tests. Importantly, this is the first study in Thai adult population and shows a high reliability for the use of the digit span, Purdue Pegboard, and VMI. They could be applied in investigations into potentially hazardous occupations, for example, pesticide-related jobs. However, there are some limitations. The lack of normative data was found for the digit span subtests and a standard score for the VMI test. As a result, we were unable to demonstrate concurrent validity in our study. Although these findings can be used to inform and enhance future studies into cognitive behavior by using the digit span, Purdue Pegboard, and VMI tests, the sample sizes are rather small. Therefore, larger sample sizes in future research are needed.

This study showed that NB tests, specifically digit span, Purdue Pegboard, and VMI, had moderate to strong reliability. All tests in our study can be applied to enable the clinical assessment of working memory, attention, hand-eye coordination, motor speed, and dexterity in the Thai adult population. Interestingly, demographic characteristics had no effects on all tests, with the exception of the Purdue Pegboard test. Therefore, further studies are needed to assess the validity of NB tests and investigate in large sample sizes.

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Authors' contributions. AT: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing – original draft preparation; RS: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing – review and editing; JR: conceptualization, data curation, methodology, resources, supervision, validation, writing – review and editing; ST: conceptualization, methodology, resources, supervision; SH: conceptualization, methodology, supervision; KW: methodology.

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Original Article

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Neuropsychiatric symptoms of dementia and caregivers' burden:
a study among Indian caregivers

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ABSTRACT. Dementia is considered a most serious and disabling condition, affecting both the individual suffering from it and their caregiver. **Objective:** The study aimed to evaluate the relationship between neuropsychiatric problems of dementia and caregiver burden. **Methods:** A total of 138 caregivers of people with dementia participated in this cross-sectional study. The caregivers completed the questionnaires containing sociodemographic information as well as neuropsychiatric problems of dementia and caregiver burden. **Results:** The findings showed that all of the care-recipients were suffering from some kind of neuropsychiatric symptoms, the most common being apathy, anxiety, motor disturbance, and hallucination. Out of 12 symptoms, 11 were significantly associated with caregivers' burden. The most important finding is that the severity of neuropsychiatric symptoms is highly responsible for severe caregivers' burden. **Conclusions:** The identification of neuropsychiatric symptoms of dementia that influence caregiver burden is very critical for both caregivers' and care-recipients' health perspective. These findings can also be utilized to create care settings for demented people and help determine policies in the future.

Keywords: Dementia; Neuropsychiatry; Caregivers; Tumor Burden.

SINTOMAS NEUROPSIQUIÁTRICOS DE DEMÊNCIA E SOBRECARGA DOS CUIDADORES: UM ESTUDO ENTRE CUIDADORES INDIANOS

RESUMO. A demência é considerada a condição mais grave e incapacitante que afeta ao mesmo tempo tanto o indivíduo que a sofre como o seu cuidador. **Objetivo:** O estudo tem como objetivo avaliar a relação entre problemas neuropsiquiátricos de demência e sobrecarga do cuidador. **Métodos:** 138 cuidadores de pessoas com demência participaram do estudo transversal. Os cuidadores preencheram os questionários contendo informações sociodemográficas, bem como problemas neuropsiquiátricos de demência e sobrecarga do cuidador. **Resultados:** Observou-se que todos os atendidos apresentavam algum tipo de sintoma neuropsiquiátrico; os mais comuns foram apatia, ansiedade, distúrbios motores e alucinações. Com exceção de um sintoma, 11 outros sintomas foram significativamente associados à sobrecarga dos cuidadores. O achado mais importante é que a gravidade dos sintomas neuropsiquiátricos é altamente responsável pela sobrecarga dos cuidadores. **Conclusões:** A identificação de sintomas neuropsiquiátricos de demência que influenciem a sobrecarga do cuidador é muito importante para a perspectiva de saúde dos cuidadores e dos receptores de cuidados. Essas descobertas também podem ser utilizadas para criar ambientes de atendimento para pessoas com demência e ajudar a determinar políticas no futuro.

Palavras-chave: Demência; Neuropsiquiatria; Cuidadores; Carga Tumoral.

INTRODUCTION

The upswing in life expectancy and the aging of the population integrally favors the occurrence of many diseases in which age is a key factor, such as dementia. Dementia has been a global concern in recent years, as increase in elderly population, especially over 80 years old, would help escalate the number of dementia individuals in near future. Predictions indicated that the number of people living with dementia would rise from 47 million in 2015 to 75 million in 2030 and 135 million in 2050[1,2]. India is one of the countries that would be heavily impacted by dementia in near future. Moreover, while having the world's second

This study was conducted by the Group of Biological Anthropology Unit, Kolkata, West Bengal, India.

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largest population, India has the fastest growing elderly population. It has previously been confirmed that dementia mostly affects the elderly and risk of having dementia doubles every 5 year for those older than 65 years and almost 40% for those aged 85 years and older[3]. In India, the number of people with dementia increases dramatically. According to a report, it has been predicted that by the year 2036, there would be 20,000–40,000 people living with dementia, even in states like West Bengal, India[4].

Dementia is a gradual, widespread, and irreversible cognitive impairment that results in memory and other higher cognitive abilities loss. It is one of the conditions which severely impairs the capacity of an individual to carry out the activities of daily life, diminishing quality of life and autonomy of the individual who is experiencing dementia. It also causes changes in behavior and personality, which have a significant impact on the patient's functional ability. As a result, the demented individual became dependent upon others with the progression of disease[5].

The care of the demented person is usually provided by the family members. Therefore, the health of caregivers who care for demented people needs to be examined as caregiver burden might affect caregivers' familial bonds, social relationships, and physical health, leading to psychological morbidity in caregivers and early institutionalization of patients. The majority of persons with dementia remain at home, and family members, mainly females (e.g., wife, daughter, sister, and daughter-in-law), are responsible for their daily care, which continues year after year[6]. Caregiving is physically and emotionally arduous as they have to provide their maximum time to their care-recipients and are unable to manage time for their leisure activities. Caregiver burden is a complex reaction to physical, psychological, emotional, social, and economic stressors connected with the caregiver's care experience[7]. It was also reported that caregiver burden among main caregivers is an independent risk factor for higher death rates[8].

A growing body of research compares between experience of dementia caregiving and caregiving for other types of dependence of family members. It was found that dementia caregivers experience tremendous burden compare to caregiving to the other types of dependence. Dementia caregiving is more time-consuming and had detrimental impact on caregivers' emotional and social life as well. Caregivers also experienced deterioration of their mental as well as physical health at the same time[9-12]. Several studies have found that being a dementia caregiver causes psychological stress and mental health difficulties. It was also notable that caregivers' health plays an essential influence on a patient's institutionalization[13]. Many studies also reported that there are other several factors that may be linked with caregivers' burden, such as age and gender of the caregiver, relationship with care-recipients, family history, types of work required, and duration of care hours and years[14-16].

Indeed, literature has also revealed that the neuropsychological symptoms of dementia are prevalent and important issues that have immense impact on the quality of life of both patients and their caregivers. These symptoms do prevail throughout the course of dementia and are basically a wide range of psychological responses and typical behavior[17]. According to Finkel et al, neuropsychiatric symptoms are characterized as "symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia"[18]. In contrast to cognitive symptoms, neuropsychiatric symptoms did not show a linear pattern of deterioration. Because of the unexpected and unruly nature of the neuropsychiatric symptoms, it is very difficult to manage. As a consequence of these symptoms, caregivers may experience higher levels of psychological health problems[19]. Several studies have found that early-stage symptoms of dementia and significant increases in symptoms are the predictors of caregiver burden over time[16,20]. A research found that wandering is the most prevalent symptom among people with dementia who experienced neuropsychiatric problems. It also has been linked to fall, injuries, and disorientation. Therefore, caregivers started worrying about the results of these incidents, which might increase their stress level[21,22]. It was found that among many other factors, these symptoms are closely associated with caregivers' burden[23].

In India, dementia is not considered as medical disorder that needs proper treatment in proper time, but rather a natural process of aging and remains as a hidden problem. Due to a lack of awareness of symptoms and progressive nature of dementia, people did not give serious attention to the condition. The challenges involved with dementia caregiving are still ignored, and gerontological research in India had not paid enough attention to them. Therefore, there is less Indian research evidence on dementia caregivers' burden and its link to dementia-related neuropsychiatric problems. This study aimed to better understand (1) the neuropsychiatric symptoms of dementia present among a group of demented individual and (2) the link between neuropsychiatric problems and the burden experienced by their caregivers.

METHODS

Selection of study participants

This is a cross-sectional study carried out in West Bengal, India. The information of the caregivers was obtained from a nongovernmental organization. A total of 450 caregivers were contacted through phone and explained the purpose of this study. Out of this, 183 caregivers who were volunteered to participate were selected. The inclusion criteria were as follows:

1. Caregiver must be a primary family caregiver of a demented person;
2. Caregiver must be an adult;
3. Caregiver should have at least 1 year of experience providing care; and
4. Care-recipient must be clinically diagnosed with dementia.

Finally, a total of 138 caregivers who met the study criteria were recruited.

Ethical clearance

The Institutional Review Board of Indian Statistical Institute in Kolkata reviewed the participant information document and the applicable informed consent form and provided an ethical clearance certificate. The majority of the participants were fluent in Bengali and English. However, a Bengali version of all instruments, fully translated by experts, was also provided to those who did not speak English well. To ensure authenticity, the same person answered each variation of the same question.

Interview procedure

Researcher visited each and every residence as per caregivers' convenience. The care-recipient's medical report was initially reviewed. Then the study objectives and consent form were given to them. After signing the consent form, data collection procedure was started. Participants' interview lasted for an hour, and selected questionnaires were given to them to fill up.

Measures

Pre-tested questionnaire was developed to elicit the sociodemographic profile of caregivers and care-recipients. It included questions about the caregivers' sex, age at the time of interview, education, occupation, marital status, relationship with care-recipients, family types, and monthly household expenditure [in Indian Rupees (INR)]. Information on care-recipient's sex, age at the time of interview, education, type of dementia, and duration of suffering from dementia was also collected.

Dementia care-recipients' neuropsychiatric symptoms, severity, and caregivers' burden were assessed with the Neuropsychiatric Inventory (NPI)[24]. The NPI is a structured interview with a caregiver who is in close contact with people with dementia. It is evaluated based on 12 neuropsychiatric domains related to dementia, namely, delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. The caregivers were asked to fill in the questionnaire prepared on the basis of their experiences with the symptoms of the care-recipients. In case of the absence of any particular symptom of care-recipient, the subsequent query was skipped and moved to the next question. While in the presence of the abnormal behaviors of care-recipient, the behavioral domain is then explored with other sub-questions that provide more detailed information on that particular neuropsychiatric disturbance. In these sub-questions, the caregiver is asked to rate the frequency of the symptoms of that domain on a scale of 1–4 (1=occasionally, 2=once a week, 3=several time in a week, 4=very frequently) as well as their severity on a scale of 1–3 (1=mild, 2=moderate, 3=severe). Caregiver's burden is rated on a 6-point scale, with 0=no burden, 1=minimal, 2=mild, 3=moderate, 4=severe, and 5=extreme. The total score for each domain is calculated by multiplying the frequency by the severity. A total score is calculated by adding all the domain scores. Severity of dementia was categories as mild, moderate, and severe. Similarly, caregiver burden score for each neuropsychiatric domain was obtained and a total burden score was calculated by adding all the 12 domains' burden scores.

Statistical analysis

Descriptive statistics were used to demonstrate the sociodemographic features of the caregivers and care-recipients as well as care-recipients' neuropsychiatric problems. Chi-square test was performed to determine whether or not neuropsychiatric symptoms of dementia are associated with caregiver burden. A logistic regression analysis was carried out to evaluate the relationship between neuropsychiatric symptoms of dementia and caregiver burden to quantify the power of the relationship. A p-value of ≤ 0.05 was considered statistically significant for all inferential statistics. Data were analyzed using Power of Advanced Statistical Analysis version 18.0 (IBM Corp.).

RESULTS

Sociodemographic characteristics of the caregivers and care-recipients are shown in Table 1. Most of the

Table 1. Information of caregivers and care-recipients.

Caregivers (n=138)			
Variables	**Category**	**n**	**%**
Gender	Male	35	25.4
	Female	103	74.6
Age group (in years)	<35	6	4.3
	36–55	37	26.8
	56+	95	68.8
	Mean age (years±sd)	61.35±13.86	
Marital status	Single	23	16.7
	Married	115	83.3
Education	Up to secondary	25	18.1
	Graduate	73	52.9
	Postgraduate and above	40	29.0
Occupation	Employed full time	10	7.3
	Employed part time	33	23.9
	No employment	95	68.8
Relationship with care-recipient	Wife	54	39.1
	Husband	24	17.4
	Daughter	26	18.8
	Son	8	5.8
	Others*	26	18.8
Monthly household expenditure (INR)	≤26,000	39	28.3
	26,001–50,000	74	53.6
	≥50,000	25	18.1
Care-recipients (n=138)			
Gender	Male	69	50.0
	Female	69	50.0
Age group (in years)	≤60	4	2.89
	61–70	31	22.46
	71–80	66	47.83
	>80	37	26.82
	Mean age (years±sd)	75.54±7.89	
Education	Up to secondary	21	15.2
	Graduate	80	58.0
	Postgraduate and above	37	26.8
Duration of suffering (in years)	≤5	76	55.1
	>5	62	44.9
Types of dementia	Alzheimer's	104	75.37
	Vascular dementia	24	17.41
	Lewy body dementia	2	1.44
	Frontotemporal dementia	6	4.34
	Others	2	1.44

*Brother, sister, in-laws.

caregivers were above 55 years of age (68%), female (74%), and married (83%). The majority of the caregivers were graduate (82%), unemployed, and were mostly involved in household activities (68%). Spousal relationship (56%) was the most common form of relationship found between caregivers and care-recipients. About 53% had reported monthly household expenditure ranging between Rs. 26,000 and Rs. 50,000. In contrast, the number of people affected by dementia was same in each sex (i.e., 50% each for male and female). Mean age of the care-recipients was 75 years. Majority (58%) of the recipients were graduate. More than 55% of the care-recipients were suffering from dementia for less than 5 years. Alzheimer's type of dementia was the most common type found among care-recipients, followed by vascular dementia. Figure 1 shows the neuropsychological symptoms of the care-recipients. The most prevalent symptom among the care-recipients was apathy (84.8%), followed by anxiety (73.2%), motor disturbances (70.3%), and hallucinations (67.4%).

Table 2 shows the association between care-recipients' neuropsychiatric symptoms and caregivers' level of burden. It was observed that overall 60% of the caregivers experienced a severe level of burden. More than 50% of the caregivers who provided care to recipients with severe level of apathy experienced severe level of burden. In addition, more than 30% of the caregivers who cared for demented persons having severe level of hallucination, anxiety, motor disturbance, and night behavior experienced higher level of burden.

Table 3 shows the relationship between care-recipients' neuropsychiatric symptoms and caregivers' level of burden. It was observed that caregivers experienced severe level of burden while providing care for persons with serious neuropsychiatric symptoms. It was also shown that caregivers' who provided care for persons with severe level of delusion, depression, anxiety, apathy, disinhibition, irritability, motor disturbances, and night behavior are likely to experience higher level of burden than caregivers who provided care to the person with moderate-to-mild level of neuropsychiatric symptoms.

Table 4 shows the association between care-recipients' neuropsychiatric problems and caregivers' burden. It was found that caregivers (66.67%) who look after recipients with severe neuropsychiatric problems have higher level of burden. Significant association was found between care-recipients' neuropsychiatric problems and caregivers' level of burden.

Table 5 shows the relationship between care-recipients' neuropsychiatric problems and caregivers' burden. It was found that caregivers who provide care

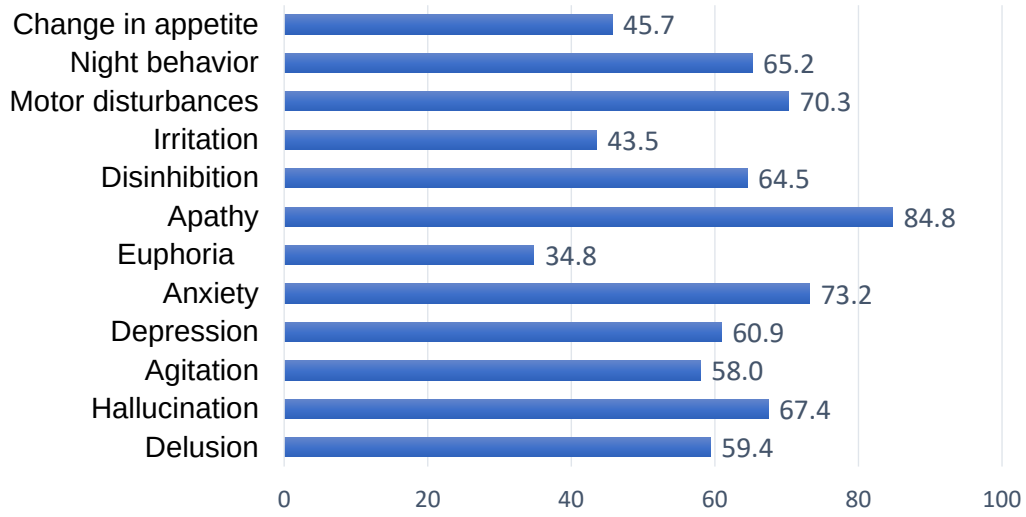

Figure 1. Graphical representation of care-recipients' neuropsychiatric symptoms.

to recipients with severe neuropsychiatric problems experienced higher level of burden than those who provided care to recipients with mild neuropsychiatric problems. Significant relationship was found between care-recipients' neuropsychiatric problems and caregivers' burden.

DISCUSSION

The literature on the health of caregivers' comes from all across the world. Noncommunicable disorders such as dementia are developing as a new health hazard as the population ages rapidly. As a result of the nature of dementia, persons suffering from it gradually lose their cognitive and functional capacities, becoming increasingly reliant on their family members for daily activities. However, studies on the neuropsychiatric issue of dementia and its impact on caregivers are rarely conducted in India. Therefore, a group of caregivers who provided care for a demented family member were chosen for this cross-sectional study to assess their degree of burden in relation to several neuropsychiatric issues associated with dementia.

Neuropsychiatric symptoms in dementia are more prevalent when dementia is well progressed. These symptoms are responsible for an individual's effective functional impairment, dependence upon others, and increased caregiver burden. These issues can be present months or years before its actual diagnosis. These kind of symptoms have been observed to be more stressful to the caregivers than cognitive impairments[19]. This study observed that neuropsychiatric problems were present among all the care-recipients and it created burden on their caregivers. Overall, 12 neuropsychiatric problems were assessed, such as delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritation, motor disturbance, night behavior, and change in appetite. It was found that apathy (84.8%) was the most common symptom found among care-recipients, followed by anxiety (73.2%), motor disturbances (70.3%), hallucination (67.4%), and night behavior (65.2%). A Brazilian study[25] found that majority (91%) of the dementia individuals exhibit more than one neuropsychiatric symptoms, among which, agitation, aberrant motor behavior, and apathy were more prevalent. Various research studies evaluating the prevalence of neuropsychiatric symptoms in dementia patients have yielded varied results. The most prevalent symptoms in dementia patients were apathy, sadness, irritability, agitation, and anxiety, whereas euphoria, hallucinations, and disinhibition were the least common. The most major symptoms were apathy and anxiety, which also corroborate with our present study[26].

Studies found that specific neuropsychiatric problems such as night behavior and agitation were more closely related to caregivers' burden[27,28]. Our findings differ slightly from the previous study. Changes in outcomes may be attributable to differences in the characteristics of the participants group and the evaluation techniques. According to our findings, about 52% of caregivers had experienced higher degree of burden while caring for demented care-recipients with severe apathy. Aside from apathy, motor disturbance, night behavior, and anxiety all had a greater influence on

Table 2. Association between care-recipients' neuropsychological symptoms and caregivers' burden.

Symptoms	Categories	Level of burden		Chi-square	p-value
		Mild	Severe		
Delusion	Mild	35 (25.36)	37 (26.81)	30.823	<0.001*
	Moderate	3 (2.17)	19 (13.78)		
	Severe	2 (1.45)	42 (30.43)		
Hallucination	Mild	32 (23.19)	35 (25.36)	23.806	<0.001*
	Moderate	3 (2.17)	12 (8.70)		
	Severe	5 (3.62)	51 (36.96)		
Agitation	Mild	31 (22.46)	47 (34.06)	10.382	0.006*
	Moderate	3 (2.17)	24 (17.39)		
	Severe	6 (4.35)	27 (19.57)		
Depression	Mild	32 (23.19)	48 (34.78)	12.094	0.003*
	Moderate	4 (2.90)	16 (11.59)		
	Severe	4 (2.90)	34 (24.64)		
Anxiety	Mild	27 (19.57)	21 (15.22)	26.026	<0.001*
	Moderate	4 (2.90)	16 (11.59)		
	Severe	9 (6.52)	61 (44.20)		
Euphoria	Mild	77 (55.80)	33 (23.91)	0.952	0.658*
	Moderate	3 (2.17)	13 (9.42)		
	Severe	4 (2.90)	8 (5.80)		
Apathy	Mild	14 (10.14)	15 (10.87)	9.005	0.011
	Moderate	7 (5.07)	11 (7.97)		
	Severe	19 (13.78)	72 (52.17)		
Disinhibition	Mild	26 (18.84)	36 (26.09)	9.342	0.009
	Moderate	8 (5.80)	31 (22.46)		
	Severe	6 (4.35)	31 (22.46)		
Irritability	Mild	33 (23.91)	54 (39.14)	9.175	0.010*
	Moderate	2 (1.45)	11 (7.97)		
	Severe	5 (3.62)	33 (23.91)		
Motor disturbances	Mild	30 (21.74)	18 (13.04)	40.166	<0.001*
	Moderate	2 (1.45)	17 (12.32)		
	Severe	8 (5.80)	63 (45.65)		
Night behavior	Mild	31 (22.47)	33 (23.91)	22.047	<0.001*
	Moderate	3 (2.17)	17 (12.32)		
	Severe	6 (4.35)	48 (34.78)		
Change in appetite	Mild	35 (25.36)	54 (39.13)	13.249	<0.001*
	Moderate	2 (1.45)	25 (18.12)		
	Severe	3 (2.17)	19 (13.77)		

*Fisher's exact test.

Table 3. Result of binary logistic regression analysis between care-recipients' neuropsychiatric symptoms and caregivers' level of burden.

Symptoms	Category	B	SE	Sig	Exp(B)	95%CI	
						Lower	Upper
Delusion	Severe	2.989	0.761	<0.001	19.865	4.468	88.310
	Moderate	1.790	0.665	0.007	5.991	1.629	22.036
	Mild	Reference					
Hallucination	Severe	2.233	0.529	<0.001	9.326	3.309	26.281
	Moderate	1.297	0.690	0.060	3.657	0.945	14.148
	Mild	Reference					
Agitation	Severe	1.088	0.507	0.032	2.968	1.098	8.020
	Moderate	1.663	0.655	0.011	5.277	1.463	19.036
	Mild	Reference					
Depression	Severe	1.735	0.576	0.003	5.667	1.833	17.515
	Moderate	0.981	0.604	0.104	2.667	0.817	8.708
	Mild	Reference					
Anxiety	Severe	2.165	0.461	<0.001	8.714	3.533	21.493
	Moderate	1.638	0.630	0.009	5.143	1.495	17.686
	Mild	Reference					
Apathy	Severe	1.263	0.452	0.005	3.537	1.458	8.583
	Moderate	0.383	0.610	0.530	1.467	0.444	4.846
	Mild	Reference					
Disinhibition	Severe	1.317	0.515	0.011	3.731	1.360	10.238
	Moderate	1.029	0.473	0.029	2.799	1.108	7.069
	Mild	Reference					
Irritability	Severe	1.395	0.528	0.008	4.033	1.432	11.360
	Moderate	1.212	0.800	0.130	3.361	0.701	16.118
	Mild	Reference					
Motor disturbances	Severe	2.575	0.479	<0.001	13.125	5.130	33.582
	Moderate	2.651	0.805	<0.001	14.167	2.926	68.599
	Mild	Reference					
Night behavior	Severe	2.017	0.500	<0.001	7.515	2.820	20.026
	Moderate	1.672	0.679	0.013	5.323	1.420	19.960
	Mild	Reference					
Change in appetite	Severe	1.412	0.658	0.032	4.105	1.130	14.909
	Moderate	2.092	0.766	0.006	8.102	1.805	36.374
	Mild	Reference					
Constant		-4.764	1.214	<0.001	0.009		

Dependent variable: caregivers' level of burden.

Table 4. Association between care-recipients' overall neuropsychiatric problem and caregivers' burden.

Level of neuropsychiatric problem among care recipients	Caregivers' burden due to neuropsychiatric problems among care recipients			
	Mild	Severe	Chi-square	p-value
Lower	28 (20.29)	6 (4.34)	62.424	<0.001
Higher	12 (8.70)	92 (66.67)		

Table 5. Result of logistic regression analysis using care-recipients' overall neuropsychiatric problems and caregivers' burden.

Dependent variable	Independent variable	Category	B	SE	Wald	Sig	Exp (B)	95%CI	
								Lower	Upper
Level of burden	Constant		2.037	0.307	44.042	<0.001	7.667		
	Neuropsychiatric problems among care-recipients	Severe	3.334	0.545	43.149	<0.001	1.028	0.081	10.233
		Mild	Reference group						

caregiver burden. Like in other research, euphoria was the least predominant neuropsychiatric symptom along with less caregiver burden in our study[29].

Hung et al made an observation among 88 dementia caregivers and found that caregivers' burden increases with higher neuropsychiatric symptoms of recipients[30]. In another study involving 67 caregivers, Matsumoto et al found higher levels of distress in caregivers of patients with more neuropsychiatric symptoms. The results of a Brazilian study also reported that caregivers who provided care for individual with neuropsychiatric issues developed higher risk of depressive disorder, anxiety, insomnia, and related problems[31]. These findings are supported with our study findings. This study revealed that 67% of the caregivers experienced higher level of burden related to neuropsychiatric problems among care-recipients[32]. Most importantly, logistic regression analysis showed that caregivers who provided care to recipients with extreme neuropsychiatric disorders experienced significantly greater burden than those caregivers who gave care to recipients with less conspicuous neuropsychiatric disorders. It was also observed that caregivers' poor mental health condition might result in low quality of life of care-recipients[33]. This study established a link between neuropsychiatric symptoms of care-recipients and caregivers' burden and its impact on care-recipients' quality of life[34].

In India, caregivers' health-related research, particularly for dementia caregivers, is extremely rare. As a result, this cross-sectional study may be regarded as a benchmark endeavor in caregivers' health research in the Indian setting, particularly in terms of dementia caregivers in the eastern region. This study might in fact contribute to the current body of knowledge about caregivers' health difficulties in India. There are some limitations as well. Due to cross-sectional nature of the study, researcher was not able to stay and observe the daily engagement of the caregivers toward their care recipients. The study is also limited to a particular ethnic group.

As the elderly population grows very fast, the demand of this area also increases with time. The identification of neuropsychiatric symptoms of dementia which influence caregiver burden is very crucial for healthy life for both caregiver and care-recipient. Overall, this study explained caregivers' burden associated with neuropsychiatric symptoms. It was clearly evident from the study that caregivers' burden was significantly associated with severity of care-recipients' neuropsychiatric symptoms. Moreover, it was found that caregivers who provided care for person with severe neuropsychiatric issues experienced severe level of burden. These findings can also be used to design the care setting for demented individual and contribute to develop policy in future, thus adding very useful results to the growing body of research.

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Authors' contributions. IB: conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing – original draft, writing – review & editing. SM: conceptualization, methodology, project administration, supervision, writing – original draft.

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Original Article

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The concurrent accuracy of the modified telephone interview for cognitive status and Mini-Mental State Examination tools in detection of cognitive impairment among older adults

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ABSTRACT. Due to the need for face-to-face administration of many cognitive screening tests, it is not always feasible to screen large-scale samples. **Objective:** This study aimed to assess the discriminant validity of the Persian version of Telephone Interview for Cognitive Status (P-TICS-m) and Mini-Mental State Examination in the middle-aged Iranian population. **Methods:** The P-TICS-m and MMSE were administered to 210 randomly selected middle-aged community-dwelling adults who had been registered in the Neyshabur Longitudinal Study on Ageing. Participants also underwent psychological examination by two neurologists to assess cognitive impairment based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)* criteria. To evaluate the discriminant validity of P-TICS-m and MMSE with *DSM-V* criteria, the sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR^+ and LR^-) were calculated. **Results:** The mean age of the participants was 59.6±6.8 years. The TICS and MMSE were highly correlated ($r=0.635$, $p<0.001$). The sensitivity, specificity, PPV, NPV, LR^+, and LR^- to discriminate cognitive impairment were, respectively, 83%, 92%, 68%, 96%, 10, and 0.182 for MMSE and 100%, 13%, 19%, 100%, 1.16, and 0 for TICS-m. The receiver operating characteristic curve analysis results showed no statistically significant differences between P-TICS-m and MMSE. **Conclusions:** Our findings indicate that the TICS-m test can be used as a screening tool instead of the MMSE. Due to the low specificity and low PPV of the TICS-m compared to MMSE, the diagnosis should be confirmed using definitive diagnostic tests when a subject is classified as having cognitive impairment.

Keywords: Interviews as Topic; Cognitive Dysfunction; Dementia; Psychological Tests; Aged; Iran.

A ACURÁCIA CONCORRENTE DA ENTREVISTA TELEFÔNICA MODIFICADA PARA O ESTADO COGNITIVO E AS FERRAMENTAS DE MINIEXAME DO ESTADO MENTAL NA DETECÇÃO DE COMPROMETIMENTO COGNITIVO EM IDOSOS

RESUMO. Diante da necessidade de administração face a face de muitos testes de triagem cognitiva, nem sempre é viável rastrear amostras em grande escala. **Objetivo:** O objetivo deste estudo foi avaliar a validade discriminante da versão persa do Telephone Interview for Cognitive Status (TICS-m) e do Miniexame do Estado Mental (MMSE) na população iraniana de meia-idade. **Métodos:** A versão persa do TICS-m (P-TICS-m) e do MMSE foi administrada a 210 adultos de meia-idade residentes na comunidade e selecionados aleatoriamente, que haviam sido registrados no Neyshabur Longitudinal Study on Ageing. Os participantes também

This study was conducted by the Group of researcher in the Social Determinants of Health Research Center, Tabriz University of Medical Sciences; Healthy Ageing Research Centre, Neyshabur University of Medical Sciences; Geriatric Research Centre, Shiraz University of medical Centre; Road Traffic Injury Research Center and Department of Epidemiology and Biostatistics, Tabriz University of Medical Sciences, and School of Psychology, Massey University, New Zealand.

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foram submetidos a exame psicológico por dois neurologistas para serem avaliados quanto ao comprometimento cognitivo com base nos critérios do Manual de Diagnóstico e Estatística de Transtornos Mentais (DSM-V). Para avaliar a validade discriminante do P-TICS-m e do MMSE com os critérios do DSM-V, foram calculados a sensibilidade, a especificidade, os valores preditivos positivo e negativo (PPV e NPV) e a razão de verossimilhança positiva e negativa (LR+ e LR-). **Resultados:** A média de idade dos participantes foi de 59,6±6,8 anos. O TICS e o MMSE foram altamente correlacionados (r = 0,635, p <0,001). A sensibilidade, a especificidade, o PPV, o NPV, a LR+ e a LR- do MMSE para discriminar comprometimento cognitivo foram 83, 92, 68, 96%, 10, 0,182; e, para TICS-m, foram 100, 13, 19, 100%, 1,16 e zero, respectivamente. Os resultados da análise da curva característica de operação do receptor (ROC) não mostraram diferenças estatisticamente significativas entre P-TICS-m e MMSE. **Conclusões:** Nossos achados mostram que o teste TICS-m pode ser utilizado como ferramenta de triagem em vez do MEEM. Por causa da baixa especificidade e do baixo PPV do TICS-m em relação ao MMSE, o diagnóstico deve ser confirmado por meio de testes diagnósticos definitivos quando um indivíduo é classificado como portador de comprometimento cognitivo.

Palavras-chave: Entrevistas como Assunto; Disfunção Cognitiva; Demência; Testes Psicológicos; Idoso; Irã.

INTRODUCTION

Dementia, a decline in memory and other cognitive functions, is a severe challenge for health care and social care systems[1]. According to the World Alzheimer's Report, 47 million people live with dementia, and due to the aging of the population, its prevalence is expected to be triple by 2050[2,3]. In future, it is expected that Iran will encounter explosive growth in the number of older adults. The number of people aged 65 years and older is projected to rise from 5.7% in 2011 to 9.7% in 2030 and 25.2% by 2060. The current prevalence of dementia in Iran is 7.9% among individuals aged over 60 years and 13% among those aged over 80 years[4]. Despite the prevalence of Alzheimer's disease (the most common cause of dementia), its diagnosis is often overlooked or mistaken[5], and the rate of undetected dementia has been reported as high (61.7%)[6]. Early detection of Alzheimer's disease provides opportunities for advanced care planning and improved prognosis[6,7]. Many cognitive screening instruments have been developed for the screening of cognitive impairment. Although the Mini-Mental State Examination (MMSE) has been used successfully to detect cognitive impairment, it is not always feasible to screen large-scale samples[8] due to the need for face-to-face administration. In addition, due to a "ceiling effect" in mild cognitive impairments, its usefulness has been limited for research purposes. To overcome these limitations, several telephone interview-based cognitive screening instruments have been developed. One of the most popular instruments for this purpose is the Telephone Interview for Cognitive Status – modified (TICS-m), which correlates highly with the MMSE in Alzheimer's disease[9]. The 13-item TICS-m is an abbreviated version of the original 21-item TICS-m and includes four cognitive domains, assigning the highest proportion of the total score to the memory component[10]. This study aimed to assess the accuracy of the Persian version of the 13-item TICS-m in comparison to the MMSE and *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-V*) criteria in the detection of cognitive impairment among healthy people.

METHODS

Study population

This cross-sectional study was conducted in Neyshabur, Northeast of Iran, between January and March 2020. A total of 210 participants were recruited from community-dwelling adults aged 50 years and older who were registered with the Neyshabur Longitudinal Study on Ageing (NeLSA), which is an aging component of the Prospective Epidemiological Research Studies in Iran (PERSIAN)[11]. To decrease selection bias, random sampling was undertaken using a table of random numbers (the number of households with older adults) and samples were selected from the indwelling populations. Selected households were invited by phone to participate in the study. Adults aged 50 years and older who were willing to participate in the research and were able to read and write were included in the study. The exclusion criteria were as follows: adults with vision and hearing loss, use of hearing aids, having problems in the lower or upper limb that prevent walking or writing, history of psychological or neurologic disorders which cause cognitive impairment, intellectual or learning disabilities, brain surgery, alcoholism, drug abuse, head trauma with loss of consciousness for more than 2 h, and use of psychotropic drugs such as benzodiazepine, neuroleptic, antidepressant, anticonvulsant, and opioid within 7 days of cognitive evaluation.

Procedure

Persian version of Telephone Interview for Cognitive Status – modified (P-TICS-m)

The P-TICS-m questionnaire, which was validated previously[12], was applied in this study. First, all participants

were screened using MMSE, and 4 weeks later, the P-TICS-m was administered by the same interviewer. All research assistants who administered the P-TICS-m and MMSE had master's degrees in psychiatry and were specifically trained in the assessment procedure. The 13-item TICS-m questionnaire of Brandt et al. consists of six cognitive dimensions , namely, orientation (7 points), registration/free recall (10 points), attention/calculation (6 points), comprehension/semantic/recent memory (5 points), language/repetition (1 point), and delayed recall (10 points). In this questionnaire, the highest score is allocated to memory, which, unlike the MMSE test, gives 20% of its score to memory; in the TICS-m test, 56% of the total score is allocated to memory[9]. The total score ranges from 0 to 39. Individuals who scored ≤31 were considered having "mild cognitive impairment" and those who scored ≤27 were considered having "severe cognitive impairment"[13].

Mini-Mental State Examination

The MMSE questionnaire includes five dimensions of cognition such as orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language (9 points). The total score ranges from 0 to 30. Individuals who scored <24 were considered having "mild cognitive impairment" and those who scored ≤17 were considered having "severe cognitive impairment"[14-17].

Standard for comparison

Two psychiatric specialists examined all subjects who completed a neurological examination and administered the Short Test of Mental Status (STMS)[18]. The diagnosis of probable cognitive impairment was based on the *DSM-V* criteria[19].

Statistical analysis

Numeric variables were expressed as mean and standard deviation, and categorical variables were expressed as frequency and percentage. The normality of data was examined using the Kolmogorov-Smirnov test. Due to the non-normal distribution of MMSE and TICS test scores, the Mann-Whitney U test and Kruskal–Wallis test were used to compare the two genders, age groups, and educational groups. The Spearman's test was used to investigate the correlation between MMSE and TICS scores tests. To determine the accuracy of TICS-m and MMSE versus *DSM-V* criteria, sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR^+, LR–) were calculated along with their 95% confidence interval (95%CI). To compare the diagnostic accuracy of the TICS-m and MMSE tests, receiver operating characteristic (ROC) curve analysis was used to evaluate the significance of the difference between area under the curve (AUC) of TICS and MMSE tests versus *DSM-V* criteria, the Hanley and McNeil's test[20] was used. Youden's index was also calculated to determine the best cutoff point for P-TICS-m with the highest sensitivity and specificity values in detecting patients with cognitive impairment. The data were analyzed using the IBM SPSS statistics software version 21 (IBM SPSS Statistics, Armonk, NY, USA) and the MS Excel 2013 software.

RESULTS

Descriptive results of P-TICS-m and MMSE questionnaires

The cognitive scores for the MMSE and P-TICS-m matched by gender, age, and education are displayed in Table 1. Out of 210 participants in the study, 108 (51.4%) were male, and 102 (48.6%) were female. The mean age of participants was 59.95±6.8 years (ranged from 50 to 87 years). The majority of participants (54%) were in the age group of 50–59 years.

Correlation between TICS and MMSE tests

Spearman's test was used to examine the correlation between TICS and MMSE tests. Despite the different

Table 1. Distribution of median and interquartile range scores of Mini-Mental State Examination and Persian version of the Telephone Interview for Cognitive Status – modified by age, sex, and education (n=210).

Variables		n (%)	MMSE	P-TICS-m
			Median score (P_{25}–P_{75})	Median score (P_{25}–P_{75})
Gender	Male	108 (51.4)	27 (26–29)	29 (26–30)
	Female	102 (48.6)	25 (22.75–28)	27 (24–30)
Age (years)	50–59	114 (54.3)	27 (25–28.25)	28 (26–31)
	60–69	78 (37.1)	27 (23.75–28)	28 (25–29)
	≥70	18 (8.6)	24 (13.75–27)	21 (15.5–27.25)
Education level illiterate	Elementary	17 (8.1)	14 (13–20)	18 (13.50–20.5)
	Secondary	49 (23.3)	25 (23–28)	27 (24–29)
	Tertiary	24 (11.4)	27 (26–28.75)	28 (26–30)
	Diploma	4 (1.9)	24 (24–25.5)	24.5 (21.5–29)
	Academic	54 (25.7)	27 (25–29)	29 (26–30.25)
	Education	62 (29.5)	27 (26–29)	29 (27–31)

MMSE: Mini-Mental State Examination; P-TICS-m: Persian version of the Telephone Interview for Cognitive Status – modified.

scoring ranges of both tests (0–30 for the MMSE test and 0–39 for the TICS test), there was a strong, direct, and significant correlation between the scores of both tests (r=0.635, p<0.001).

Concurrent validity of P-TICS-m with MMSE (As a most commonly used screening test) in the detection of cognitive impairment

The sensitivity, specificity, PPV, and NPV of P-TICS-m compared with MMSE were 100%, 14%, 23%, and 100%, respectively (Table 2). According to the results of ROC analysis, the AUC of the P-TICS-m was 0.88 (95%CI 0.83–0.93, p<0.0001). This AUC indicates that P-TICS-m has a good performance in identifying cognitive impairment subjects from healthy ones compared to MMSE (Table 2).

Discriminant accuracy of P-TICS-m and MMSE for cognitive impairment versus DSM-V criteria (as a standard test)

Having cognitive impairment or not

The sensitivity, specificity, PPV, and NPV of the P-TICS-m using *DSM-V* criteria were 100%, 13%, 19%, and 100%, respectively. The sensitivity, specificity, PPV, and NPV of the MMSE test using *DSM-V* criteria were 83, 92, 68, and 96%, respectively (Table 3). Also, Table 3 shows the results of the ROC curve analysis for the assessment of the discriminant validity of the P-TICS and MMSE. The AUC of MMSE was higher than the P-TICS-m (0.959 vs. 0.896), but there was no significant difference between the P-TICS-m and MMSE (difference of both AUC=0.06, p=0.188073) (Table 3 and Figure 1). The P-TICS-m had 94.4% sensitivity and 67.8% specificity at the optimal cutoff score of ≤27.5, and the MMSE showed 97.2% sensitivity and 86.8% specificity at the optimal cutoff score of ≤24.5 (Table 3).

Table 2. Accuracy of the Persian version of the Telephone Interview for Cognitive Status – modified versus MMSE test in identifying cognitive impairment from healthy older adult (n=210).

	Estimate	95%CI
Sensitivity	1	0.92–1
specificity	0.145	0.099–0.206
PPV	0.237	0.181–0.303
NPV	1	0.862–1
LR^+	1.17	1.098–1.244
LR^-	0	0 to 0
AUC	0.888	0.837–0.938

PPV: positive predictive value; NPV: negative predictive value; LR^+: positive likelihood ratio; LR^-: negative likelihood ratio; AUC: area under the curve.

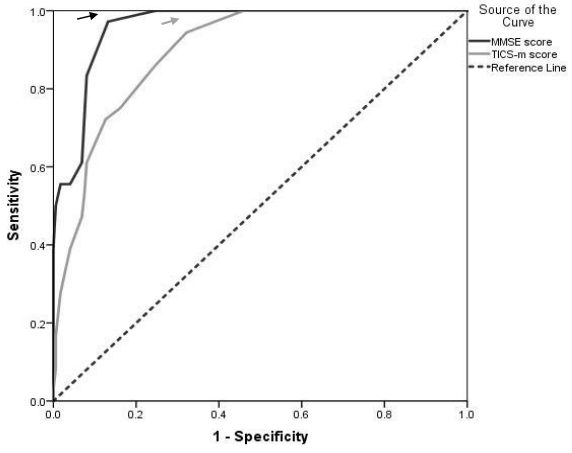
Detection of mild and severe cognitive impairment from those without cognitive impairment

The sensitivity of P-TICS-m in identifying those with severe and mild cognitive impairment was 100% and

Table 3. Discriminant accuracy of Telephone Interview for Cognitive Status – modified and Mini-Mental State Examination questionnaire for cognitive impairment using Diagnostic and Statistical Manual of Mental Disorders-V criteria.

Diagnostic test characteristics	MMSE		TICS-m	
	Estimate	95%CI	Estimate	95%CI
Sensitivity	0.833	0.681–0.921	1	0.904 to 1
specificity	0.92	0.869–0.951	0.138	0.094–0.197
PPV	0.682	0.534–0.8	0.194	0.143–0.256
NPV	0.964	0.923–0.983	1	0.862–1
LR+	10.413	6.138–17.475	1.16	1.093–1.231
LR^-	0.182	0.087–0.377	0	0–0
AUC	0.959	0.935–0.983	0.896	0.850–0.942
Cutoff point; sensitivity/ specificity	24.5; 0.972/0.868		27.5; 0.944/0.678	

MMSE: Mini-Mental State Examination; TICS-M: Modified Telephone Interview for Cognitive Status; PPV; positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR^-: negative likelihood ratio; AUC: area under the curve.



MMSE: Mini-Mental State Examination; P-TICS-m: Persian version of the Telephone Interview for Cognitive Status – modified.

Figure 1. Receiver operating characteristics of the TICS-m and MMSE instruments.

9.5%, and its PPV was 16% and 0%, respectively. The sensitivity of the MMSE in the detection of those with severe and mild cognitive impairment was 86% and 71%, and its PPV was 100% and 48%, respectively (Table 4).

DISCUSSION

The present study showed a significant correlation between the P-TICS-m and the widely used cognitive function test of MMSE. The original version of the TICS test also correlates very highly with the MMSE in Alzheimer's disease[9,21]. However, in the study by de Jager et al., the correlation was relatively low[10]. In terms of discriminant validity of the P-TICS-m compared with MMSE in detection of subjects with cognitive impairment from subjects without cognitive impairment, results showed that the sensitivity, specificity, PPV, and NPV of P-TICS-m were 100, 14, 23, and 100%, respectively. These results indicate that the P-TICS-m can detect all the MMSE diagnoses as having cognitive impairment. In addition, when a subject is diagnosed as healthy using the P-TICS-m, it is 100% probable that the same subject will be assessed as healthy using the MMSE. However, the P-TICS-m classifies many participants as having a cognitive impairment that the MMSE classifies as healthy. The MMSE test is not the gold standard test for diagnosing cognitive impairment and thus may not provide an accurate assessment of the TICS-m test[22]. For more specific conclusions about the discriminant validity of these tests, neuropsychological evaluation by two neurologists and diagnosis based on *DSM-V* criteria were used. According to our results, the sensitivity and NPV of the P-TICS-m using *DSM-V* criteria were high (100%), but its specificity and PPV were low (13 and 19%, respectively). Also, its LR^+ ratio was low (1.16), which means that the probability of over-diagnosis of the P-TICS-m is high and that 80% of healthy subjects are mistakenly classified as cognitive impaired (FP=80%). Therefore, the probability of further follow-ups will increase. However, the P-TICS-m correctly rules out cognitive impairment. The predictive value of a test is not just a test property and is influenced by prevalence and the setting in which the test is used. When the test is applied in a specialist setting such as a cognitive disorder clinic, it will have a higher predictive value than when the test is applied in non-specialist settings, such as community or primary care. In other words, the interpretation of a positive or negative diagnostic test result varies from setting to setting, according to the prevalence of disease in the particular setting. In these cases, it is recommended to use LR^+ and LR^-[22]. In this study, the LR^- of both TICS-m and MMSE was very low. Therefore, the probability of a false-negative test result to the possibility of a true negative test result[23] is very low. This means that these tests do not misdiagnose healthy people. According to our results, the diagnostic accuracy of MMSE using *DSM-V* criteria was better than TICS-m, in particular its specificity, PPV, and LR^+ (LR^+=10.83). That is, the chance of true positive test results to false-positive test results is 10 times.

In addition, out of the three positive results of the MMSE in suspected participants, two subjects were correctly classified as having a cognitive impairment (PPV=68%). The results of a meta-analysis that evaluated the accuracy of the MMSE indicated that the accuracy of a diagnostic test varies with the context in which it is used. For example, in clinics or specialized hospitals, the PPV of the MMSE was high, but the NPV of the MMSE in these settings was moderate. Conversely, in a community or primary care setting, the NPV of the MMSE was high, and the PPV of the MMSE was low. The results of our study were also in line with the findings of this study. Therefore, it is suggested that the MMSE be used for ruling out dementia in the community or primary care settings, but to confirm the diagnosis of dementia, other definitive diagnostic tests should be used[24]. Comparing the accuracy of P-TICS and MMSE using ROC curve analysis, our findings revealed that although the AUC of the MMSE was higher than TICS-m, there was no statistically significant difference between the two tests. However, given that the AUC of the MMSE is slightly higher than the TICS-m, it can be concluded that the MMSE works better[25,26].

Table 4. Discriminant accuracy of Telephone Interview for Cognitive Status – modified and Mini-Mental State Examination questionnaire for mild and severe cognitive impairment from those without cognitive impairment using Diagnostic and Statistical Manual of Mental Disorders-V criteria.

Diagnostic test characteristics	MMSE		TICS-m	
	Severe cognitive impairment	Mild cognitive impairment	Severe cognitive impairment	Mild cognitive impairment
Sensitivity	0.867	0.714	1	0.095
PPV	1	0.484	0.167	0.0
LR+	10.837	8.925	1.160	1.102
LR^-	0.144	0.310	0	0.362

MMSE: Mini-Mental State Examination; TICS-M: Modified Telephone Interview for Cognitive Status; PPV; positive predictive value; LR+: positive likelihood ratio; LR^-: negative likelihood ratio.

Considering the high NPV and the low LR^- of the TICS-m compared to the MMSE, there is no need for confirmatory tests when a person is classified as healthy. However, due to the low specificity and low PPV of the TICS-m compared to MMSE, the probability of false positive increases. Therefore, when a person is classified as cognitive impaired, the diagnosis should be confirmed using definitive diagnostic tests.

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AUTHORS' CONTRIBUTIONS

DL: conceptualization, formal analysis, writing – original draft. NA: conceptualization, data curation, formal analysis, supervision, writing – review & editing. SMS: conceptualization, data curation, writing – review & editing. AJ: conceptualization, methodology, writing – review & editing. ZG: conceptualization, writing – review & editing. NG: data curation, writing – review & editing. MAJ: data curation, writing – review & editing. FA: conceptualization, methodology, writing – review & editing.

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Original Article

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Cognitive impairment among older adults living in the community and in nursing home in Indonesia: a pilot study

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ABSTRACT. The demographic phenomenon of population aging has brought some consequences, including a higher prevalence of cognitive impairment. **Objective:** This study aimed to assess and compare cognitive impairment and its risk factors between older persons living in the community and in nursing home in Indonesia. **Methods:** A cross-sectional study was employed among 99 older adults living in the community and 49 nursing home residents. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). **Results:** Older people living in the community showed a higher score on MMSE than those living in nursing home (p=0.044). Age, marital status, education level, and literacy status were significantly related to the cognitive function of older adults living in the community (p=0.003, p=0.007, p=0.005, p=0.001, respectively), while gender, education level, and literacy status were significantly related to that of nursing home residents (p=0.012, p=0.004, p=0.001, respectively). **Conclusions:** Older adults living in the nursing home were more likely to experience cognitive decline than their counterparts in the community. Factors associated with cognitive decline differ between community-dwelling older adults and nursing home residents.

Keywords: Cognitive Dysfunction; Frail Elderly; Nursing Homes.

COMPROMETIMENTO COGNITIVO ENTRE IDOSOS QUE VIVEM NA COMUNIDADE E EM CASA DE REPOUSO NA INDONÉSIA: UM ESTUDO PILOTO

RESUMO. O fenômeno demográfico do envelhecimento da população trouxe algumas consequências, incluindo uma maior prevalência de comprometimento cognitivo. **Objetivo:** Este estudo teve como objetivo avaliar e comparar o comprometimento cognitivo e seus fatores de risco entre os idosos que vivem na comunidade e no lar de idosos na Indonésia. **Métodos:** Um estudo transversal foi empregado entre 99 idosos que vivem na comunidade e 49 residentes de casa de repouso. A função cognitiva foi avaliada usando o *Mini-Mental State Examination* (MMSE). **Resultados:** Os idosos que vivem na comunidade mostraram uma pontuação mais alta no MMSE do que aqueles que vivem em casa de repouso (p=0,044). Idade, estado civil, nível de educação e alfabetização estavam significativamente relacionados à função cognitiva de idosos que vivem na comunidade (p=0,003, p=0,007, p=0,005, p=0,001, respectivamente), enquanto gênero, nível educacional e alfabetização estavam significativamente relacionados aos idosos residentes da casa de repouso (p=0,012, p=0,004, p=0,001, respectivamente). **Conclusões:** Os idosos que vivem na casa de repouso tinham maior probabilidade de experimentar um declínio cognitivo do que seus colegas na comunidade. Os fatores associados ao declínio cognitivo diferem entre os idosos que habitam a comunidade e os residentes da casa de repouso.

Palavras-chave: Disfunção Cognitiva; Idoso Fragilizado; Casas de Saúde.

INTRODUCTION

Globally, the number of older people is increasing at a faster rate than all other age groups[1]. This rapid aging demographic transition has resulted in greater levels of cognitive decline, which is a growing public health issue. Previous studies demonstrated that about half of older people experienced a decline in cognitive function as part of the aging process[2,3].

This study was conducted by School of Nursing, Faculty of Health Sciences, Universitas Jenderal Soedirman, Indonesia.

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The range of cognitive function decline in the older population encompasses normal aging, mild cognitive impairment (MCI), and severe cognitive impairment[4]. Changes in cognitive abilities that occur as a normal part of the aging process should not impair an older person's abilities to perform daily life activities[5]. However, the changes can progress at different rates, with many individuals suffering from cognitive decline severe enough to interfere with their ability to perform activities of daily living, the later diagnosed as dementia[5].

Studies on cognitive function in older adults in different countries have predominantly identified sociodemographic and health characteristics as risk factors[6-8]. Among demographic variables, place of residence has not been much investigated. Living arrangement has been an emerging aging-related issue. In general, in most countries, most older people lived in private households and only small number of them lived in institutional settings[9]. However, changes in living arrangements of older people have occurred in many regions, and the number of older people living in an institution is expected to increase[9].

The place of residence has been linked to the health status, well-being, and quality of life of older people[10-12]. Few previous studies have compared cognitive function and associated risk factors of older adults who live at home and in an institution. However, respondents of this study were those with MCI and dementia, not aging-related decline[13,14].

Like many other countries, Indonesia is also experiencing a rapid increase in the older population[1]. Regarding living arrangement, most of the older people in Indonesia lived in a multigenerational household and only a minority lived in institutional settings[15]. Few studies have examined the cognitive functioning of older people in Indonesia[16,17]. However, there is a lack of studies comparing the cognitive function of older adults across the different living settings. Thus, this study aimed to identify and compare the cognitive decline and risk factors between older people living in the community and those living in nursing home in Indonesia.

METHODS

Settings and participants

This is a descriptive analytical study using a cross-sectional method. The study was conducted from June to September 2019. This study was conducted among older people who live in the community and in nursing home in Banyumas Regency, Central Java Province, Indonesia.

Based on the 2019 Indonesian Population Census, the population of older people in Banyumas accounted for about 236,193 people, or approximately 14% of its total population, a bit higher than the national average (9.6%). Most older people in Banyumas live in the community, and only a few live in nursing homes. There are two nursing homes in the regency: one is a private religious-based, and the other is a state-owned nursing home, with a total number of 147 residents in 2019.

The sample size was calculated using a simple formula for a pilot study[18]. An online calculator is available at http://www.pilotsamplesize.com. With a confidence level of 95% and a probability of 0.068 based on the previous study in Indonesia[19], the sample size was small with 43 subjects in each group. Considering the low response rate based on our previous study (≤50%) (unpublished), a total of 100 community-dwelling older adults and 100 nursing home residents were invited to participate in the study.

The community samples were conveniently selected from the participants of Posyandu Lansia (integrated health service post for older people) in the nearby area, following the recommendation by cadres (community volunteers). A total of 100 community-dwelling older people were visited at their homes, and 99 of them were eligible for this pilot study. Meanwhile, the nursing home samples were conveniently recruited from the state-owned nursing home. The nursing home has a total of 100 residents, but only 49 of them met the study criteria. Eligible participants were no less than 60 years old, willing to participate, and able to speak the language(s) used to administer (Bahasa and/or Javanese). Participants who had visual or auditory impairment or active psychiatric symptoms that preclude them from completing the assessment were excluded from the study.

Instruments

The studied variables were cognitive function, health status, and demographic characteristics. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) that consists of the following sub-functions: orientation, registration, attention and calculation, repetition/recalled, and language[20]. MMSE score ranges from 0 to 30. The higher the score, the better the cognitive functioning. An MMSE score <24 indicates cognitive deficits.

This study used the adapted version of the MMSE in Indonesian language[21]. In this validity study, the tool was adapted and translated into several languages, including Bahasa and Javanese, using the procedure back-translation. The tool showed optimum sensitivity using a similar cutoff value of 24.

Health status characteristics included blood pressure, nutritional status, smoking, and illness history. Blood pressure measurement was conducted at the beginning of the research interview and then classified into "normal (normotension)" or "hypertension" using JNC 7 algorithm[22]. Nutritional status was determined by measuring body mass index (BMI) and then classified into normal or abnormal (underweight, overweight, obese, or extreme obese)[23]. Smoking and illness history referred to any cigarettes consumption and presence of any cardiovascular/neurological/metabolic diseases in the past 6 months as reported by the respondents.

Meanwhile, demographic variables included age, sex, marital, educational, literacy, and living arrangement status.

Ethical consideration

Before collecting the data, respondents were given an explanation about the aim and nature of this study, and they signed an informed consent form if they agreed to participate. The five rights of human subjects in the research, including self-determination, privacy, dignity, anonymity, and confidentiality, were maintained throughout the study. This study has gained an ethical approval from the Health Research Ethics Committee no. 2516/KEPK/V/2019 dated May 29, 2019.

Data analysis

The demographic and health status characteristics of respondents were described using frequency tables of categorical variables and descriptive statistics of numerical variables. Chi-square tests were used to compare the categorical variables. Fisher's exact tests used as an alternative to the chi-square tests when one or more cells had expected count of less than 5 (i.e., presence of cardiovascular/neurological disease). Independent t-tests compared the means between two unrelated groups on the same continuous variables. Mann-Whitney U tests were used as an alternative to independent t-tests when variables followed the non-parametric distribution. Spearman's rank tests were used instead of Pearson's correlation to measure the correlation between two continuous variables, which were not normally distributed. This study used $p \leq 0.05$ to define the level of statistical significance. Data processing was carried out using the IBM SPSS version 25.0 software.

RESULTS

Older people living in both the community and nursing homes had relatively similar characteristics in terms of gender, years of education, and literacy, but were significantly different in terms of age and marital status (Table 1). Older people in both groups were more likely to be of female gender with less years of education (<9 years) and literate. However, nursing home residents were significantly older and more likely to be single (i.e., widowed) than their community-dwelling counterparts (p=0.029 and p=0.000, respectively).

In terms of health status, both older adults living in the community and nursing home had relatively similar characteristics (Table 1). Most of them had normal BMI, did not smoke, and did not have cardiovascular/neurological/metabolic diseases. However, about two-thirds of both groups had high blood pressure (hypertension).

The total MMSE score of nursing home residents was significantly lower than those of community-dwelling older people (p=0.044). The two groups showed a significant differences in the language function (p=0.004) (Table 2). When cognitive decline was defined as MMSE<24, it was found that it was present in 20.2% and 44.9% of older adult living in the community and in nursing homes, respectively (p=0.002).

There were factors related to MMSE scores among older adults living in the community and in nursing home (Table 3). Results showed that education level and literacy status were significantly related to the cognitive function of older adults in both groups (p=0.005, p=0.001 and p=0.004, p=0.001, respectively). Better educated and literate older adults are more likely to have MMSE score above or very close to the threshold (≥24).

Age had a significant negative correlation with MMSE scores, but only among community-dwelling older people (p=0.003, *cc*=-0.298). The effect of marital on cognitive functioning was also demonstrated by this group. Married older people showed higher MMSE scores above the threshold (≥24) compared to their counterparts (p=0.007). Meanwhile, a significant difference in MMSE scores between gender was only found among those living in nursing home (p=0.012). Male older people showed a higher score above the threshold than their female counterparts.

DISCUSSION

This pilot study determined cognitive decline among older people in two different living settings, that is, community and nursing home, and their related characteristics. Findings showed that older adults living in nursing home showed a lower cognitive function than those living in the community. The results from this study support a previous study which reported that older people who admitted to nursing homes showed

Table 1. Demographic and health status characteristics of respondents.

		Community-dwelling (n=99)	Institutional-dwelling (n=49)	p-value
Age, mean±SD		**68.01±6.910**	**71.71±9.381**	**0.029*,+**
Gender, n (%)	Male	26 (26.3)	18 (36.7)	0.190§
	Female	73 (73.7)	31 (63.3)	
Marital status, n (%)	Married	59 (59.6)	3 (6.1)	0.001§,+
	Single (unmarried, widowed)	40 (40.4)	46 (93.9)	
Years of education, years, n (%)	≥9	13 (13.1)	11 (22.4)	0.148§
	<9	86 (86.9)	38 (77.6)	
Literacy, n (%)	Literate	78 (78.8)	35 (71.4)	0.321§
	Illiterate	21 (21.2)	14 (28.6)	
Blood pressure, n (%)	Normal	39 (39.4)	19 (38.8)	0.942§
	Hypertension	60 (60.6)	30 (61.2)	
BMI, n (%)	Normal	57 (57.6)	35 (71.4)	0.102§
	Abnormal	42 (42.4)	14 (28.6)	
Smoking status, n (%)	Not smoking	84 (84.8)	41 (83.7)	0.853§
	Smoking	15 (15.2)	8 (16.3)	
Cardiovascular/neurological/ metabolic disease, n (%)	No	92 (92.9)	46 (93.9)	1.000‖
	Yes	7 (7.1)	3 (6.1)	

SD: standard deviation; BMI: body mass index; *Mann-Whitney U test; +p≤0.05; §Chi-square test; ‖Fisher's exact test.

Table 2. Cognitive functioning.

	Community (n=99)	Nursing home (n=49)	p-value
MMSE score (mean±SD)	24.09±5.043	22.59±5.082	0.044*,+
Orientation	8.20±1.969	8.00±2.363	0.798*
Registration	2.79±0.689	2.86±0.408	0.797*
Attention and calculation	3.23±1.640	2.71±1.696	0.083*
Recalled	2.24±1.001	2.20±0.979	0.727*
Language	7.63±1.549	6.82±1.787	0.004*,+

MMSE: Mini-Mental State Examination; SD: standard deviation; *Mann-Whitney U test; +p≤0.05.

a greater cognitive decline after their admission than those who remained at home[24].

The reasons for the decline are still unclear, but are probably linked to physical and psychological consequences of living in institution on older people. A previous study reported that many long-term care residents suffered from depression due to perceived inadequacy of care[25]. A previous study in Indonesia indicated that admitting older people in nursing home is unusual due to the perception that it is against the cultural values of filial obligation as well as having a detrimental effect on older people's physical and psychological health[26].

However, it is also highly possible that the decline was not a result of institutionalization. Older adults might have already been suffering from cognitive decline when they were admitted to the nursing home. A previous longitudinal study found that dementia was the strongest predictors of living in institution in old age[27]. A previous systematic review also suggested that cognitive impairment was one of the main underlying conditions of nursing home placement[28]. The causal relationship between cognitive decline and institutionalization in this study, however, could not be determined due to the study design.

The difference in cognitive decline between community-dwelling older adults and nursing home residents could also be explained by the difference in respondents' characteristics, namely, age and marital status. In this

Table 3. Factors related to cognitive function among older people living in community and nursing home residents.

		Community (n=99)		Nursing home (n=49)	
		MMSE score (mean±SD)	p-value	MMSE score (mean±SD)	p-value
Age (correlation coefficient)		r=-0.298	0.003*,+	r=-0.270	0.061*
Gender	Male	24.69±4.038	0.804§	24.94±4.277	0.012+,‖
	Female	23.88±5.364		21.23±5.071	
Marital status	Married	25.27±4.046	0.007+,§	26.33±2.887	0.185‖
	Single (unmarried, widowed)	22.35±5.860		22.35±5.117	
Years of education (years)	≥9	27.08±2.397	0.005+,§	26.27±4.474	0.004+,§
	<9	23.64±5.190		21.53±4.786	
Literacy	Literate	25.55±3.410	0.001+,§	23.89±5.184	0.001+,§
	Illiterate	18.67±6.374		19.36±3.054	
Blood pressure	Normal	25.15±3.957	0.145§	21.58±5.480	0.370§
	Hypertension	23.40±5.561		23.23±4.797	
BMI	Normal	24.35±4.658	0.735§	22.77±5.292	0.700‖
	Abnormal	23.74±5.561		22.14±4.672	
Smoking status	Not smoking	23.99±5.180	0.818§	22.37±5.333	0.487‖
	Smoking	24.67±4.304		23.75±3.576	
Cardiovascular/neurological/ metabolic disease	No	23.98±5.146	0.607§	22.46±5.124	0.471‖
	Yes	25.57±3.309		24.67±4.726	
Living arrangement	Multi-generation	24.32±4.964	0.318§		
	Independent living	23.27±5.347			

BMI: body mass index; *Spearman's rank test; +p≤0.05; §Mann-Whitney U test; ‖Independent t-test.

study, nursing home respondents were significantly older than their counterparts in the community. Cognitive function generally declines with age among older adults[29]. However, after controlling the living setting, age was associated with cognitive decline in community-dwelling older adult, but not in nursing home residents. This finding is in accordance with a previous study conducted among nursing home residents that found no significant association between age and cognitive decline[30].

Regarding marital status, in this study, nursing home residents were also more likely to be single than their community-dwelling older people. Previous studies demonstrated that marriage was related to a reduced likelihood of having cognitive decline[31,32]. Marriage has been suggested as having psychological benefits, which protect individuals from cognitive decline in later life. Married individuals would have more cognitive and social engagement and experience less loneliness and psychological distress[32]. It has been indicated in previous studies that high levels of distress and loneliness were related to a decline in cognitive ability among older people[33,34]. However, like the age variable, after the living setting was controlled, marital status was related to cognitive functioning only in community respondents. The lack of association between marital status and cognitive decline among nursing home residents in the present study was possibly related to the fact that married individuals who lived in nursing homes could be considered "single" without the presence of their spouse. Thus, it seems that not the relationship status but the meaningful social interaction affects the cognitive function. However, it warrants further investigation since these data were not available.

The female gender was associated with lower cognitive functioning among nursing home residents. Some studies have found gender differences in cognitive functioning. They found that gender discrepancies were suggested to involve complex interactions with other factors, for example, education period, specific cognitive domains, genetic vulnerability, and hormonal status[35-37]. In another study, hypertension and stroke accounted for gender differences in cognitive decline in women and men, respectively[29].

Shorter periods of education and illiteracy were related to declines in cognitive functioning in both community- and institutional-dwelling older people. The protective benefits of education and literacy on cognitive performance have been demonstrated in several studies[6,7,17]. Poorer cognitive functioning among lower educated and illiterate older adults is possibly due to the fact that they are relatively lacking in cognitive stimulation. A previous study suggested that the length of education had a considerable impact on cognitive ability in relation to the individual's work situation, socioeconomic status, and social activity[35].

Interestingly, none of the health status indicators in the present study were associated with cognitive function. Previous studies showed contrary results, which found that high blood pressure, obesity, smoking, and chronic diseases, including diabetes, heart disease, and stroke, have all been suggested to have an influence on cognitive function[5,38-40]. Further research in this area is required.

This study has several limitations:

1. The number of respondents in both groups was not equal due to the limited number of nursing home residents who met the study criteria;
2. The cross-sectional design cannot determine a cause-effect relationship between variables; and
3. This study only investigated a few factors, although there might be other factors that affect cognitive functioning in older adults.

This study suggests that older people living in nursing home presents a more significant cognitive decline than those living in the community. Female gender, shorter years of education, and illiteracy were related to lower cognitive function among nursing home residents, while advanced age, not being married, shorter years of education, and illiteracy were related to that of community-dwelling older people. Health promotion strategies to prevent further cognitive decline should be focused on those vulnerable sub-groups.

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Authors' contributions. RS: conceptualization, formal analysis, funding acquisition, methodology, resources, validation, writing – original draft, writing – review & editing; AI: data curation, funding acquisition, investigation, project administration, supervision, visualization, writing – review & editing.

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Can the choice reaction time be modified after COVID-19 diagnosis? A prospective cohort study

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ABSTRACT. Assessment of cognitive processing speed through choice reaction time (CRT) can be an objective tool to assess cognitive functions after COVID-19 infection. **Objective:** This study aimed to assess CRT in individuals after acute COVID-19 infection over 1 year. **Methods:** We prospectively analyzed 30 individuals (male: 9, female: 21) with mild-moderate functional status after COVID-19 and 30 individuals (male: 8, female: 22) without COVID-19. Cognitive and neuropsychiatric symptoms were evaluated using the Montreal Cognitive Assessment (MoCA) and Hospital Anxiety and Depression Scale (HADS), respectively. CRT (milliseconds) was evaluated by finding the difference between the photodiode signal and the electromyographic (EMG) onset latency of anterior deltoid, brachial biceps, and triceps during the task of reaching a luminous target. CRT was evaluated three times over 1 year after COVID-19: baseline assessment (>4 weeks of COVID-19 diagnosis), between 3 and 6 months, and between 6 and 12 months. **Results:** The multiple comparison analysis shows CRT reduction of the anterior deltoid in the COVID-19 group at 3-6 ($p=0.001$) and 6-12 months ($p<0.001$) compared to the control group. We also observed CRT reduction of the triceps at 6-12 months ($p=0.002$) and brachial biceps at 0-3 ($p<0.001$), 3-6 ($p<0.001$), and 6-12 months ($p<0.001$) in the COVID-19 compared to the control group. Moderate correlations were observed between MoCA and CRT of the anterior deltoid ($r=-0.63$; $p=0.002$) and brachial biceps ($r=-0.67$; $p=0.001$) at 6–12 months in the COVID-19 group. **Conclusions:** There was a reduction in CRT after acute COVID-19 over 1 year. A negative correlation was also observed between MoCA and CRT only from 6 to 12 months after COVID-19 infection.

Keywords: COVID-19; Reaction Time; Cognition.

O TEMPO DE REAÇÃO DE ESCOLHA PODE SER MODIFICADO APÓS O DIAGNÓSTICO DE COVID-19? UM ESTUDO DE COORTE PROSPECTIVA

RESUMO. A avaliação da velocidade de processamento cognitivo por meio do tempo de reação de escolha (TRE) pode ser uma ferramenta objetiva para acompanhar as alterações cognitivas após a COVID-19. **Objetivo:** Avaliar o TRE em pacientes após infecção aguda por COVID-19 ao longo de um ano. **Métodos:** Foram avaliados 30 indivíduos (sexo masculino: nove; feminino: 21) com estado funcional leve-moderado após infecção por COVID-19 e 30 (sexo masculino: oito; feminino: 22) sem COVID-19. A avaliação foi feita pelo *Montreal Cognitive Assessment* (MoCA) e pela Escala Hospitalar de Ansiedade e Depressão. O TRE (milissegundos) foi avaliado pela diferença entre o sinal luminoso e a latência de início da atividade muscular (EMG) do deltoide anterior (DA), do bíceps braquial (BB) e do tríceps durante uma tarefa de alcance. O TRE foi avaliado ao longo de um ano: avaliação inicial (>4 semanas após diagnóstico de COVID-19), em 3–6 meses e em 6–12 meses. **Resultados:** Houve redução do TRE do DA no grupo COVID-19 em 3–6 meses ($p=0,001$) e 6–12 meses ($p<0,001$) em comparação com o grupo de controle. Também foi observada redução na TRE do tríceps em 6–12 meses ($p=0,002$) e do BB em 0–3 meses ($p<0,001$), 3–6 meses ($p<0,001$) e 6–12 meses ($p<0,001$) no grupo COVID-19 em comparação com o grupo de controle. Correlações moderadas foram observadas entre MoCA e TRE do DA ($r=-0,63$; $p=0,002$) e BB ($r=-0,67$; $p=0,001$) aos 6–12 meses no grupo COVID-19. **Conclusões:** Houve redução do TRE após COVID-19 ao longo de um ano, além de correlação negativa entre MoCA e TRE no período de seis a 12 meses após COVID-19.

Palavras-chave: COVID-19; Tempo de Reação; Cognição.

This study was conducted by the Group of Neuroscience and Rehabilitation, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brazil.

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INTRODUCTION

Some studies have demonstrated associations between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and neurological dysfunction in the early phase[1] and long term, mainly cognitive deficits in executive function, attention, language, and delayed recall[2,3]. The virus can enter the cerebral circulation by interacting with the angiotensin-converting enzyme-2 (ACE-2) receptor and infect neural cells[3,4] or cross the blood-brain barrier and activate the brain's immune cell to produce neural cytokines, leading to brain dysfunction[5].

The spread and persistence of the virus in brain cells remains debatable. However, several studies have observed that coronavirus disease 2019 (COVID-19) can change brain activity and connectivity[6-8], causing cognitive dysfunction for months after infection[9,10]. In addition, there are increasingly frequent reports of memory impairment, concentration difficulties, and long-term neuropsychiatric symptoms[11,12]. This long COVID-19 status is defined as "brain fog," which is the cognitive complaint of slow and confused thinking[9,10].

Assessment of cognitive processing speed through choice reaction time (CRT) can be an objective tool to assess brain fog after acute COVID-19. Decision-making is the reaction time (RT) for more than one visual stimulus (choice RT) and the onset of muscle activity to assess cognitive function and processing speed[13]. The CRT process includes many cognitive functions, such as recognition, association, coordination, inhibition, and decision planning stages[14,15]. These cognitive changes after the acute period of COVID-19 can have long-term negative impacts, resulting in cognitive, behavioral, and emotional changes[9,10].

Long-term monitoring of neurological and cognitive function in individuals after COVID-19 infection is necessary to understand changes in cognitive behavior and verify possible neurodegenerative diseases. In addition, Hellmuth et al. showed that cognitive deficits were not captured by common cognitive screens, such as the Mini-Mental State Examination or Montreal Cognitive Assessment (MoCA), suggesting that systematic and objective cognitive tests can be more beneficial after acute COVID-19[16]. Therefore, this study aimed to assess CRT in individuals with acute COVID-19 after over 1 year. In addition, the correlation between MoCA, anxiety, depression, and CRT was also evaluated in the COVID-19 group.

METHODS

Study design, setting, and participants

This was a 12-month prospective cohort study of individuals with acute COVID-19 in Uberaba, Minas Gerais, Brazil. The research was conducted at the Laboratory of Neuroscience and Motor Control of the Universidade Federal do Triângulo Mineiro (UFTM) between September 2020 and July 2021.

We prospectively analyzed 60 individuals (30 individuals with SARS-CoV-2 laboratory-positive [SARS-CoV-2+] and 30 individuals with SARS-CoV-2 laboratory-negative [SARS-CoV-2-]) who met the study inclusion criteria. The diagnosis of COVID-19 was confirmed by SARS-CoV-2 reverse transcription-polymerase chain reaction of nasopharyngeal swabs and/or SARS-CoV-2 antibody testing. Among the 60 participants, 30 participants had a positive result for SARS-CoV-2 infection (SARS-CoV-2+), while 30 participants had a negative result for SARS-CoV-2 infection (SARS-CoV-2-).

Individuals diagnosed with COVID-19 were recruited from the Uberaba Municipal Health Department and the Clinical Hospital of the Universidade Federal do Triângulo Mineiro. The control group was recruited via radio, television, and digital media. The control group criteria are that they should be negative for COVID-19 at the time of evaluation and should not have a positive diagnosis of COVID-19 since the beginning of the pandemic. This study was approved by our institutional review board (CAAE: 30684820.4.0000.5154).

Eligibility criteria

We included individuals with mild to moderate functional status after COVID-19 (grades 0–3 in Post-COVID-19 Functional Status Scale — PCFS)[17], who have an education level >9 years and could complete the tests independently. The PCFS was recently translated into Brazilian Portuguese (https://osf.io/tgwe3/) and has been an excellent strategy to assess limitations after SARS-CoV-2 infection. It is graded as follows: 0: no functional limitations, 1: negligible functional limitations, 2: slight functional limitations, 3: moderate functional limitations, 4: severe functional limitation, and D: death. It can be applied in outpatient follow-ups to monitor functional status. The control group comprised individuals who were COVID-19-negative, aged ³18 years old, and were able to understand the tests. The exclusion criteria were individuals with severe and critical COVID-19; a history of mental disorders or current treatment of mental illnesses, such as taking antipsychotics, antidepressants, mood stabilizers, antiepileptics, benzodiazepines, and other drugs that may interfere with the assessment; severe physical illnesses that may interfere with the assessment; history of drug abuse or drug dependence; serious suicidal thoughts;

pregnant or lactating women; and individuals with hearing or visual impairments. Participants who did not complete the proposed tests at the time of collection, did not attend reassessments, were exposed to a new COVID-19 infection, or had a neurological or psychiatric disease unrelated to COVID-19 infection during follow-up were excluded from the study.

Procedures

All tests were performed three times by the research team during 1 year after COVID-19 diagnosis: (a) baseline assessment (after 4 weeks of COVID-19 diagnosis), (b) between 3 and 6 months, and (c) between 6 and 12 months. The individuals reported demographic and clinical variables, such as age, race, and formal education; previous comorbidities were also analyzed, such as hypertension, diabetes, obesity, and sedentary, because preexisting conditions could contribute to slow CRT. Dominance was evaluated using the Edinburgh Handedness Inventory[18], and cognitive and neuropsychiatric symptoms were evaluated using the MoCA[19] and Hospital Anxiety and Depression Scale (HADS)[20], respectively.

CRT evaluation

The CRT was evaluated according to the protocol described by Caires et al.[13] Participants were seated in a height-adjustable chair in the following positions: hips, knees, and ankles in 90° of flexion; shoulders between 10° and 15° of flexion; elbows in 90° of flexion; and forearms pronated. A smart TV monitor was placed in front of the individual at 100% of the upper limb length. Seat height was adjusted to 100% of the length of the lower limb. Participants had to reach a luminous target projected on a monitor as quickly as possible with their upper limbs and return to the initial position at the end of the stimulus for five trials with the dominant arm (Figure 1).

CRTs were evaluated using electromyographic (EMG) signals according to stimulus onset in the anterior deltoid, brachial biceps, and triceps of the upper limbs. EMG signals were recorded using a Delsys Trigno™ wireless telemetry sensor at 2,000Hz according to the SENIAM protocol (surface EMG for noninvasive assessment of muscles) [21]. The EMG electrode sites were shaved and cleaned with alcohol. EMG onset latency was defined as the time when the EMG amplitude exceeded

Figure 1. Participant's position and choice reaction time evaluation.

five standard deviations of the mean of a 100 ms baseline value taken before the onset of the stimulus[22]. A photodiode was used to synchronize the EMG signal with the visual stimulus. The upper limb CRT (measured in milliseconds) was calculated by determining the difference between the photodiode signal and the EMG onset latency in the upper limb while reaching the luminous target.

Statistical analysis

Data normality was assessed using the Shapiro-Wilk test. Continuous variables were described as means and standard deviations, and categorical variables were expressed as percentages. The outcomes were analyzed using an analysis of variance model with fixed effects due absence of confounders. The goodness of fit was evaluated through the normality of ordinary residuals and homoscedasticity using the Levene's test. Pairwise post-hoc comparisons were performed using the Bonferroni correction. The Spearman's test was performed to analyze the correlation between the MoCA, HADS, and CRT values. Statistical significance was set at $p<0.05$. All statistical analyses were performed by using IBM SPSS Statistics for Windows/Macintosh (version 24.0; IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of the participants

A total of 60 participants (COVID-19: 30; control group: 30) were included. The COVID group had a mean age of 40.5 years and 70% of the individuals were female. The control group had a mean age of 37.9 years and 73.3% of the individuals were female. Among the individuals with COVID-19 evaluated in this study, only five were hospitalized in the acute phase; however, none required intubation or mechanical ventilation. Baseline clinical and demographic data are summarized in Table 1.

In the first evaluation, the individuals presented with the following clinical manifestations: anosmia (18), dysgeusia (15), muscle weakness (21), irritability (10), brain fog (9), headache (8), walking problems (8), arthralgia (7), and myalgia (7). In the second evaluation (3–6 months), the clinical manifestations were hyposmia (16), dysgeusia (13), muscle weakness (12), brain fog (15), and fatigue (16). In the third evaluation (6–12 months), clinical manifestations were hyposmia (12), dysgeusia (8), brain fog (17), and fatigue (16). All individuals (both COVID-19 and control groups) were vaccinated during the follow-up period. Most individuals did not report any adverse effects.

Table 1. Clinical and demographic profile of both groups.

		COVID-19 (n=30)	Control (n=30)	p-value
Age, year, median (IQR)[1]		40.5 (25-69)	37.9 (21-55)	0.81
Sex[2], n (%)	Males	9 (30.0)	8 (26.7)	>0.99
	Females	21 (70.0)	22 (73.3)	>0.99
Race[2], n (%)	White	22 (73.3)	24 (80.0)	0.76
	Black	6 (20.0)	5 (16.7)	>0.99
	Asian	2 (6.7)	1 (3.3)	>0.99
Previous comorbidities, n (%)	Hypertension	13 (43.3)	11 (36.7)	0.79
	Diabetes mellitus	8 (26.7)	6 (20.0)	0.76
	Obesity	5 (16.7)	6 (20.0)	>0.99
	Sedentary	9 (30.0)	10 (33.3)	>0.99
BMI, kg/m^2, median (IQR)[1]		27.2 (19.0-42.0)	26.4 (20.8-34.8)	0.32
Years of study, median (IQR)[1]		14.3 (12-19)	14.5 (10-22)	0.81
HAD, median (IQR)[1]		10.0 (1.0-19.0)	9.0 (3.0-21.0)	0.37
MoCA, median (IQR)[1]		25.0 (16.0-30.0)	25.0 (21.0-30.0)	0.23
PFCS, median (IQR)[1]		2 (1–3)	0	<0.001

IQR: interquartile range; BMI: body mass index; HAD: Hospital Anxiety and Depression Scale; MoCA: Montreal Cognitive Assessment; PFCS: post-COVID-19 Functional Status Scale. [1]Mann-Whitney U test; [2]χ^2 test.

Outcomes

The analysis of CRT between the two groups is shown in Figure 2. There was a significant interaction between GROUP and TIME in the CRT of the anterior deltoid [F(2.211, 64.12)=20.40; p<0.001]. Post-hoc analyses showed a significant reduction in CRT of the anterior deltoid in the COVID-19 group at 3-6 (MD, -63.04; 95%CI -103.0 to -23.07; p=0.001) and 6-12 months (MD, -105.2; 95%CI -151.4 to -58.96; p<0.0001) compared to the control group (Figure 2A).

There was a significant interaction between GROUP and TIME in the CRT of the triceps [F(1.979, 57.40)=17.37; p<0.001]. Post-hoc analyses showed significant CRT reduction of triceps in the COVID-19 group at 6-12 months (MD, -67.29; 95%CI -111.8 to -22.82; p=0.002) compared to the control group (Figure 2B).

There was a significant interaction between GROUP and TIME in the CRT of the brachial biceps [F(1.848, 53.59)=42.84; p<0.001). Post-hoc analyses showed a significant CRT reduction of the brachial biceps in the COVID-19 group at 0–3 (MD, -53.16; 95%CI -77.61 to -28.71; p<0.0001), 3-6 (MD, -63.27; 95%CI -88.60 to -37.93; p<0.0001), and 6-12 months (MD, -90.40; 95%CI -117.74 to -63.09; p<0.0001) compared to the control group (Figure 2C).

The mean and standard deviation of the CRT values of the anterior deltoid, triceps, and brachial biceps of all participants are shown in Table 2.

Moderate negative correlations were also observed between MoCA and CRT of the anterior deltoid at 6–12 months (r=-0.63; p=0.002) and between MoCA and CRT of the brachial biceps at 6–12 months (r=-0.67; p=0.001). The other variables did not show statistically significant associations.

DISCUSSION

This study found a reduction in CRT in individuals after COVID-19 infection over 1 year. CRT reduction was found at 3-6 and 6-12 months after acute infection of the anterior deltoid, 6-12 months for triceps, and the brachial biceps in all evaluations compared to the control group. In other words, individuals who have had COVID-19 showed reduced CRT compared to the control group over 1 year. In addition, we observed moderate negative correlations between MoCA and CRT of the anterior deltoid and brachial biceps at 6–12 months.

There are four cognitive processes that can be distinguished in CRT tasks: (1) stimulus perception,

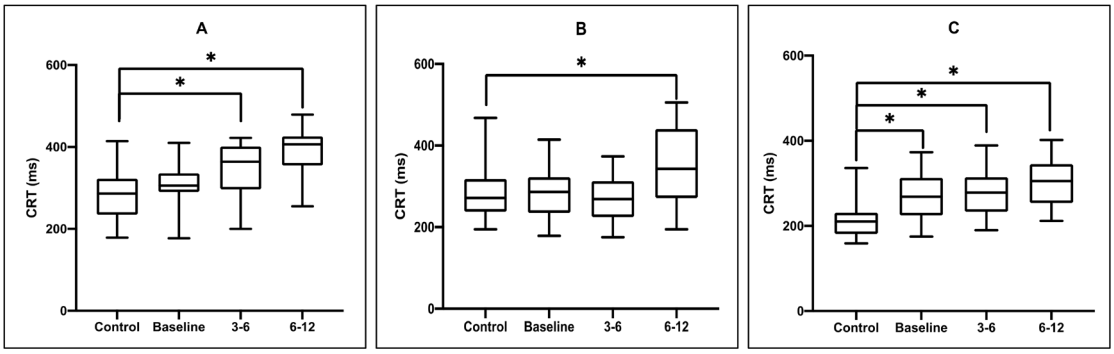

Figure 2. (A) Comparison of the choice reaction time of the anterior deltoid muscle between the control group and the COVID-19 group at baseline, 3-6 months, and 6-12 months after acute infection; (B) Comparison of the choice reaction time of the triceps muscle between the control group and the COVID-19 group at baseline, 3-6 months, and 6-12 months after acute infection; (C) Comparison of the choice reaction time of the brachial biceps muscle between the control group and the COVID-19 group at baseline, 3-6 months, and 6-12 months after acute infection.

Table 2. Mean and standard deviation of choice reaction time values of anterior deltoid, triceps, and brachial biceps of individuals after COVID-19 infection over 1 year and control group.

	COVID-19			Control
	0–3 months	3–6 months	6–12 months	
Anterior deltoid (ms)	307.1±52.30	349.7±61.77	391.9±54.22	286.7±63.11
Triceps (ms)	288.4±61.09	269.3±53.16	353.0±94.61	285.7±62.64
Brachial biceps (ms)	269.3±52.06	279.4±54.79	306.5±57.83	216.1±45.76

(2) stimulus discrimination, (3) response choice, and (4) motor response[23]. RT is important for activities of daily living, requires sensory skills, cognitive processing, and motor performance[24], and correlates with neuropsychological tests of processing speed and higher order cognitive processes in younger and older adults[25]. Prolonged CRT is associated with decreased cognitive function[23]. Some studies showed that COVID-19 could also alter the brain's functional connectivity pattern, causing cognitive dysfunction for months after infection resolution[26,27]. Hugon et al. also showed marked attentional and executive cognitive impairment in a patient with mild COVID-19[20].

Based on the CRT changes observed, can SARS-CoV-2 cause neurological damage to decrease cognitive decision-making in the first year after COVID-19? Can CRT be a resource to diagnose early alterations or post-COVID syndrome? Is CRT a potential predictor of the progression of cognitive loss in long-term COVID-19? The long-term course of these brain lesions and clinical symptoms in mild forms of COVID-19 is difficult to predict. Some authors have mentioned that the evolution toward neurodegenerative diseases could be seen over a prolonged period of time[19,20,28]. In addition, recovery from COVID-19 infection may be associated with particularly pronounced problems in aspects of higher cognitive or "executive" function[29].

In this study, a correlation was observed between MoCA and CRT only in the period from 6 to 12 months; that is, the lower the MoCA value, the greatest the CRT of the anterior deltoid and brachial biceps muscles. Some authors have presented hypotheses about long-term neurocognitive alterations in individuals who have had COVID-19. These authors reported direct and indirect effects to explain these changes. Regarding direct effects, the authors observed the presence of viral reactivation or hyperactivity of the immune system[30]; and in relation to indirect factors, they report associated extrinsic aspects, such as environmental changes, social isolation, personal and economic factors, as well as lifestyle changes that could later modify neurological and neuropsychiatric function[30]. In addition, associated clinical factors such as fatigue or cardiorespiratory changes can secondarily interfere with cognitive ability; however, these variables were not controlled in this study[31].

Some limitations of this study should be highlighted. The first is small sample size — which limits the statistical power of our analysis; in order to obtain the best reliability of our analyses, we established strict inclusion criteria to avoid interpretation errors. Even limiting the power of our analysis, the possibility of focusing on a homogeneous subgroup allowed us to minimize the effect of all possible confounders. The second limitation is that due to technical and operational limitations, accuracy and precision were not evaluated during the CRT test, and therefore, they are variables to be controlled in future studies. The third limitation is that objective analysis of fatigue and cardiovascular performance was not performed, which may interfere with cognitive response. Finally, the fourth limitation is that there was no functional MRI analysis to understand the changes at the structural level.

Our findings have important clinical implications in the subacute and chronic phases of COVID-19 because CRT is a simple, low-cost method that can be used as a diagnostic method for brain fog in post-COVID syndrome. Furthermore, these results will help plan and develop multidisciplinary care strategies to improve cognitive performance after COVID-19 infection.

In conclusion, there was a reduction in CRT after acute COVID-19 over 1-year period. CRT reduction was found in the anterior deltoid at 3-6 and 6-12 months, triceps at 6-12 months, and brachial biceps in all evaluations. In addition, a negative correlation was observed between MoCA and CRT only from 6 to 12 months after COVID-19 infection.

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Authors' contributions. GJL, LAPSS: conceptualization, data curation, formal analysis, writing – original draft preparation, project administration, supervision, writing – review & editing; ATS, PAA, KSMBS, EMN: investigation, original draft, writing – review & editing.

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Case Report

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Diagnostic approach in a patient with Creutzfeldt-Jakob disease

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ABSTRACT. Prion diseases are an important cause of rapidly progressive dementias. Among them, the most common is sporadic Creutzfeldt-Jakob disease (CJD). It is a rare and incurable disease, with rapid progression to death. **Objective:** To describe the diagnostic approach of a patient with Creutzfeldt-Jakob disease. **Methods:** The diagnosis is established through the clinical picture associated with characteristic changes in the brain magnetic resonance imaging, the electroencephalogram, and analysis of specific changes in the cerebrospinal fluid. **Results:** The present report describes the case of a 53-year-old patient in the city of Fortaleza-CE. The diagnosis was made based on the clinical condition and through diagnostic tests, including 14-3-3 protein and RT QUIC analysis. Differential diagnosis was performed with other rapidly progressive causes, such as infectious and immune-mediated diseases. **Conclusions:** The diagnosis of probable sporadic CJD was established.

Keywords: Prion Diseases; Creutzfeldt-Jakob Syndrome; Dementia.

ABORDAGEM DIAGNÓSTICA EM UMA PACIENTE COM DOENÇA DE CREUTZFELDT-JAKOB

RESUMO. As doenças priônicas são uma importante causa de demências rapidamente progressivas. Entre elas, a mais comum é a doença de Creutzfeldt-Jakob (DCJ) esporádica. É uma enfermidade rara e incurável, com rápida progressão para óbito. **Objetivo:** Descrever a abordagem diagnóstica de uma paciente com doença de Creutzfeldt-Jakob. **Métodos:** O diagnóstico é estabelecido pelo quadro clínico associado a alterações características na ressonância magnética cerebral, no eletroencefalograma e pela análise de alterações específicas no líquido cefalorraquidiano. **Resultados:** O presente relato descreve o caso de um paciente de 53 anos na cidade de Fortaleza (CE). O diagnóstico foi feito com base na condição clínica e por meio de testes diagnósticos, incluindo proteína 14-3-3 e análise *Real-Time Quaking-Induced Conversion* (RT QUIC). O diagnóstico diferencial foi realizado com outras causas rapidamente progressivas, como doenças infecciosas e imunomediadas. **Conclusões:** Por fim, foi estabelecido o diagnóstico de provável DCJ esporádica.

Palavras-chave: Doenças Priônicas; Síndrome de Creutzfeldt-Jakob; Demência.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is the prototype of prion diseases, one of the main causes of rapidly progressive dementia (RPD). It is an incurable disease. CJD is subdivided into sporadic, familial, variant, and iatrogenic subtypes[1]. The sporadic subtype is the most common. It was first described in 1920 by Hans Creutzfeldt and later in 1921 and 1923 by Alfons Jakob[2,3]. Etiologically, it is caused by an agent called a prion, which was recognized in 1960 by Stanley Prusiner, which later gave him the Nobel Prize[4]. The disease-causing prion protein undergoes a conformational change, which in turn causes a change in the previously normal

This study was conducted by the Neurologist Group at Monte Klinikum Hospital, Fortaleza, Ceará, Brazil.

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cellular prion protein[5]. Pathological changes in the disease include vacuolar lesions that give a spongiform appearance to the brain, preferably in the basal ganglia, thalamus, cerebellum, and cerebral cortex[6].

CASE REPORT

A previously healthy 53-year-old patient started to complain of asthenia, fatigue, and anxiety, with excessive fear about contracting coronavirus. In the first week after the onset of symptoms, he started to present mental confusion with forgetfulness for recent facts, imbalance, and a few episodes of falls. Within 2 weeks of the onset of symptoms, she was evaluated by a neurologist, who found mild gait ataxia and suggested for cranial magnetic resonance imaging (MRI), in addition to brain arterial and venous angio MRI and electroencephalogram (EEG) video. The angio MRI showed no changes and the EEG video revealed nonspecific encephalopathy, whereas the MRI showed hypersignal in the diffusion, along with restriction, bilateral in insula, basal ganglia, and anterior cingulate (Figure 1). In addition to neuroimaging, she performed laboratory tests concurrently, which did not reveal abnormalities, but showed nonreactive VDRL, normal serum ammonia level, as well as normal renal, thyroid, and liver functions, in addition to negative serologies for HIV and hepatitis. After a few days, she worsened from mental confusion and imbalance, without new abnormalities observed under the neurological examination, and underwent a lumbar puncture. The partial analysis of the cerebrospinal fluid (CSF) revealed normal cells, glucose and protein levels, direct research and culture for normal pyogenic germs, fungi, and tuberculosis, as well as negative PCR for herpes virus types 1 and 2. In addition, CSF autoantibodies and 14-3-3 protein were requested. At that time, the hypothesis of RPD was formulated, with an emphasis on two major possibilities: prion disease or immune-mediated encephalitis. Given the delay in obtaining 14-3-3 protein, it was opted for hospitalization for pulse therapy with methylprednisolone 1 g/day for 5 days, followed by intravenous administration of immune globulin (IGIV) at a dose of 2 g/kg for 5 days. During hospitalization, MRI and EEG video were repeated without any change, and a worsening of the clinical picture was observed on memory and the appearance of spastic tetraparesis, hypophonia, and bradykinesia in the upper limbs and lower limbs, as well as optic ataxia and oculomotor apraxia. The evolution was rapid and, in 2 weeks of hospitalization, the patient was in akinetic mutism; therefore, gastrostomy (GTT) was performed due to dysphagia. She later developed fever due to aspiration pneumonia and was treated with antibiotics. She was discharged with GTT and akinetic mutism. After 30 days, she started to develop myoclonus and hence underwent the remaining examination, and the

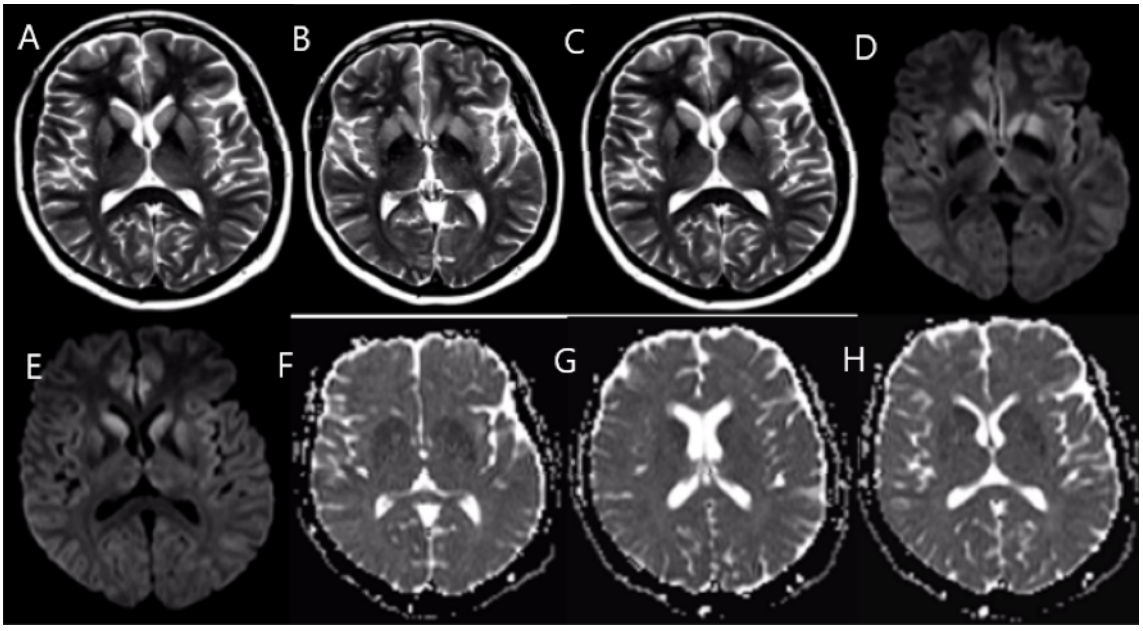

Figure 1. Brain magnetic resonance imaging scans demonstrating hypersignal in bilateral basal ganglia, insula, and anterior cingulate gyrus in T2 sequence (A, B, C) and hypersignal in the same regions in the diffusion sequence (D, E) with corresponding low signal in the ADC map (F, G, H), characterizing a true restriction to water molecules.

result revealed the presence of 14-3-3 protein in high titers. The family members were informed about the institution of palliative care, avoiding invasive measures. During evolution, the patient underwent three EEGs. In the first two EEGs, only a nonspecific slowing was revealed, while the third one, which was performed in November 2020, revealed bilateral generalized periodic activity (Figure 2). Subsequently, the patient underwent a lumbar puncture for RT QUIC analysis of the CSF which showed a positive result.

DISCUSSION

The annual incidence of CJD is about 1 case per million people[7]. It is, therefore, a rare and incurable disease. The rarity of this condition is evidenced in different series of services specialized in dementia, when specifically evaluating the etiologies of RPD[8]. Sporadic CJD is the main form of CJD and is characterized by cognitive, visual, cerebellar, and motor (pyramidal/extrapyramidal) signs and symptoms, which are part of the existing diagnostic criteria for the disease[9].

In addition to the clinical picture, some complementary examinations help in the diagnosis of the disease. The brain MRI shows lesions with hypersignal in the diffusion and FLAIR/T2 in the cerebral cortex and basal ganglia, like the patient in question[10]. The EEG, despite its low sensitivity, can demonstrate findings suggestive of triphasic waves or periodic complexes[11]. The CSF analysis can help in the research of proteins 14-3-3, tau, and p-tau that show an increase in the referred disease[12]. In addition, the detection of pathological prion protein in the nasal mucosa or CSF using an amplification technique reveals a high specificity and this analysis is called RT QUIC[13].

The present case study demonstrates the importance of an appropriate investigation in situations of RPD[14]. This investigation involves the search of autoimmune encephalitis, central nervous system (CNS) infections, and metabolic and demyelinating conditions[15]. In our patient, clinical course after immunotherapy, CSF examination (including RT QUIC), laboratory tests, systemic neoplasms research, and brain MRI confirmed CJD, in addition to ruling out CNS infections, metabolic diseases, autoimmune, and paraneoplastic encephalitis. The possibility of performing RT QUIC in suspected cases is extremely important, given its high specificity in prion disease diagnosis[13]. In addition, investigation of autoimmune and paraneoplastic encephalitis and CNS infections in CSF is essential[14].

In summary, patient in this report presented a typical clinical picture, corroborated by a typical MRI and

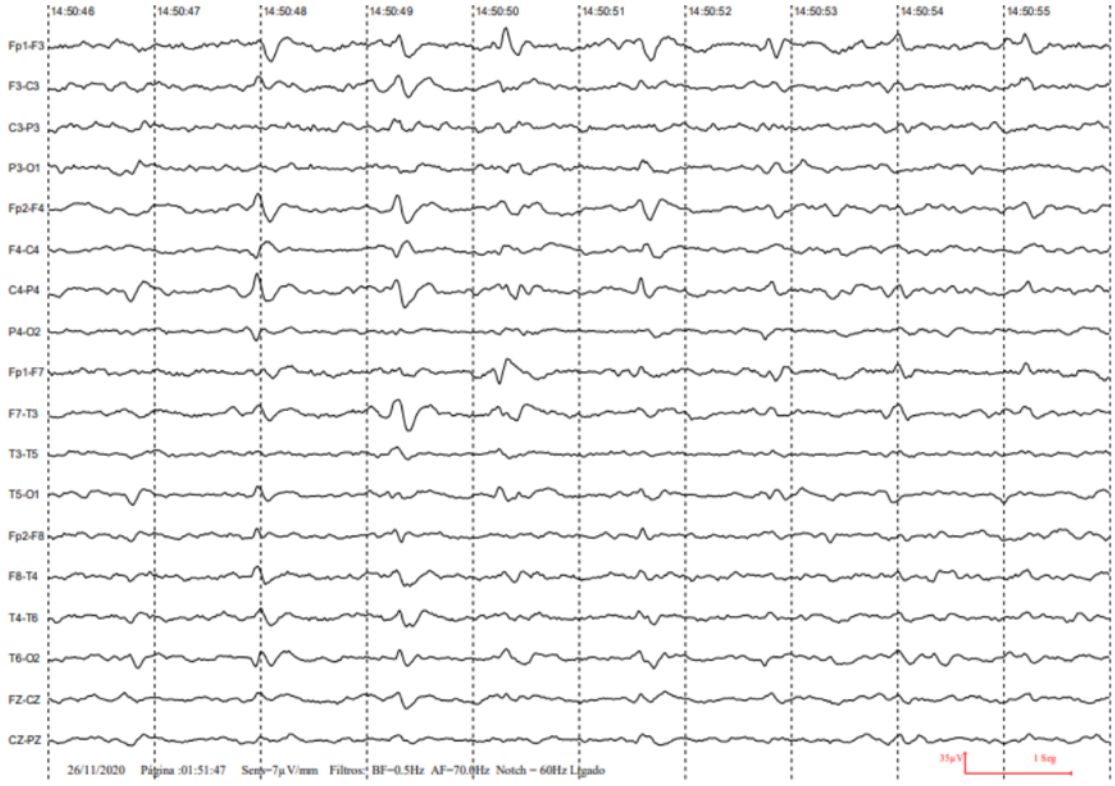

Figure 2. Periodic discharges on electroencephalogram.

EEG, and also high titers of 14-3-3 protein in the CSF, in addition to positive RT QUIC. The present case was investigated in the context of a COVID-19 pandemic, which raised concerns about hospitalization by the family. The presence of a health care plan by the patient made it possible for the family to carry out the tests quickly. However, even with the rapidity, the delay in the results of tests and the financial impossibility in the performance of autoantibodies in the CSF imposed the empirical treatment for encephalitis immune-mediated with MPIV and IGIV without improvement. Despite difficulties and limitations in carrying out elective tests imposed by the pandemic in the city of Fortaleza (hospitalization occurred at the peak of the pandemic in May 2020 in the city of Fortaleza), there was a rapidity in the formulation of the diagnostic hypothesis, performance of examinations, and hospitalization (from the first visit to the completion of the IGIV, it took exactly 20 days). The report of the present case helps keep the memory of this diagnosis alive in clinical practice, emphasizes the logistical difficulties faced in carrying out the most detailed CSF examinations even in the context of private medicine, and demonstrates the importance of defining the diagnosis of the cause of RPD for better acceptance of the diagnosis and end-of-life programming by the family.

Authors' contributions. JWLTJ, DAD, JJFdC: conceptualization; JWLTJ: methodology, visualization, project administration; JWLTJ, RdOC, JJFdC: writing – original draft preparation; JWLTJ, JJFdC: writing – review & editing; JWLTJ, JJFdC: supervision. All authors have read and agreed to the published version of the manuscript.

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https://doi.org/10.1590/1980-5764-DN-2021-0021erratum

Erratum

In the article "Random number generation and the ability of mentally reconstructing context in patients with organic amnesia", with DOI code number 10.1590/1980-5764-DN-2021-0021, published in the Dement Neuropsychol 2022 March;16(1):19-27, on page 19:

Where it was written:
[4]Centro Paulista de Neuropsicologia, São Paulo SP, Brazil.

Should read:
[4]Centro Universitário São Camilo, São Paulo SP, Brazil.

INSTRUCTIONS TO AUTHORS

SCOPE AND POLICY

Dementia & Neuropsychology is to publish research in cognitive and behavioral sciences, focusing on clinical epidemiology, basic and applied neurosciences, and cognitive tests devised or adapted for populations with heterogeneous cultural, educational, and socioeconomic backgrounds.

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The policy requesting disclosure of conflicts of interest applies to all manuscript submissions, including letters to the editor and case reports.

Informed consent

For experimental investigations involving human or animal subjects, state in the "Methods" section of the manuscript that an appropriate institutional review board has approved the project. A copy of the approval by the Ethics Committee should be mailed with the manuscript. For those investigators who do not have access to a formal ethics review committee (institutional or regional), the principles outlined in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) should be followed. For investigations of human subjects, state in the "Methods" section the manner in which informed consent was obtained from the subjects. A letter of consent must accompany all photographs of patients in which a possibility of identification exists. It is not sufficient to cover the eyes to mask identity. Refer to patients by number (or in anecdotal reports, by assigning fictitious names). Real names or initials should not be used in the text, tables, or illustrations.

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Manuscripts are received on the understanding that they are not under simultaneous consideration by another journal or title. This information must be included in the cover letter. Dementia & Neuropsychologia uses tools for detecting possible text similarity to check for plagiarism. When plagiarism is detected, the journal follows the *Core Practices* of the *Committee on* Publication Ethics - COPE (http://publicationethics.org/).

Clinical trials

In concert with the International Committee of Medical Journal Editors (ICMJE), Dementia & Neuropsychologia requires, as a precondition to be considered for publication, registration of clinical trials in a public trials registry. Acceptable trial registries include http://clinicaltrials.gov, http://isrctn.org, http://actr.org.au, http://trialregister.nl, and http://www.umin.ac.jp/ctr. For this purpose, the ICMJE defines a clinical trial as any study that prospectively assigns human subjects to intervention or comparison groups to evaluate the cause-and-effect relationships between a medical intervention and a health outcome. The trial registry name, its URL and the registration number should be included at the end of the abstract. Trials must be registered at or before commencement of patient enrollment. In agreement with BIREME/PAHO/WHO recommendations for reporting randomized trials, authors are advised to adhere to the guidelines in the CONSORT STATEMENT (www.consort-statement.org).

Funding/support and role of sponsor

All financial and material support for the research and work should be clearly and fully identified in the acknowledgment.

Data access and responsibility

For clinical trials sponsored by pharmaceutical companies, authors must state in their letter of submission that: (1) they have had full access to all the data; (2) they had the right to publish all the data; and (3) they have had the right to obtain independent statistical analyses of the data. Manuscripts containing statistical evaluations should include the name and affiliation of the statistical reviewer.

Preprint

Dementia & Neuropsychology accepts submission of manuscripts previously deposited in preprint repositories. For submission of deposited manuscripts, the author must indicate the repository data in the Cover Letter.

FORM AND PREPARATION OF MANUSCRIPTS

Title page. Include manuscript title, running title and authors' names. The title should be concise and descriptive, up to 150 characters (with spaces), carrying essential information on the manuscript content. The name of the authors should include the first name. At the bottom of the

title page indicate: the name of the department and institution, up to 100 characters, city and country in which the study was conducted; contribution of each author to or elaborate or manuscript, and ORCID of all authors, the academic title of each author and their institutional affiliation; grant support; acknowledgements; name and address (postal and electronic) for mail.

Abstract. The abstract of original manuscripts or short communications should be structured and contain the following items: background, objective(s), methods, results and conclusions. Abstracts may contain up to 250 words. Abstracts of case reports, history notes or reviews may be unstructured and contain up to 150 words.

Key words. Include 4-6 key words in English, according to the DeCS – Descriptors for Health Sciences (http://decs.bvs.br/) or MeSH – Medical Subject Headings (http://www.ncbi.nlm.nih.gov/mesh). **Title, abstract and key words** must also be provided in Portuguese. For those who do not write in Portuguese, the editorial office will translate these items.

Text. Original manuscripts may have up to 3,000 words and contain only four sections: introduction (which usually finishes by defining the objectives); methods (material and/or subjects; statistical methods; bioethical approach with the name of the Ethics Committee that approved the study and patient Informed Consent); results; discussion (which should include the limitations of the study and conclusions); and acknowledgements. Data presented in tables and illustrations should not be repeated in the text. Observations: Short communication, history note and case report: up to 2,000 words of text; reviews up to 5,000 words."Neuroimaging through clinical cases" up to 750 words.

References. Up to 50 references may be included for original manuscripts, numbered consecutively in the order they are cited. For case reports, history note or short communications, up to 30, for "Neuroimaging through clinical cases" up to 20 and for reviews up to 150 references are allowed. In the body of the text, references must be identified with Arabic numerals, in exponent. The presentation of the references is in accordance with the standard defined by the International Committee of Medical Journal Editors - ICMJE (https://www.nlm.nih.gov/bsd/uniform_requirements.html) and the titles of the journals must be abbreviated according to the Medicus Index : journal title abbreviations (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng).

- Articles: Author(s), (mark the first six authors followed by et al.). Title. Journal year; volume: page numbers (initial-final) and DOI.
- Books: Author(s) or editor(s). Title. Edition - if not the first. City where published: publisher; year: number of pages
- Chapter of a book: Author(s). Title. In: Book editor(s) followed by (eds), Title, Edition- if not the first. City where published: publisher; year:page numbers (initial-final).
- Abstracts: Author(s).Title, followed by (Abstr). Journal year; volume (Supplement and number if necessary):page(s) or, in case of abstracts not published in journals: Title of the publication. City where published: publisher, year:page(s).
- Works consulted on the internet: link and date of the consult.

Tables. Up to 5 tables are allowed in original manuscripts (up to **3** tables in short communications, history note or case reports), each presented on a separate page together with its title, notes and sequence number. Tables should contain all information required to be understood by the reader. Vertical lines should not be used for separating data within the table. Type each table double spaced on a separate page. Do not submit tables as photographs. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations used in each table. For footnotes use the following symbols, in this sequence: *, +, §, ||, ¶, **, ++, etc. The editor, on accepting a manuscript, may recommend that

additional tables containing important supporting data too extensive to publish be deposited with an archival service, such as the site of the journal (www.demneuropsy.com.br), or be made available by the authors. In this case, an appropriate statement will be added to the text. Submit all tables for consideration together with the manuscript.

Illustrations. Up to 4 figures, graphs or photos are allowed, with their title and notes on separate pages (up to 3 illustrations in short communications, history note or case reports). Figures must be submitted in JPEG or TIFF format, with the following resolutions: a) Artwork in black and white: 1,200 dpi/ppi; b) Half-tones: 300 dpi/ppi; c) Combination of half-tones: 600 dpi/ppi.

The table below presents a summary of the requirements defined for each type of contribution:

Manuscript Types	Abstract	Keywords	Text	References	Tables and Figures
Original Article	Structured 250 words	4 to 6	3.000	50	5 tables + 4 figures
Review Article	Unstructured 150 words	4 to 6	5.000	150	5 tables + 4 figures
Short Communication	Structured 250 words	4 to 6	2.000	30	3 tables + 3 figures
Case Report	Unstructured 150 words	4 to 6	2.000	30	3 tables + 3 figures
Historical Notes	Unstructured 150 words	4 to 6	2.000	30	3 tables + 3 figures
Neuroimaging through Clinical Cases	–	–	750	20	1 table + 2 figures
Letter	–	–	750	20	1 table + 2 figures

SEND OF THE MANUSCRIPTS

Submissions must be made online: https://mc04.manuscriptcentral.com/dn-scielo.

Manuscripts must be written in English, and present title, abstract and keywords in both English and Portuguese. For those who do not write in Portuguese, the editorial office will translate these items.

Submissions must be accompanied by a cover letter, declaration of Authorship Responsibility, Financial Disclosure and Copyright Transfer/Publishing Agreement. Studies involving humans should be accompanied by a copy of the Ethics Committee authorization from the institution involved. Clinical trial studies will be accepted for publication, pending the presentation of Clinical Trial Registers.

The authors may be asked for additional information regarding previous presentations at Scientific Meetings. This information can be supplied in the cover letter sent at the time of manuscript submission.

Note. Before submitting your manuscript, please go through the Author's checklist and complete the Authorship, non-financial, and financial disclosure forms in annex: Authorship Disclosure.

There are no fees for manuscript submission or manuscript review.

Review Process

All submitted manuscripts are reviewed initially by Editors-in-Chief. Manuscripts with insufficient priority for publication are rejected promptly.

Initial screening will be performed by one of the Editors-in-Chief to verify the formal eligibility of the manuscript according to the editorial norms **Dementia & Neuropsychologia**. Submission of manuscripts that do not comply with the format described in this document may incur its return.

After approval of formal aspects, the manuscript is submitted to peer-review and to ad-hoc consultants, as well as international and national specialists. Each manuscript is evaluated by at least two reviewers.

Based on the reviewers' comments and the Associate Editors' recommendations, the Editors-in-Chief may: a) accept the publication of the manuscript; 2) ask authors to review and resubmit the manuscript – Minor or Major Revision; or c) reject and no longer consider the manuscript for publication.

To submit the revised version of the manuscript, authors will have **30** days for a minor review and **60** days for a major review.

The entire process is overseen by the Editor-in-Chief who determines the number of appropriate re-submissions, with a focus on the quality of the work being published at all times.

Authors will be informed by the Editor-in-Chief of the likely date of publication after their final decision.

The journal adopts the double-blind peer-review mode. In this way, peer reviewers' identities are kept confidential, and authors' identities are also not disclosed to reviewers.

INSTRUÇÕES AOS AUTORES

ESCOPO E POLÍTICA EDITORIAL

Dementia & Neuropsychologia é um periódico dedicado à publicação de pesquisas em ciências cognitivas e do comportamento, com foco em epidemiologia clínica, neurociências básicas e aplicadas e testes cognitivos desenvolvidos ou adaptados para populações com diferentes substratos culturais, educacionais e socioeconômicos.

Dementia & Neuropsychologia está particularmente envolvido com a publicação de pesquisas relevantes de países em desenvolvimento e também procura publicar artigos originais e disseminar revisões e relatos de caso que sejam contribuições importantes para o campo da neurociência cognitiva.

O periódico segue as recomendações do *International Committee of Medical Journal Editors - ICMJE*, intituladas de *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* (http://www.icmje.org/recommendations/), atualização de dezembro de 2019.

Para as questões éticas, o periódico segue o documento *Core Practices* elaborado pelo *Committee on Publication Ethics – COPE* (http://publicationethics.org).

Os conceitos e declarações contidos nos referidos manuscritos são de inteira responsabilidade dos autores.

Autoria

Para ser incluído como autor, espera-se que a pessoa tenha feito uma contribuição significativa para o manuscrito submetido à **Dementia & Neuropsychologia**. Conforme recomendação do *International Committee of Medical Journal Editors (ICMJE),* a autoria se baseia nos seguintes critérios:

- Contribuição substancial para o desenho do projeto do estudo ou para a aquisição, análise e interpretação dos dados;
- Contribuição intelectual na redação do manuscrito ou sua revisão crítica;
- Aprovação da versão final a ser publicada; e
- Concordância em relação à responsabilidade por todos os aspectos do trabalho.

O texto completo das recomendações do ICMJE está disponível a partir de:
http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

Conflito de interesse

Um conflito de interesse pode existir quando um autor (ou a instituição ou empregador do autor) tem relações financeiras e pessoais que possam inapropriadamente influenciar (ou enviesar) a decisão sobre a autoria do trabalho ou manuscrito. Todos os autores são requisitados a relatar potenciais conflitos de interesse, incluindo interesses financeiros específicos relevantes ao assunto do manuscrito, na sua carta de apresentação e no formulário de declaração financeira de interesses de Dementia & Neuropsychologia. Autores sem interesses financeiros relevantes, devem indicar a ausência de interesse no manuscrito.

São solicitadas aos autores informações detalhadas quanto ao suporte material e financeiro para a pesquisa a trabalho, incluindo fontes de fundos e provisão de equipamentos e suprimentos, não limitados ao auxílio pesquisa.

Espera-se que os autores forneçam informações detalhadas sobre qualquer interesse financeiro relevante ou conflitos financeiros até 5 anos atrás e num futuro próximo, particularmente, aqueles presentes durante a pesquisa e o período de publicação. Além disso, os autores que não tiverem

interesses financeiros devem providenciar uma declaração indicando não haver interesse financeiro relacionado ao material do manuscrito.

Estas regras de declarações de conflitos de interesse devem ser aplicadas a todos os manuscritos submetidos, incluindo cartas ao editor e relatos de caso.

Consentimento informado

Para investigações experimentais em seres humanos ou animais, coloque na sessão de "Métodos" do manuscrito que um comitê institucional aprovou o projeto. Para aqueles investigadores que não possuam um comitê de ética em pesquisa formal (institucional ou regional) os princípios exibidos na Declaração de Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) devem ser seguidos. Uma carta de consentimento deve acompanhar todas as fotografias e/ou videos de pacientes na qual uma possível identificação possa ocorrer. Não é suficiente cobrir olhos para mascarar a identidade. Refira-se ao paciente por número (ou, em relatos anedóticos, por nomes fictícios). Nomes reais ou iniciais não devem ser usados no texto, tabelas ou ilustrações.

Publicação prévia ou submissão duplicada

Manuscritos são recebidos entendendo-se que não estejam sob outra consideração para publicação. Esta informação deve ser inserida na carta de apresentação. Dementia & Neuropsychologia usa ferramentas para detectar semelhança de texto para verificar plágio. Quando é detectado plágio, a revista segue o documento intitulado *Core Practices* do *Committee on Publication Ethics – COPE* (http://publicationethics.org/).

Ensaios clínicos

Em acordo com o ICMJE, **Dementia & Neuropsychologia** requer, como condição para consideração de publicação, o registro do ensaio clínico nos centros de registro. Os sites para registros de ensaio clínico aceitáveis incluem: http://clinicaltrials.gov, http://isrctn.org, http://actr.org.au, http://trialregister.nl , ensaiosclinicos.gov.br (REBEC-Registro Brasileiro de Ensaios Clínicos) http://www.umin.ac.jp/ctr. Para este propósito, o ICMJE define ensaio clínico como qualquer estudo que prospectivamente submete indivíduos a intervenções ou comparações de grupos para avaliar as relações de causa e efeito entre uma intervenção médica e a evolução do estado de saúde. O nome do ensaio registrado, sua URL e número de registro deverão constar ao final do resumo. Os ensaios devem ser registrados no início, ou antes, do recrutamento dos indivíduos. Em acordo com as recomendações da BIREME/OPAS/OMS para relato de ensaios clínicos, os autores deverão trabalhar seguindo as diretrizes recomendadas no CONSORT STATEMENT (www.consort-statement.org).

Fundos e suporte e papel do financiador

Todo suporte financeiro e material para a pesquisa e trabalho deve ser clara e completamente identificado nos agradecimentos.

Acesso aos dados e responsabilidade

Para ensaios clínicos financiados pela indústria farmacêutica, os autores devem relatar na sua carta de submissão que (1) eles tiveram total acesso aos dados, (2) tiveram o direito de publicar todos os dados e (3) tiveram o direito de obter análises estatísticas independentes. Manuscritos contendo avaliações estatísticas devem conter o nome e afiliação do revisor estatístico.

Preprint

Dementia & Neuropsychologia aceita a submissão de manuscrito previamente depositados em repositórios de *preprint*. Para a submissão de manuscritos depositados, o autor deve indicar os dados do repositório na Carta de Apresentação.

FORMA E PREPARAÇÃO DOS MANUSCRITOS

Página de Título. Inclui o título do manuscrito e os nomes dos autores. O título deve ser conciso e descritivo, com informação essencial sobre o conteúdo do manuscrito, com até 150 caracteres incluindo espaços. O nome dos autores deve incluir o primeiro nome. Ao final da página de título informe: o nome do departamento e instituição, com até 100 caracteres, cidade e país no qual o estudo foi conduzido, contribuição de cada autor ao elaborar o manuscrito e o número de ORCID de todos os autores, título acadêmico de cada autor e sua afiliação institucional, suporte financeiro, agradecimentos, nome e endereço (postal e eletrônico) para correspondência.

Resumo. Os resumos de artigos originais ou comunicações breves devem ser estruturados e conter os seguintes itens: embasamento, objetivo(s), métodos, resultados e conclusões. Os resumos podem conter até 250 palavras. Resumos de relatos de caso ou revisões não necessitam ser estruturados e podem conter até 150 palavras.

Palavras-chave. Adicione 4 a 6 palavras-chave, seguindo os DeCS – Descritores em Ciências da Saúde (http://decs.bvs.br/) ou MeSH – Medical Subject Headings (http://www.ncbi.nlm.nih.gov/mesh).

Título, resumo e palavras-chave devem ser fornecidos também em português. Aqueles que não escrevem na língua portuguesa, contarão com a tradução dos editores.

Texto. Os manuscritos originais deverão apresentar até 3000 palavras, contendo: introdução e objetivos; métodos (material e/ou casuística; método estatístico; menção à aprovação pelo Comitê de Ética, o nome desse Comitê e o consentimento informado); resultados; discussão (que deve incluir as conclusões); e agradecimentos. Os dados apresentados nas tabelas e ilustrações não devem ser repetidos no texto. Observações: O limite para comunicações breves, nota histórica e relato de caso é até 2000 palavras e para revisões até 5000 palavras; "Neuroimagem através de casos clínicos" até 750 palavras.

Referências. Até 50 para manuscritos originais, numeradas consecutivamente na ordem em que são citadas no texto. Para relatos de caso, nota histórica ou comunicações breves até 30, para "Neuroimagem através de casos clínicos" até 20, e nas revisões, até 150. No corpo do texto, as referências devem ser identificadas com algarismos arábicos, em expoente. A apresentação das referências dever estar de acordo com o padrão definido pelo *International Committee of Medical Journal Editors* – ICMJE (https://www.nlm.nih.gov/bsd/uniform_requirements.html) e os títulos dos periódicos deverão ser abreviados conforme *Index Medicus: abbreviations of journal titles* (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng).

- Artigos: autor(es), marque os seis primeiros e segue com et al.) . Título. Jornal ano; volume: páginas inicial-final e DOI .
- Livros: autor(es) ou editor (es). Título. Edição, se não for a primeira. Cidade de publicação: editora; ano: número de páginas.
- Capítulo de livro: autor (es). Título. In: Editores do livro seguido por (Eds),Título, edição, se não for a primeira. Cidade de publicação: editora, ano: páginas inicial e final.
- Resumos: autor(es). Título, seguido por (abstr). Jornal ano; volume (suplemento e seu número, se necessário): página(s) ou, no caso de resumos não publicados em jornais: Título da publicação. Cidade de publicação: editora, ano: página(s).
- Trabalhos consultados na internet: colocar o link e a data da consulta.

Tabelas. Até cinco tabelas em manuscritos originais (até três em comunicações breves ou relatos de caso), cada uma apresentada em página separada, com seu título, legenda e sequência numérica. As tabelas devem conter toda a informação requerida para compreensão do leitor. Não devem ser utilizadas linhas verticais para separar os dados dentro da tabela. Não submeta tabelas como fotografias. Numere a tabela consecutivamente em ordem de sua primeira citação no texto e forneça um breve título para

cada uma. Dê a cada coluna um cabeçalho curto ou abreviado. Coloque notas informativas no rodapé, não no cabeçalho. Explicite no rodapé todas as abreviações usadas em cada tabela. Para o rodapé use os seguintes símbolos, nesta sequência: *, +, §, ||, ¶, **, ++, etc. O Editor ao aceitar um manuscrito, pode recomendar que tabelas adicionais contendo dados importantes de suporte, muito extensos para publicação, possam ser deixadas num arquivo, tal como no sítio da revista (www.demneuropsy.com.br), ou que possa ser disponibilizado pelos autores. Neste caso, uma declaração apropriada será adicionada ao texto. Submeta todas as tabelas junto com o manuscrito.

Ilustrações. Até quatro figuras, gráficos ou fotos, com seu título e legenda em páginas separadas (até três ilustrações em comunicações curtas ou relatos de caso). As figuras deverão ser submetidas em formato JPEG ou TIFF, com as seguintes resoluções: a) arte em preto e branco: 1.200 dpi/ppi; b) combinação de meios-tons: 600 dpi/ppi; e c) meios tons: 300 dpi/ppi.

O quadro a seguir apresenta o resumo dos requisitos definidos para cada tipo de contribuição:

Tipo de Manuscrito	Resumo	Palavras-Chave (Decs Ou Mesh)	Palavras no Texto	Referências	Tabelas e Figuras
Artigo Original	Estruturado, com até 250 palavras	4 a 6	3.000	50	5 tabelas + 4 figuras
Artigo de Revisão	Não necessariamente estruturado, com até 150 palavras	4 a 6	5.000	150	5 tabelas + 4 figuras
Comunicações Breves	Estruturado, com até 250 palavras	4 a 6	2.000	30	3 tabelas + 3 figuras
Relato de Caso	Não necessariamente estruturado, com até 150 palavras	4 a 6	2.000	30	3 tabelas + 3 figuras
Nota Histórica	Não necessariamente estruturado, com até 150 palavras	4 a 6	2.000	30	3 tabelas + 3 figuras
Neuroimagem através de Casos Clínicos	–	–	750	20	1 tabela + 2 figuras
Carta ao Editor	–	–	750	20	1 tabela + 2 figuras

SUBMISSÃO DE MANUSCRITOS

As submissões de manuscritos deve ser realizada de forma online, a partir de: https://mc04.manuscriptcentral.com/dn-scielo.

Os manuscritos deverão ser submetidos no idioma inglês, incluindo título, resumo e palavras-chave em português.

Devem ser anexados: a carta de apresentação, declarações de responsabilidade de autoria, declaração financeira e transferência de direitos autorais. Cada uma destas três declarações deve ser lida e assinada por todos os autores. (Veja o formulário de autoria e um exemplo de carta de apresentação). Estudos que utilizem seres vivos devem submeter uma cópia da autorização pelo Comitê de ética da instituição envolvida. Ensaios clínicos serão aceitos para publicação, mediante apresentação do registro de ensaio clínico.

Os autores podem ser solicitados a fornecer informações adicionais sobre a apresentação prévia em encontros científicos. Esta informação pode ser dada na carta de apresentação, enviada na ocasião da submissão do manuscrito.

Atenção. Antes de submeter seu manuscrito, por favor, complete o *checklist* e as declarações de autoria, conflitos financeiros e não financeiros, disponíveis em: Formulário de Revelação de Autoria.

Não há taxas para submissão ou para a publicação de manuscritos.

Revisão dos manuscritos

Os manuscritos submetidos são inicialmente avaliados pelos editores-chefes. Manuscritos com insuficiente prioridade para publicação serão prontamente rejeitados.

Na avaliação inicial, um dos editores-chefes também verificará a adequação formal dos manuscritos às normas editoriais adotadas pela **Dementia & Neuropsychologia**. A submissão de manuscritos em desacordo com o formato descrito neste documento, poderá incorrer em sua devolução.

Após aprovação dos aspectos formais, o manuscrito é submetido para revisão por pares e consultores *ad-hoc*, especialistas nacionais e internacionais. Cada manuscrito será avaliado por pelo menos dois revisores.

A partir dos comentários dos revisores e das recomendações dos Editores Associados, os Editores-chefes poderão: a) aceitar a publicação do manuscrito; 2) solicitar aos autores que revisem e submetam o manuscrito revisado– Menor ou Maior Revisão; ou c) rejeitar e não considerar mais o manuscrito para publicação.

Para a submissão da versão revisada do manuscrito, os autores terão 30 dias para uma revisão menor e 60 dias para uma revisão maior.

O processo inteiro é supervisionado pelos Editores- Chefes que determinam o número apropriado de submissões dos artigos corrigidos, quantas forem necessárias, sempre focando na qualidade do trabalho a ser publicado.

Os autores serão informados pelos Editores-Chefes da provável data de publicação após sua decisão final.

O periódico adota a modalidade de revisão por pares do tipo *duplo cego*. Desta forma, as identidades dos revisores serão mantidas confidenciais, a identidade dos autores não será informada aos revisores.